The Aging Male

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/itam20

Relationship among CT-based abdominal adipose tissue areas and pancreatic ductal adenocarcinoma in male

Elif Gündoğdu, Emre Emekli & Mahmut Kebapçı

To cite this article: Elif Gündoğdu, Emre Emekli & Mahmut Kebapçı (2020) Relationship among CT-based abdominal adipose tissue areas and pancreatic ductal adenocarcinoma in male, The Aging Male, 23:5, 1455-1459, DOI: 10.1080/13685538.2020.1793940

To link to this article: https://doi.org/10.1080/13685538.2020.1793940

Published online: 16 Nov 2020.

THE AGING MALE
2020, VOL. 23, NO. 5, 1455–1459
https://doi.org/10.1080/13685538.2020.1793940

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Relationship among CT-based abdominal adipose tissue areas and pancreatic ductal adenocarcinoma in male

Elif Gündoğdu, Emre Emekli and Mahmut Kebapçı

Department of Radiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

ABSTRACT

Purpose: It is known that obesity can be a risk factor for many types of cancer, including the pancreas. Visceral obesity rather than overall obesity is held more responsible for this relationship. This study aimed to evaluate the relationship of adipose tissue areas and their distribution (subcutaneous and visceral) with pancreatic ductal adenocarcinoma (PDAC) in male patients.

Materials and-Method: The medical data and abdominopelvic computed tomography (CT) examinations of male patients diagnosed with PDAC who underwent surgery or a biopsy in our hospital between January 2015 and January 2020 were retrospectively evaluated. An age-matched control group was formed from 49 male patients who underwent CT with a preliminary diagnosis of urinary stone without a history of malignancy and weight loss and no malignancy on CT at the time of presentation. Adipose tissue areas (total [TAT], visceral [VAT] and subcutaneous [SAT]) were measured in both groups, their VAT/TAT, VAT/SAT and SAT/TAT ratios were calculated, and the data were compared between the two groups.

Results: Patients with PDAC had significantly greater TAT, VAT and SAT areas than the control group ($p = 0.002$, $p = 0.01$, and $p = 0.003$, respectively). However, there was no significant differences in the VAT/TAT, VAT/SAT and SAT/TAT ratios between the two groups ($p = 0.60$, $p = 0.60$, and $p = 0.73$, respectively).

Conclusion: In this study, all adipose tissue areas (VAT, SAT, and TAT) were shown to be increased in male patients with PDAC. Both visceral obesity and overall obesity present as risk factors for PDAC in male patients.

ARTICLE HISTORY
Received 22 June 2020
Revised 4 July 2020
Accepted 6 July 2020
Published online 13 November 2020

KEYWORDS
Pancreatic ductal adenocarcinoma; obesity; abdominal adipose tissue area; computed tomography

Introduction

The pancreas is an organ that has both exocrine and endocrine secretory functions. The most common exocrine tumor of the pancreas is pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of cases [1]. PDAC is one of the most lethal malignant neoplasms across the world [2]. Most of these neoplasms are metastatic or unresectable at the time of diagnosis. PDAC has a poor prognosis [3,4] with a five-year survival rate of approximately 8% [5].

PDAC has nonmodifiable risk factors, such as age, diabetes mellitus, family history, and genetic syndromes and modifiable risk factors, including smoking, obesity, alcoholism, and physical inactivity [6]. Many cohort studies have shown a strong connection between obesity and PDAC incidence [7]. It is known that adipose tissue, especially the accumulation of intra-abdominal fat acts like an endocrine organ and leads to chronic inflammation through adipokine, cytokine and growth factors it secretes [8–12]. This mechanism is implicated in obesity-related oncogenesis [13]. However, molecular mechanisms linking obesity to PDAC is still under extensive investigation, and the link between obesity and PDAC is not yet fully understood [7,14].

Although body mass index (BMI) has been widely used as a conventional measurement of obesity, it does not provide any information about the distribution (subcutaneous and visceral) of body adipose tissue [15,16]. Visceral adipose tissue (VAT) has greater hormonal and metabolic activities than subcutaneous adipose tissue (SAT) [17,18] and there are publications reporting that increased VAT poses a higher risk in obesity-related cancers [19]. Waist circumference (WC) is superior to BMI for defining visceral obesity [20,21]. However, cross-sectional imaging methods, computed tomography (CT) and magnetic resonance imaging (MRI) are essential imaging techniques to

CONTACT Elif Gündoğdu elif_basbay@hotmail.com, Faculty of Medicine, Department of Radiology, Eskişehir Osmangazi University, Meşelik Yerleşkesi, Eskişehir 26480, Turkey

quantitatively determine the adipose distribution in subcutaneous and visceral compartments [22,23].

In the literature, studies evaluating the relationship between obesity and PDAC have used anthropometric parameters, such as WC and BMI [24–26]. To the best of our knowledge, there is only one study that investigated the relationship between fat tissue areas (VAT and SAT) measured by CT and PDAC [27]. This study is weak due to the insufficient number of patients and the inability to generalize the results. In this study, we aimed to evaluate the relationship between CT-detected adipose tissue area and its distribution (subcutaneous and visceral) with PDAC in male patients.

Materials and method

Before the study, the approval of the local ethics committee was obtained (date: 02/06/2020, number: 25403353-050.99-E.51596). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study participants

Medical data and abdominopelvic CT examinations of male patients with a pancreatic mass that underwent surgery or a biopsy in our hospital between January 2015 and January 2020 were retrospectively evaluated. A total of 113 patients were included in the evaluation. Patients were excluded from the study if they fulfilled any of the following criteria: a history of weight loss at the time of presentation ($n = 26$), a known history of malignancy prior to the CT scan ($n = 13$), a diagnosis of non-adenocarcinoma pathology ($n = 17$; neuroendocrine tumors in 11, schwannoma in one, adenoma in one, sarcoid tumor in one, chronic pancreatitis in two, and hamartoma in one), a history of surgery that could affect the abdominal adipose tissue ($n = 1$; sleeve gastrectomy), and poor-quality or unacceptable CT scans ($n = 2$). The patients have a history of weight loss at the time of presentation were excluded because PDAC is asymptomatic for a long time and weight loss might be its initial presentation. Early of the this period, patients may have high AT areas but sudden decrease of AT areas may occur after progression of the disease. This condition may lead to false evaluation of the AT areas at the time of diagnosis. As a result, 54 male patients with histopathologically proven PDAC who met the inclusion criteria were enrolled in the study. An age-matched control group was formed from 49 male patients who underwent CT with a preliminary diagnosis of urinary stone without a history of malignancy and weight loss and no malignancy on CT. The adipose tissue areas (total adipose tissue [TAT], VAT, and SAT) were measured in both groups. In addition, the ratios of VAT/TAT, VAT/SAT and SAT/TAT were calculated and compared between the two groups.

None of the patients and control groups had known hereditary disease.

CT protocols

CT imaging was performed using 64-slice (Toshiba, Aquillon 64, Japan) or 128-slice (GE, Revolution EVO, USA) multi-detector CT scanners. The subjects were examined in a supine position with their arms extended above their heads. All CT examinations were performed using a routine portal venous phase abdominal CT protocol after the intravenous bolus administration of an iodinated contrast agent (65 s). The intravenous contrast agent (1.5 ml/kg; iopromide 370, Bayer Schering Pharma AG, Germany or iohexol 350, GE Healthcare, USA) was administered through the antecubital veins with an automatic injector at a rate of 3 ml/sec. The CT parameters were as follows: 1:1 pitch, 200-250 mAs, 120 kVp, and 0.5-0.625 isotropic spatial resolution.

CT image analysis and measurement of fat

CT images were evaluated by two radiologists with consensus (EG, 12 years of experience; EE, 4 years of experience). All measurements of the investigated parameters (TAT and VAT) were performed twice and averaged.

An axial view was used for the measurement of the fat areas on CT. A single slice at the level of L1-2 intervertebral disc space was evaluated. The L1-2 intervertebral disc space was identified for the measurements because VAT at the T12-L1 and L1-L2 landmarks hasa been reported to have a much stronger association with metabolic syndrome than adipose tissue in other sites [28]. Using a dedicated workstation (GE, Advantage Workstation 4.3, USA), the TAT and VAT ROI were delineated by manually tracing a contour of each region (Figure 1). Fat pixels; i.e. fat areas were identified based on the threshold attenuation values between − 190 and − 30 Hounsfield units (HU), as described by Yoshizumi *et al.* [22]. TAT was measured by drawing a contour around the skin. Another contour was drawn around the visceral fat by identifying the innermost part of the abdominal wall muscles and anterior aspect of the vertebral column. SAT was

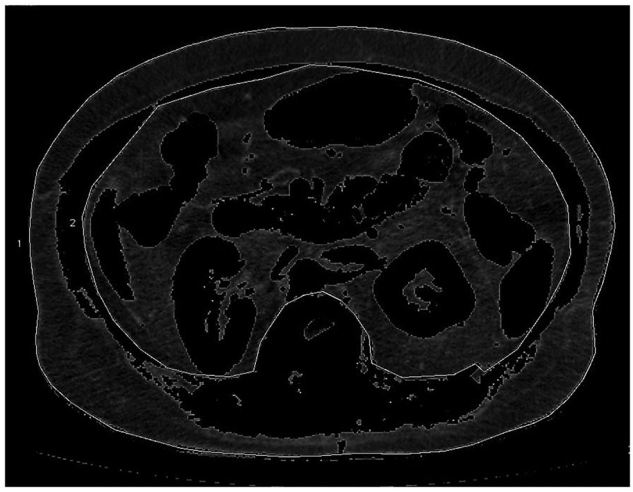

Figure 1. TAT was measured by drawing a contour around the skin, VAT was measured by drawing around the visceral fat by identifying the innermost part of the abdominal wall muscles and anterior aspect of the vertebral column by manually. The SAT area was calculated by subtracting the VAT area from the TAT area.

defined as the area of adipose tissue between the skin and the outermost aspect of the abdominal muscle wall. The SAT area was calculated by subtracting the VAT area from the TAT area.

Statistical analysis

SPSS software v.22.0 (Chicago, IL) was used for statistical analysis. The normality analysis was performed with the Shapiro–Wilk test. Descriptive statistics were presented as mean, standard deviation, minimum and maximum values for the continuous data and percentage values for the discrete data. Student's t-test was used to compare the parameters between the groups (PDAC and control). The level of statistical significance was considered as $p < 0.05$.

Results

The mean age of the PDAC patients was 65.6 ± 12.3 years (40–95 years). The mean age of the individuals in the control group was 67.7 ± 10.8 years (48–87). There was no statistically significant difference between the two groups in terms of age ($p = 0.35$). All adipose tissue areas (TAT, VAT, and SAT) were significantly higher in the PDAC group than in the control group ($p = 0.002$, $p = 0.01$, and $p = 0.003$, respectively). However, there was no significant difference in the VAT/TAT, VAT/SAT and SAT/TAT ratios between the two groups ($p = 0.60$, $p = 0.73$, and $p = 0.60$, respectively). Table 1 presents the data of the groups.

Table 1. Data of the patient and control groups.

Parameters	PDAC Group	Control Group	*p* Value
	Mean±*SD* *(min-max)*	Mean±*SD* *(min-max)*	
TAT area (cm^2)	310.24 ± 134.70 (113.2-744.49)	240.04 ± 82.21 (38.66-460.93)	**0.002**
VAT area (cm^2)	181.61 ± 83.85 (57.93-411.15)	144.87 ± 59.48 (12.98-351.83)	**0.01**
SAT area (cm^2)	128.62 ± 68.35 (47.65-393.42)	95.16 ± 35.10 (24.52-172.51)	**0.003**
VAT/TAT ratio	0.58 ± 0.10 (0.36-0.74)	0.59 ± 0.09 (0.33-0.76)	0.60
VAT/SAT ratio	1.55 ± 0.63 (0.57-2.99)	1.59 ± 0.62 (0.50-3.22)	0.73
SAT/TAT ratio	0.41 ± 0.10 (0.25-0.63)	0.40 ± 0.09 (0.23-0.66)	0.60

PDAC: Pancreatic ductal adenocarcinoma; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; TAT: total adipose tissue; SD: standard deviation; min: minimum; max: maximum.
The level of statistical significance was considered as $p < 0.05$ in the study. Bold values are <0.05 and statistically significant.

Discussion

The results of our study showed that both subcutaneous and visceral adipose tissue areas were significantly increased in male patients with PDAC. Accordingly, it is possible to conclude that both general and central obesity increases the risk of PDAC in male patients.

Epidemiological studies have shown that obesity can be a risk factor for many types of cancer, including PDAC [29,30]. It is also known that anatomically different fat areas show different tissue characterization and metabolic activity. Therefore, especially in recent years, studies have been conducted to evaluate the relationship of various cancer types with VAT area rather than overall obesity. Greco *et al.* found an increased VAT area and VAT/SAT ratio in both non-clear cell and clear cell renal carcinoma in male patients [16,31]. Massl *et al.* found that increased VAT area was a risk factor for the development of esophageal adenocarcinoma [32]. Montano-Loza *et al.* reported that increased VAT area was an independent risk factor for the development of hepatocellular carcinoma (HCC) in male patients with cirrhosis and also posed a risk for recurrence of HCC after transplantation [33]. Oh *et al.* determined that increased VAT area was an independent risk factor for colorectal neoplasms [34]. In addition, another study showed that increased VAT area constituted a risk for prostate cancer [35].

In the large PanScan study funded by the National Cancer Institute, a positive correlation between increased BMI and risk of pancreatic cancer was observed [26]. In our study, although BMI was not evaluated, the TAT area, which is an indicator of overall obesity, was higher in the PDAC group than in the

control group, and we similarly found overall obesity as a risk factor. In a meta-analysis evaluating 23 prospective studies, Aune *et al.* reported that the relative risk for PDAC was 1.10 for every five-unit increase in BMI, 1.11 for 10-cm increase in WC, and 1.19 for each 0.1-unit increase in the waist-to-hip ratio [24]. In that study, BMI was used as the overall obesity marker while WC and the waist-to-hip ratio were used as central obesity markers. Both visceral and overall obesity were found to be risk factors for PDAC. Our results are similar to those of this meta-analysis. We used VAT as a visceral obesity marker, and SAT and TAT as overall obesity markers, and observed that all these parameters increased in PDAC patients compared to the control group.

To our knowledge, the literature contains only one study (that conducted by Kwee TC and Kwee RM), which evaluated the relationship between PDAC and adipose tissue areas determined on CT [27]. In that study, the authors did not find a relationship between the VAT, SAT and TAT areas and PDAC. However, they reported that their study had low statistical power and their results could not be generalized due to the low number of participants (two females, seven males). In contrast, our study showed that both subcutaneous and visceral adipose tissue areas were increased in patients with PDAC. Furthermore, the number of patients constituting our study group was sufficient for an accurate evaluation of statistical data. It is also known that men and women have different adipose tissue distribution. There is more visceral adipose tissue in men while more subcutaneous adipose tissue is seen in women [36]. In addition, in the postmenopausal period, visceral obesity increases in women [36]. Therefore, in studies investigating adipose tissue areas, gender discrimination analysis and the investigating of the menopause status in female patients can provide more definitive results. In the study of Kwee TC and Kwee RM, the assessment was performed without any gender discrimination. We consider that this is not appropriate, and studies evaluating adipose tissue areas should perform this assessment in separate groups considering the differences between the genders. This is why we only evaluated male patients in our study and formed the control group from male patients, which is considered to be one of the strengths of our study. This may be another reason why our results differed from those of Kwee TC and Kwee RM, in addition to our larger sample size.

Our study has certain limitations. First is the retrospective nature of the study, which did not allow us to evaluate other risk factors of PDAC, including smoking and diabetes mellitus. However, the random selection of the control group prevented bias. Secondly, since the study had a cross-sectional design, we were not able to determine the effect of the duration of increased TAT, VAT and SAT areas on the development of PDAC. Lastly, we were not able to reach enough female patients to meet the inclusion criteria to separately evaluate them since pancreatic cancers are observed more frequently in males, and most patients had a history of weight loss at the time of diagnosis.

Conclusion

In this study, all adipose tissue areas (VAT, TAT, and SAT) were found to be increased in male patients with PDAC. Not only visceral but also overall obesity present as factors for PDAC in male patients. Larger-scale studies can provide more reliable data to provide an explanation concerning the relationship between TAT, SAT and VAT areas and PDAC.

Disclosure statement

The authors declare that they have no conflict of interest.

ORCID

Elif Gündoğdu http://orcid.org/0000-0002-1729-6958
Emre Emekli http://orcid.org/0000-0001-5989-1897
Mahmut Kebapçı http://orcid.org/0000-0002-2856-9923

References

[1] Paternoster S, Falasca M. The intricate relationship between diabetes, obesity and pancreatic cancer. Biochim Biophys Acta Rev Cancer. 2020;1873(1):188326.
[2] Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016;22(44):9694–9705.
[3] Hidalgo M. Pancreatic cancer. N Engl J Med. 2010;362(17):1605–1617.
[4] Chari ST. Detecting early pancreatic cancer: problems and prospects. Semin Oncol. 2007;34(4):284–294.
[5] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
[6] Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. Cancer Lett. 2016;381(1):269–277.
[7] Cascetta P, Cavaliere A, Piro G, et al. Pancreatic cancer and obesity: molecular mechanisms of cell transformation and chemoresistance. IJMS. 2018;19(11):3331.
[8] Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013;9(2):191–200.
[9] Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444(7121):881–887.

[10] Goh VH, Hart WG. Association of general and abdominal obesity with age, endocrine and metabolic factors in Asian men. Aging Male. 2016;19(1):27–33.
[11] Angelova P, Kamenov Z, Tsakova A, et al. Interleukin-18 and testosterone levels in men with metabolic syndrome. Aging Male. 2018;21(2):130–137.
[12] Mohamad NV, Wong SK, Wan Hasan WN, et al. The relationship between circulating testosterone and inflammatory cytokines in men. Aging Male. 2019; 22(2):129–140.
[13] Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer. 2011;11(12):886–895.
[14] Wörmann SM, Algül H. Risk factors and therapeutic targets in pancreatic cancer. Front Oncol. 2013;3:282.
[15] Hu Z, Wu J, Lai S, et al. Clear cell renal cell carcinoma: the value of sex-specific abdominal visceral fat measured on CT for prediction of Fuhrman nuclear grade [published online ahead of print, 2020 Mar. Eur Radiol. 2020;30(7):3977–3986.
[16] Greco F, Mallio CA, Grippo R, et al. Increased visceral adipose tissue in male patients with non-clear cell renal cell carcinoma. Radiol Med. 2020;125(6): 538–543.
[17] Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11(1):11–18.
[18] Greco F, Mallio CA, Cirimele V, et al. Imaging of renal angiomyolipomatosis. jrenhep. 2018;2(2):10–19.
[19] Greco F, Quarta LG, Grasso RF, et al. Increased visceral adipose tissue in clear cell renal cell carcinoma with and without peritumoral collateral vessels. Br J Radiol. 2020;93:20200334. [published online ahead of print].
[20] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23(5):469–480.
[21] Groti K, Žuran I, Antonič B, et al. The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. Aging Male. 2018;21(3):158–169.
[22] Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. Radiology. 1999; 211(1):283–286.
[23] Borkan GA, Gerzof SG, Robbins AH, et al. Assessment of abdominal fat content by computed tomography. Am J Clin Nutr. 1982;36(1):172–177.
[24] Aune D, Greenwood DC, Chan DSM, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23(4):843–852.
[25] Larsson SC, Permert J, Håkansson N, et al. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer. 2005;93(11):1310–1315.
[26] Arslan AA, Helzlsouer KJ, Kooperberg C, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010;170(9):791–802.
[27] Kwee TC, Kwee RM. Abdominal adiposity and risk of pancreatic cancer. Pancreas. 2007;35(3):285–286.
[28] Kuk JL, Church TS, Blair SN, et al. Does measurement site for visceral and abdominal subcutaneous adipose tissue alter associations with the metabolic syndrome? Diabetes Care. 2006;29(3):679–684.
[29] Duarte MF, Luis C, Baylina P, et al. Clinical and metabolic implications of obesity in prostate cancer: is testosterone a missing link? Aging Male. 2019;22(4): 228–240.
[30] Mathur A, Hernandez J, Shaheen F, et al. Preoperative computed tomography measurements of pancreatic steatosis and visceral fat: prognostic markers for dissemination and lethality of pancreatic adenocarcinoma. HPB (Oxford). 2011;13(6):404–410.
[31] Greco F, Cirimele V, Mallio CA, et al. Increased visceral adipose tissue in male patients with clear cell renal cell carcinoma. Clin Cancer Investig J. 2018;7(4): 132–136.
[32] Massl R, Blankenstein M, Jeurnink S, et al. Visceral adipose tissue: the link with esophageal adenocarcinoma. Scand J Gastroenterol. 2014;49(4):449–457.
[33] Montano-Loza AJ, Mazurak VC, Ebadi M, et al. Visceral adiposity increases risk for hepatocellular carcinoma in male patients with cirrhosis and recurrence after liver transplant. Hepatology. 2018;67(3):914–923.
[34] Oh TH, Byeon JS, Myung SJ, et al. Visceral obesity as a risk factor for colorectal neoplasm. J Gastroenterol Hepatol. 2008;23(3):411–417.
[35] von Hafe P, Pina F, Pérez A, et al. Visceral fat accumulation as a risk factor for prostate cancer. Obes Res. 2004;12(12):1930–1935.
[36] Nedungadi TP, Clegg DJ. Sexual dimorphism in body fat distribution and risk for cardiovascular diseases. J Cardiovasc Transl Res. 2009;2(3):321–327.