INTRODUCTION

Diabetes mellitus (DM) is characterized by chronic hyperglycemia resulting from increased peripheral insulin resistance and/or decreased insulin secretion. Type 1 DM (T1DM) is caused by autoimmune destruction of pancreatic beta cells, while in type 2 DM (T2DM) the pathogenic mechanism is related to an increase in insulin resistance and a relative deficiency in insulin secretion. There are other types of diabetes, including the monogenic maturity onset diabetes of the young, which may be associated with pancreatic morphological changes.

ABSTRACT

Objectives: The objectives of the study was to compare pancreatic perfusion by computed tomography in type 2 diabetes and non-diabetic subjects.

Material and Methods: In this case–control study, 17 patients with type 2 diabetes and 22 non-diabetic controls were examined with a dynamic 192-slices perfusion computed tomography for estimating pancreatic perfusion parameters.

Results: Thirty-nine patients were included (22 with Type 2 diabetes mellitus [T2DM]), with a mean age of 64 years. There were significant differences in some pancreatic perfusion parameters in patients with and without type 2 diabetes. Blood volume (BV) was lower in pancreatic head (with T2DM: 14.0 ± 3.4 vs. without T2DM: 16.1 ± 2.4 mL/100 mL; \(P = 0.033\)), pancreatic tail (with: 14.4 ± 3.6 vs. without: 16.8 ± 2.5 mL/100 mL; \(P = 0.023\)), and in whole pancreas (with: 14.2 ± 3.2 vs. without: 16.2 ± 2.5 mL/100 mL; \(P = 0.042\)). Similar behavior was observed with mean transit time (MTT) in pancreatic head (with: 7.0 ± 1.0 vs. without: 7.9 ± 1.2 s; \(P = 0.018\)), pancreatic tail (with: 6.6 ± 1.3 vs. without: 7.7 ± 0.9 s; \(P = 0.005\)), and in whole pancreas (with: 6.8 ± 1.0 vs. without: 7.7 ± 0.9 s; \(P = 0.016\)). BV in head, tail, and whole pancreas had negative correlations with age (head \(r = -0.352, P = 0.032\); tail \(r = -0.421, P = 0.031\); whole pancreas \(r = -0.439, P = 0.007\)), and fasting plasma glucose (head \(r = -0.352, P = 0.032\); tail \(r = -0.421, P = 0.031\); whole pancreas \(r = -0.439, P = 0.007\)), and fasting plasma glucose (head \(r = -0.352, P = 0.032\); tail \(r = -0.421, P = 0.031\); whole pancreas \(r = -0.439, P = 0.007\)). In a multivariate linear regression model, HbA1c was independently associated with decrease in BV in whole pancreas (\(\beta = -0.884; CI95\%: -1.750 to -0.017; P = 0.046\)).

Conclusion: Pancreatic BV and MTT were significantly lower in patients with type 2 diabetes. BV was decreased with older age and poorer glycomic control.

Keywords: Pancreatic BV and MTT were significantly lower in patients with type 2 diabetes. BV was decreased with older age and poorer glycomic control.
led to interest in defining if pancreatic volume,\textsuperscript{[5–8]} shape, and blood flow would vary in the most common forms of diabetes.

Despite accounting for only 1–2% of pancreatic mass, islets of Langerhans receive around 10–23% of the total pancreatic blood flow.\textsuperscript{[9,10]} In Computed tomography (CT), there is a linear relationship between concentration of iodinated contrast media and the recorded density in Hounsfield units, and it is considered the ideal technique for perfusion images acquisition.\textsuperscript{[11]} Some studies have assessed normal values of pancreatic perfusion by CT.\textsuperscript{[12,13]} Pancreatic perfusion impairments have been evaluated in pancreatic\textsuperscript{[12,14–18]} and hepatic\textsuperscript{[19]} diseases, and modifications of pancreatic perfusion after oncologic therapy have been reported.\textsuperscript{[20]} Satisfactory intra-observer reproducibility of pancreatic perfusion parameters measured by CT, such as time to peak (TTP), blood flow (BF), and blood volume (BV) has already been shown,\textsuperscript{[21]} although experience in performing the readings is essential. Therefore, the aim of this study is to compare quantitatively the pancreatic perfusion by CT in T2DM and non-diabetic subjects.

**MATERIAL AND METHODS**

We retrospectively investigated seventeen patients with T2DM and 22 non-diabetic subjects who were referred to abdominal CT scan for reasons not related to pancreatic symptoms or disease, from October 2015 to September 2016. The study was performed in accordance non the Helsinki Declaration and was approved by the Ethics Committee of our institution. Exclusion criteria were pregnancy, history of allergic reaction to iodinated contrast media, kidney failure, and history of pancreatic disease.

All patients were scanned in a Siemens Somatom® Force 192-slices scanner. The CT protocol is shown in Table 1. Images were analyzed by a radiologist with 25 years of experience in abdominal imaging blinded to the clinical information, who participated in a training program on abdominal perfusion CT. The following parameters were measured on a workstation Syngo.via® (Siemens) with commercial perfusion CT software (CT Body Perfusion, Siemens) based on the maximum slope model: BF, BV, mean transit time (MTT), and TTP. BF is defined as the volume of flowing blood moving through a given volume of tissue in a specific amount of time. BV is defined as the volume of flowing blood for a given volume of tissue. MTT is defined by the formula – MTT = BV/BF – corresponding to the average amount of time blood takes to transit through a given volume of tissue. TTP is defined as the time elapsed to reach the peak of enhancement in each tissue.

Reading sections were performed twice by the single reader (session 1 and 2). The reader placed three circular ROI in each part of the pancreas (head, body, and tail) to measure these parameters. The mean value of each parameter on each part of the pancreas was considered for analysis.

**Statistical analysis**

Data are expressed as mean (±SD), median (interquartile range) or absolute and relative frequencies. Variables were compared by student t test and \( \chi^2 \) between subjects with and without T2DM. Correlations between CT perfusion parameters and clinical and laboratory characteristics were performed by Pearson correlations coefficients. A model of multivariate regression was carried out for CT perfusion parameters and clinical and laboratory characteristics.

**RESULTS**

A total of 39 patients (M: F ratio = 1.16) were included in the study, with a mean age of 64-year-old and a body mass index of 27.9 kg/m\(^2\). Seventeen patients had T2DM, while 22 did not. One patient from each group was excluded due to technical difficulties, which lead to impossibility in measuring pancreatic perfusion parameters (large ascites and improper contrast media injection); the final analysis included 37 patients.

Clinical and laboratory characteristics of patients, according to the DM status, are presented in Table 2. T2DM subjects were older and had higher fasting plasma glucose levels than those without diabetes, as expected. There were more men in T2DM group than in control group. Of note, low-density lipoprotein (LDL)-cholesterol was lower in T2DM group.

Pancreas volume was similar in patients with and without T2DM (with: 64.3 ± 28.1 vs. without: 63.6 ± 23.1; \( P = 0.929 \)).

\begin{table}
\centering
\caption{CT acquisition protocol.} \label{tab:CT_acquisition}
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{CT parameters} & \textbf{Precontrast} & \textbf{Perfusion} & \textbf{Venous} \\
\hline
Voltage (kVp) & 90 & 80 & 90 \\
Delay after contrast injection (s) & test* & 70 & 70 \\
Collimation (mm) & 192×0.6 & 48×1.2 & 128×0.6 \\
Rotation time (s) & 0.5 & 0.25 (full rotation) & 0.5 & 0.5 \\
Pitch & 1.5 (cycle time) & 0.6 & 0.6 & 0.5 \\
Slice thickness reconstructed (mm) & 3 & 5 & 3 & 3 \\
Contrast agent dose (mL) & 50 & 70 & 70 & 70 \\
Contrast injection rate (mL/s) & 4 & 4 & 4 & 4 \\
Bolus NaCl (mL) & 20 & 20 & 20 & 20 \\
\hline
\end{tabular}

\textsuperscript{*}Depends on test phase. CT: Computed tomography.
\end{table}
Considering the mean values of BF and TTP in both sessions, no significant differences between these pancreatic perfusion parameters in T2DM patients and controls were found. BV and MTT in pancreatic head, tail, and whole pancreas were lower in patients with T2DM than in controls [Table 3]. No differences between T2DM subjects and controls were observed for BF and TTP. An example of perfusion CT images is shown in Figure 1.

**DISCUSSION**

In this sample of subjects undergoing pancreatic perfusion CT, BV and MTT were decreased in those with T2DM in comparison with controls, and no significant differences in pancreatic BF and TTP was observed between these two groups. In addition, we demonstrated that there is a negative correlation between pancreatic BV and MTT and some clinical aspects, such as age, fasting plasma glucose, HbA1c and C-peptide, and higher HbA1c values were independently associated with lower pancreatic perfusion, measured by BV.

Few studies have compared pancreatic perfusion parameters in patients with diabetes and health controls. Miles et al.,[12]

---

**Table 2:** Clinical and laboratory characteristics of patients.

|                        | Diabetes          | P-value |
|------------------------|-------------------|---------|
|                        | No (n=21)         | Yes (n=16) |
| Age (years)            | 59±13             | 70±10    | 0.004 |
| DM duration (years)    | 11±5              |          |       |
| Men – n (%)            | 7 (33)            | 12 (75)  | 0.012 |
| BMI (kg/m²)            | 27±5              | 28±4     | 0.434 |
| Fasting plasma glucose | 105±33            | 170±60   | <0.001|
| HbA1c                  | 5.7±0.3           | 7.6±2.4  | 0.065 |
| C-peptide              | 1.6±1.4           | 1.8±0.4  | 0.902 |
| Cholesterol            | 196±46            | 181±55   | 0.493 |
| HDL                    | 64±21             | 41±46    | 0.131 |
| LDL                    | 112±38            | 73±43    | 0.028 |
| Triglycerides          | 96±28             | 175±147  | 0.093 |
| DM treatment           |                    |          |       |
| Diet                   | 1                 |          |       |
| Oral medications       | 12                |          |       |
| Insulin                | 3                 |          |       |

DM: Diabetes mellitus, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

**Table 3:** Mean values of BF, BV, MTT, and TTP of the reader in both sessions.

|                        | Diabetes          | P-value |
|------------------------|-------------------|---------|
|                        | No (n=21)         | Yes (n=16) |
| BF head                | 132.5±33.0        | 125.7±40.3 | 0.577 |
| BF body                | 139.6±37.7        | 131.6±41.6 | 0.543 |
| BF tail                | 144.3±32.9        | 133.9±38.8 | 0.385 |
| BF whole pancreas      | 138.8±32.4        | 130.4±38.5 | 0.476 |
| BV head                | 16.1±2.4          | 14.0±3.4  | 0.033 |
| BV body                | 15.7±3.3          | 14.3±3.8  | 0.223 |
| BV tail                | 16.8±2.5          | 14.4±3.6  | 0.023 |
| BV whole pancreas      | 16.2±2.5          | 14.2±3.2  | 0.042 |
| MTT head               | 7.9±1.2           | 7.0±1.0   | 0.018 |
| MTT body               | 7.4±1.4           | 7.0±1.4   | 0.302 |
| MTT tail               | 7.7±0.9           | 6.6±1.3   | 0.005 |
| MTT whole pancreas     | 7.7±0.9           | 6.8±1.0   | 0.016 |
| TTP head               | 21.2±2.8          | 22.3±2.0  | 0.193 |
| TTP body               | 20.6±2.6          | 21.6±1.7  | 0.215 |
| TTP tail               | 20.5±2.5          | 21.5±2.0  | 0.190 |
| TTP whole pancreas     | 20.8±2.5          | 21.8±1.8  | 0.182 |

TTP: Time to peak, BF: Blood flow, BV: Blood volume, MTT: Mean transit time

**Figure 1:** Blood volume color-coded map on computed tomography (CT). Axial CT image showing pancreatic perfusion processed on a workstation (Syngo.via®, Siemens) with commercial perfusion CT software (CT Body Perfusion, Siemens) based on the maximum slope model. Red colored areas show more perfused regions of the pancreas (white arrow on the pancreatic tail). Green/blue colored areas indicate less perfused regions (white arrowhead in the pancreatic body).
in 1995, reported reduced BF in one patient with diabetes; this patient, however, was the only one with diabetes from a total of 12 individuals evaluated. Our study advanced in the evaluation of pancreatic perfusion in patients with T2DM. By comparing a group of T2DM patients with a control group, we demonstrated that BV and MTT are lower in patients with T2DM.

We observed reduced BV in T2DM patients, which may be explained by ischemia in pancreatic microvascular network or by the absence of trophic effect of insulin in pancreatic microcirculatory system. As defined previously, MTT is directly related to BV and inversely to BF. As no differences in BF were detected in this sample, and BV was decreased in the T2DM group, lower MTT was expected in T2DM patients. Pancreatic BV is also reduced in other pancreatic diseases, such as pancreatic adenocarcinoma[14,15] and acute and chronic pancreatitis.[14]

Tal[22] hypothesized that pancreatic microvascular endothelial dysfunction and subsequent islet ischemia is the cause of initial dysfunction and subsequent apoptosis of beta cells seen in T2DM as disease progresses. This mechanism of lesion is like to the observed in other tissues classically associated with damage caused by hyperglycemia, such as the retina, kidney, and peripheral nerves. The same injury is likely to cause vascular endothelial dysfunction and affects blood vessels within the pancreas. In this sense, besides being the main cause of the disease, the pancreas could be also a target-organ for diabetes complications, perpetuating the beta cell damage observed as the disease progress.

The relationship between altered perfusion by CT and microvascular disease has been already demonstrated in other organs, such as the brain[23] and the heart.[23,24] We showed for the first-time differences in pancreatic perfusion CT in patients with T2DM in comparison to non-diabetic patients, probably related to microvascular changes in the pancreas.

Our study had some limitations. First, pancreatic perfusion parameters were obtained by only one reader, which limits reproducibility of our results. Second, this sample was powered to detect differences in BF and some of the negative results may be due to lack of power for other variables.

CONCLUSION

Pancreatic perfusion, assessed by BV and MTT, was significantly lower in T2DM patients in comparison to controls.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Standards of medical care in diabetes-2016: Summary of revisions. Diabetes Care 2016;39 Suppl 1:S4-5.
2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2018. Diabetes Care 2018;41 Suppl 1:S13-27.
3. Haldorsen IS, Raeder H, Vesterhus M, Molven A, Njølstad PR. The role of pancreatic imaging in monogenic diabetes mellitus. Nat Rev Endocrinol 2012;8:148-59.
4. Moens SJ, Mooij HL, Hassing HC, Kruit JK, Witjes JJ, van de Sande MA, et al. Carriers of loss-of-function mutations in EXT display impaired pancreatic beta-cell reserve due to smaller pancreas volume. PLoS One 2014;9:e15662.
5. Goda K, Sasaki E, Nagata K, Fukai M, Ohsawa N, Hahafusa T. Pancreatic volume in Type 1 and Type 2 diabetes mellitus. Acta Diabetol 2001;38:145-9.
6. Saih Y, Butler AE, Meier JJ, Monchamp T, Allen-Auerbach M, Rizza RA, et al. Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of Type-2 diabetes. Clin Anat 2007;20:933-42.
7. Burute N, Nisenbaum R, Jenkins DJ, Mirrhami A, Anthwal S, Colak E, et al. Pancreas volume measurement in patients with Type 2 diabetes using magnetic resonance imaging-based planimetry. Pancreatology 2014;14:268-74.
8. Weir GC, Bonner-Weir S, Leahy JL. Islet mass and function in diabetes and transplantation. Diabetes 1990;39:401-5.
9. Bonner-Weir S. The microvasculature of the pancreas, with emphasis on that of the islets of Langerhans. In: Vay Lyang W. editor. The Pancreas: Biology, Pathobiology, and Disease. 2nd ed. New York: Raven Press; 1993. p. 759-68.
10. Lifson N, Kramlinger KG, Mayrand RR, Lender EJ. Blood flow to the rabbit pancreas with special reference to the islets of Langerhans. Gastroenterology 1980;79:466-73.
11. Kandel S, Kloetser C, Meyer H, Hein P, Hilbig A, Rogalla P. Whole-organ perfusion of the pancreas using dynamic volume CT in patients with primary pancreatic carcinoma: Acquisition technique, post-processing and initial results. Eur Radiol 2009;19:2641-6.
12. Miles KA, Hayball MP, Dixon AK. Measurement of human pancreatic perfusion using dynamic computed tomography with perfusion imaging. Br J Radiol 1995;68:471-5.
13. Li HO, Sun C, Xu ZD, Miao F, Zhang DJ, Chen JH, et al. Low-dose whole organ CT perfusion of the pancreas: Preliminary study. Abdom Imaging 2014;39:40-7.
14. Klauss M, Stillier W, Fritz F, Kieser M, Werner J, Kauczor HU, et al. Computed tomography perfusion analysis of pancreatic carcinoma. J Comput Assist Tomogr 2012;36:237-42.
15. Klauss M, Stillier W, Pahn G, Fritz F, Kieser M, Werner J, et al. Dual-energy perfusion-CT of pancreatic adenocarcinoma. Eur J Radiol 2013;82:208-14.
16. D’Onofrio M, Gallotti A, Mantovani W, Crosara S, Manfrin E, Falconi M, et al. Perfusion CT can predict tumoral grading of pancreatic adenocarcinoma. Eur J Radiol 2013;82:227-33.

17. Wan Y, Hao H, Meng S, Li Z, Yu F, Chi N, et al. Application of low dose pancreas perfusion CT combined with enhancement scanning in diagnosis of pancreatic neuroendocrine tumors. Pancreatology 2020;21:240-5.

18. O’Malley RB, Soloff EV, Coveler AL, Cox DH, Desai N, Busey JM, et al. Feasibility of wide detector CT perfusion imaging performed during routine staging and restaging of pancreatic ductal adenocarcinoma. Abdom Radiol (NY) 2021;46:1992-2002.

19. Kanda T, Yoshikawa T, Ohno Y, Fujisawa Y, Kanata N, Yamaguchi M, et al. Perfusion measurement of the whole upper abdomen of patients with and without liver diseases: Initial experience with 320-detector row CT. Eur J Radiol 2012;81:2470-5.

20. Park MS, Klotz E, Kim MJ, Song SY, Park SW, Cha SW, et al. Perfusion CT: Noninvasive surrogate marker for stratification of pancreatic cancer response to concurrent chemo-and radiation therapy. Radiology 2009;250:110-7.

21. Garcia TS, Engelholm JL, Vouche M, Hiramata VN, Leitão CB. Intra-and interobserver reproducibility of pancreatic perfusion by computed tomography. Sci Rep 2019;9:6043.

22. Tal MG. Type 2 diabetes: Microvascular ischemia of pancreatic islets? Med Hypotheses 2009;73:357-8.

23. Yan AT, Gibson CM, Larose E, Anavekar NS, Tsang S, Solomon SD, et al. Characterization of microvascular dysfunction after acute myocardial infarction by cardiovascular magnetic resonance first-pass perfusion and late gadolinium enhancement imaging. J Cardiovasc Magn Reson 2006;8:831-7.

24. Mohlenkamp S, Lerman LO, Lerman A, Behrenbeck TR, Katusić ZS, Sheedy PF 2nd, et al. Minimally invasive evaluation of coronary microvascular function by electron beam computed tomography. Circulation 2000;102:2411-6.

How to cite this article: Garcia TS, Engelholm JL, Vouche M, Leitão CB. Decrease in pancreatic perfusion of patients with type 2 diabetes mellitus detected by perfusion computed tomography. J Clin Imaging Sci 2021;11:50.