Subcutaneous Adipose Tissue as a Biomarker of Pancreatic Cancer: A Pilot Study in Male Patients

Abstract

Purpose: The purpose of this study was to evaluate the relationship between subcutaneous adipose tissue (SAT) and pancreatic cancer (PC) in male patients. **Methods:** In this retrospective study, two groups were included. Quantitative assessment of adipose tissue was performed by measuring total adipose tissue (TAT) area, visceral adipose tissue (VAT) area, and the SAT area in both the groups. Then, VAT/SAT ratio was calculated. **Results:** Statistically significant differences between the two groups were found in the SAT area ($P < 0.05$), TAT area was slightly above the threshold of significance, while no significant difference was found in the VAT area and VAT/SAT ratio. **Conclusions:** The results of this study suggest an association between SAT reduction and PC risk.

Keywords: *Adrenomedullin, computed tomography, pancreatic cancer, subcutaneous adipose tissue*

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer death worldwide.[1] Due to its aggressive nature, prognosis is poor and 5-year survival rates are as much as 9%.[1] Most PC patients die within 6 months after the diagnosis, usually showing locally advanced or metastatic disease.[2,3] The large majority of pancreatic malignancies are pancreatic ductal adenocarcinoma (>90%).[4] Approximately 60%–70% of the lesions are located at the level of the head, neck, or uncinate process, 5%–10% at the body, and 10%–15% at the pancreatic tail.[5]

Jaundice commonly occurs in patients with a localized lesion in the head, neck, or uncinate process. Many patients have abdominal pain or back pain, followed by obstructive jaundice. Diabetes mellitus and pancreatitis may also be present. The most common manifestations of advanced disease are anorexia, weight loss, gastric outlet obstruction, and ascites.[6] PCs located in the left side of the gland may remain asymptomatic for a long time and be diagnosed when they reach a large size (4–5 cm), showing symptoms of advanced disease.[7] The incidence of thromboembolism in PC patients is 17%–57%.[8]

The severe and rapid loss of adipose tissue and skeletal muscle mass is an important contribution to early mortality in PC.[9] Many months before the onset of cachexia, weight loss occurs in PC patients.[10] The development of new-onset diabetes is paradoxically related to weight loss mostly related to a reduction of adipose tissue.[9,10] It has been postulated that mediators secreted by PC are responsible for adipose tissue loss.[10] In particular, it has been shown that adrenomedullin (AM), contained in exosomes released by PC, determines lipolysis in the subcutaneous adipose tissue (SAT).[9] Computed tomography (CT) and magnetic resonance imaging are fundamental techniques for noninvasive tissue evaluation and characterization, including visceral adipose tissue (VAT) and SAT.[11-17]

We hypothesized that SAT reduction, as measured with a quantitative CT imaging-based approach, is associated with the occurrence of PC in male patients.

Methods

Patients

In this retrospective study, two groups of patients were included: the PC group and the control group. All of the recruited participants underwent a CT examination in our institution between December 2012 and May 2016.

In the PC group, a total of 20 male patients with PC at the first diagnosis were enrolled (mean age: 73.4 years, range: 44–83).

All CT images were acquired for disease staging. The disease staging was 4 T1N0M0, 1 T1N1M0, 2 T2N0M0, 1 T2N1M0, 3 T3N0M0, and 9 T3N1M0.

None of the patients enrolled in the PC group had a past medical history of malignancies before the diagnosis of PC.

We included 20 male patients who have undergone a chest–abdomen CT for preoperative cardiovascular surgery as a control group (mean age: 69.4 years, range: 57–82) because of the fact that abdominal CT is not usually performed in healthy patients.

Patients included in the control group underwent the following cardiac surgery: mitral valve replacement (6), aortic valve replacement (6), mitral and tricuspid valve replacement (1), left atrial myxoma resection (1), combined coronary artery bypass and mitral valve replacement (3), combined coronary artery bypass and aortic valve replacement (1), combined coronary artery bypass with mitral and tricuspid valve replacement (1), and aortic valve and ascending aorta replacement (1). None of the patients of the control group had a history of malignancies.

Computed tomography analysis

CT scans were performed with SOMATOM Sensation 64, Siemens, Forchheim, Germany. OsiriX MD version 2.6 was used to analyze cross-sectional CT images to calculate total adipose tissue (TAT) area, VAT area, and SAT area. All measurements were obtained as areas (cm^2), on the axial plane 3 cm above the lower margin of L3 [Figure 1].[12,18]

Statistical analysis

The TAT, VAT, and SAT areas and the VAT/SAT ratio were compared using the Student's *t*-test between the two groups. The level of statistical significance was considered to be $P < 0.05$.

Results

Statistically significant differences between the two groups were found in the SAT area ($P < 0.05$), TAT area was slightly above the threshold of significance, while no significant difference was found in the VAT area and VAT/SAT ratio [Figure 2]. The results are summarized in Table 1.

Discussion

We have evaluated the SAT area in PC male patients.

The results show a significant difference of SAT between the control group and the PC group, suggesting an association between the reduction of SAT and PC.

In PC-induced diabetes, as well as in type 2 diabetes, there is evidence of beta-cell dysfunction and peripheral insulin resistance. However, the control of glucose level is challenging in PC-induced diabetes, leading to continuous and severe weight loss. Indeed, diabetes and cachexia can be paraneoplastic phenomena induced by PC.[10]

Cancerous cachexia is a multifactorial metabolic syndrome that leads to gradual functional deterioration. The loss of adipose tissue and skeletal muscles of cancer cachexia cannot be completely resolved by conventional nutritional support.[19] The depletion of adipose tissue as well as muscle is associated with a poor outcome.[20] Cachexia affects 80% of all cancer patients and is the direct cause of 22%–40% of cancer deaths.[21-23]

The reduction of adipose tissue in cachexia is determined by several factors: the increased lipolysis of the triglycerides, the reduction of fatty acid synthase and lipoprotein lipase activity that determine a reduction of lipogenesis and fatty acid esterification, and the interruption of organization and development of adipose tissue due to impaired turnover of adipocytes.[20,24-26]

Weight loss precedes the appearance of PC symptoms several months before. This weight loss is not due to cachexia.[10] Moreover, weight loss occurs months before the onset of diabetes. This phenomenon could be an

Table 1: Mean of the two groups and Student's *t*-test results

	TAT area (cm^2)	VAT area (cm^2)	SAT area (cm^2)	VAT/SAT ratio
Control group	349.83	190.27	157.55	1.31
PC group	266.09	155.98	110.11	1.61
P	0.056	0.237	0.022	0.260

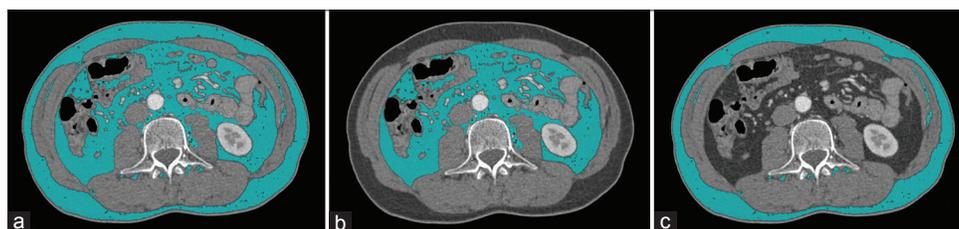TAT: Total adipose tissue, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue

Figure 1: Axial computed tomography images showing the regions of interest of the total adipose tissue area (a), visceral adipose tissue area (b), and subcutaneous adipose tissue area (c)
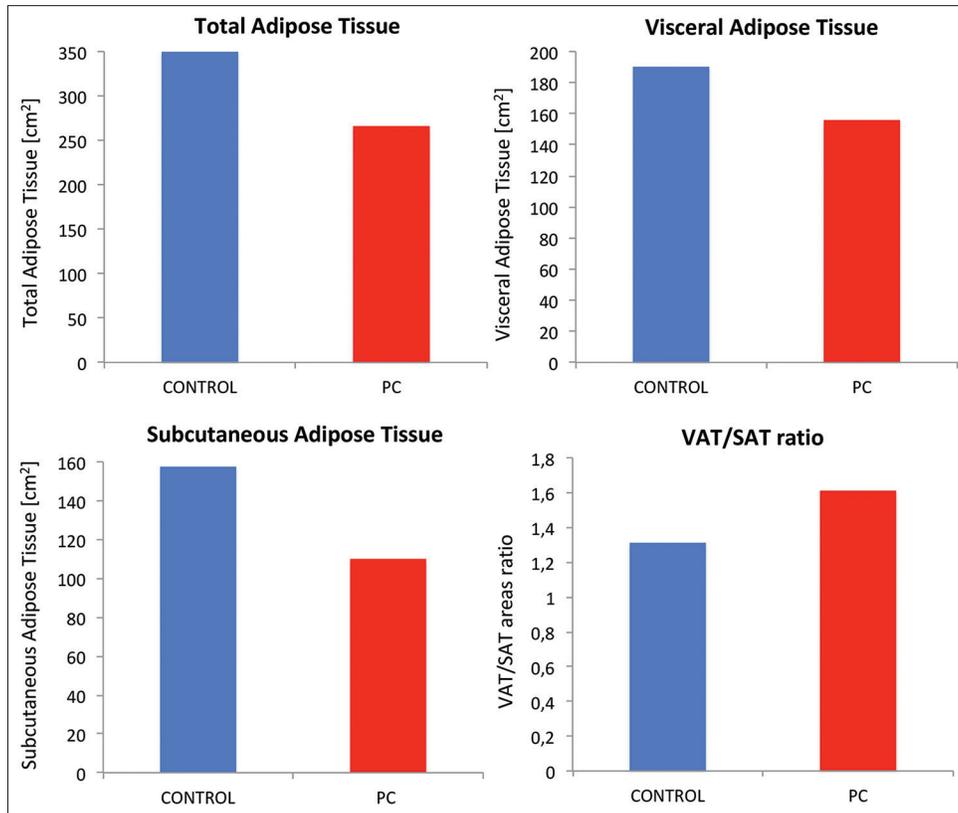
Figure 2: Mean value of total adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue areas and visceral adipose tissue/subcutaneous adipose tissue ratio in control and pancreatic cancer groups

important predictor of the development of PC-induced diabetes.[27]

Studies show that fat loss occurs more quickly and earlier than muscle mass loss.[28,29] It has been shown that, during the development of the disease, the adipose tissue, in particular the subcutaneous, is a possible relative systemic reservoir of inflammatory molecules.[30]

Adipose tissue atrophy is characterized by the reduction in size of the adipocytes, associated with a significant increase in fibrosis of tissue matrix.[31]

Fibrosis and inflammatory cell infiltration induced by cachexia have been shown in SAT of gastrointestinal cancer patients; macrophages and lymphocytes were present in the fibrotic areas of SAT.[32]

Surgical removal of subcutaneous fat by liposuction did not affect insulin resistance, whereas surgical removal of visceral fat led to improvements or to equivocal result.[33-35]

In our study, we did not find a significant difference of mean VAT values between the PC group and the control group.

The progressive worsening of glycemia and insulin resistance is probably controlled by the VAT which remains substantially conserved, while the reduction of SAT could explain weight loss.[10]

It has been shown that the exosomes released by PC induce lipolysis at the SAT level, determining the paraneoplastic effect. The lipolytic effect is induced by AM, contained in exosomes secreted by the PC. The plasma levels of PC exosomes containing AM were higher than those of the non-PC controls, even though a certain degree of variability was found between the participants. In addition, PC patients had a total number of exosomes much higher than non-PC controls. Furthermore, the lipolytic effect promoted by the exosomal AM was interrupted with AM inhibitor treatment.[9]

The results of our study show significant differences in the mean SAT area between PC patients and controls. SAT area could be considered a promising quantitative imaging biomarker of PC occurrence [Figure 3].

The limitations of our study are as follows: retrospective analysis, lack of clinical information such as body mass index and hormonal status, the low number of patients, and different cancer staging.

Future studies should be performed in female patients to see if similar changes in adipose tissue can be found.

In addition, further studies with a greater number of patients should be performed to see the modifications of SAT area in the different PC stages.
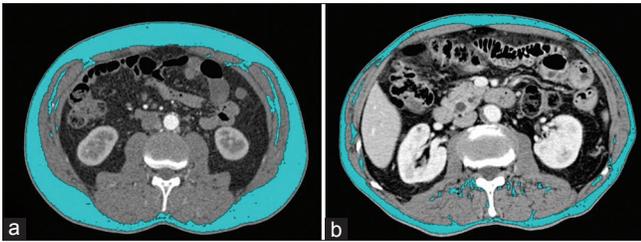
Figure 3: Axial computed tomography images show the regions of interest of the subcutaneous adipose tissue area in control (a) and pancreatic cancer (b) groups

Conclusions

The results of this study suggest an association between SAT reduction and PC risk.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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