Original Article

Increased Visceral Adipose Tissue in Male Patients with Clear Cell Renal Cell Carcinoma

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Abstract

Background: Excessive accumulation of adipose tissue, mainly visceral, can determine adipocyte- and adipose tissue-related disorder. Visceral adipocytes secrete mediators associated with carcinogenesis. Several studies have shown a correlation between blood levels of these mediators and clear cell renal cell carcinoma (ccRCC). Indeed, specific biomarkers, including adipokines, have been considered as a possible link between obesity and RCC. **Objective:** The objective of the study is to test the hypothesis that there is an increase of visceral adipose tissue (VAT) in male patients with ccRCC. **Methods:** In this retrospective study, two groups were included: A group of patients with ccRCC and a control group without a history of malignancies. Total adipose tissue (TAT) area, VAT area, and subcutaneous adipose tissue (SAT) area were measured in both groups. VAT/SAT ratio was subsequently calculated. **Results:** Statistically significant differences between the two groups were found in VAT area ($P = 0.01$) and VAT/SAT ratio ($P < 0.05$), while no significant difference was found in TAT area and SAT area. **Conclusions:** This study shows an increased VAT in male patients with ccRCC.

Keywords: *Adiposopathy, clear cell renal cell carcinoma, computed tomography, visceral adipose tissue*

Introduction

Renal cell carcinoma (RCC) is the seventh most common cancer in men and the tenth most common cancer in women, accounting for 2%–3% of adult malignancies.[1,2] This disease typically occurs in patients with an average age of about 60 years.[3] The main subtypes of RCC are clear cell renal cell carcinoma (ccRCC), which represents 65%–70% of RCC, papillary renal cell carcinoma (pRCC) and chromophobe renal cell carcinoma (chRCC), which constitute, respectively, 15%–20% and 5%–7% of RCC.[4]

Known risk factors for RCC are body mass index (BMI), hypertension, and smoking.[5] Increased BMI is associated with an increased risk of developing RCC in both men and women.[6] BMI, however, does not distinguish between excess of adipose tissue, muscle tissue, or bone tissue, and therefore, it does not provide any specific information about the distribution of adipose tissue among individuals, not allowing to quantify anthropometric differences between two compartments of adipose tissue: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).[7] The recognized functions of adipose tissue have been classically considered to be energy storage, thermal regulation, and mechanical protection. Moreover, it is now recognized as an endocrine/metabolic organ.[8] The importance of quantitative evaluation of the two different compartments relates to the fact that VAT differs from SAT in terms of anatomic, cellular, and molecular compositions. The former showing greater hormonal and metabolic activities as compared to the latter.[9,10] The growth factors, pro-inflammatory cytokines, and adipokines secreted from visceral adipocytes are mediating factors associated with the carcinogenesis of process of some obesity-related tumors.[11]

Imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) are essential tools for *in vivo*

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noninvasive assessment of body tissue compartments, including VAT and SAT.[12]

The aim of this study was to test the hypothesis that there is an increase VAT in male patients with ccRCC, using a quantitative CT imaging-based approach.

Methods

Patients

In this retrospective study, we included two groups: the ccRCC group and the control group. All of the participants enrolled underwent a CT examination in our institution between April 2009 and January 2017.

In the ccRCC group, a total of 10 Caucasian male patients with ccRCC at first diagnosis were included (mean age: 62.9 years, range 44–72).

All the patients received a histologically confirmed diagnosis of ccRCC, without previous history of other malignancies.

CT images were acquired before any medical or surgical treatment.

As the abdominal CT is usually not performed in healthy subjects, as a control group, we included 35 Caucasian male patients who have undergone a chest-abdomen CT for preoperative cardiovascular surgery planning (mean age: 61.1 years, range: 40–82).

Patients included in the control group underwent the following cardiac surgery: 18 mitral valve replacement, eight aortic valve replacement, one mitral and tricuspid valve replacement, two left atrial myxoma resection, three combined coronary artery bypass and mitral valve replacement, one combined coronary artery bypass and aortic valve replacement, one combined coronary artery bypass with mitral and tricuspid valve replacement, and one aortic valve and ascending aorta replacement. None of the patients included in the control group had a history of malignancies.

Computed tomographic analysis

CT images were acquired using the clinical scanner Somatom, Sensation 64, Siemens, Forchheim, Germany. To calculate TAT area, VAT area, and SAT area, Osirix MD v. 2.6 was used to analyze cross-sectional CT images. All measurements were obtained as areas (cm^2), on the axial plane 3 cm above the lower margin of L3 [Figure 1].[13] First, region of interest (ROI) of TAT area was segmented and calculated for each subject using a function of Osirix MD v. 2.6. Then, ROI of SAT area was generated and calculated by removing ROI of VAT area from those of TAT area. Finally, values of VAT area were calculated for each patient by subtracting values of SAT area from those of TAT area [Figure 1].

Statistical analysis

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

Results

Statistically significant differences between the two groups were obtained for VAT area ($P = 0.01$) and VAT/SAT ratio ($P < 0.05$).

No distinctively significant difference was obtained for TAT area and SAT area [Figure 2]. The results are summarized in Table 1.

Discussion

The results of our study show a significant increase of VAT in male patients with ccRCC, potentially suggesting a link between visceral adiposity and ccRCC.

The concept of "adiposopathy" originates from the evidence that an excessive accumulation of adipose tissue, mainly visceral, can determine adipocyte- and adipose tissue-related disorder. This concept indicates adipocytes and adipose tissue dysfunctions that promote metabolic syndrome.[14,15] Visceral adipocytes secrete growth factors, pro-inflammatory cytokines, and adipokines considered mediating factors associated with tumorigenesis.[11]

Increased BMI has been correlated with an increased risk of developing RCC.[6] Moreover, specific biomarkers have been considered as a possible link between obesity and the development of RCC; among these, there are adipokines which include adiponectin, leptin, resistin, and visfatin; these hormones are secreted mainly by adipose tissue and are associated with metabolic syndrome.[16,17] Previous studies have shown that adipokines may influence pro-neoplastic mechanisms, such as inflammation, cell growth, and proliferation and are predictors of risk and progression of different types of cancer.[15,18,19]

Spyridopoulos *et al*. showed that low levels of adiponectin are associated with RCC; in this study were included 70 RCC patients: 52 ccRCC, eight pRCC, six chRCC, one collecting duct carcinoma, and three unclassified.[20]

Zhang *et al*. have suggested that visfatin and resistin are high-risk factors for the development of ccRCC, whereas leptin and adiponectin have shown an inverse correlation with the risk of ccRCC.[21]

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	328.82	172.53	155.6	1.19
RCC group	416.25	258.04	158.21	1.71
P	0.076	0.015	0.9	0.04

TAT: Total adipose tissue, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, RCC: Renal cell carcinoma

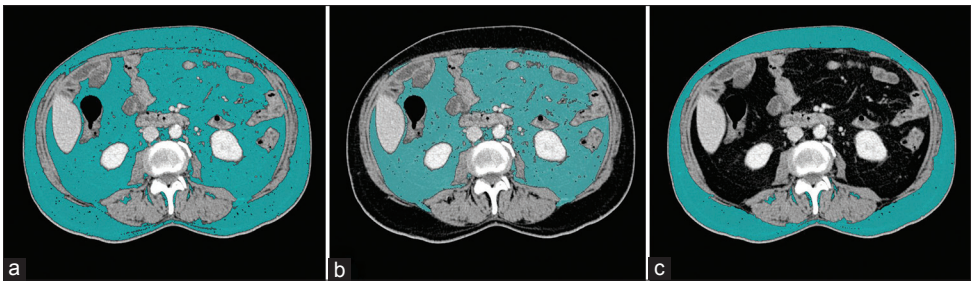

Figure 1: Axial computed tomographic images show the regions of interest of the total adipose tissue area (a), visceral adipose tissue area (b), and subcutaneous adipose tissue area (c)

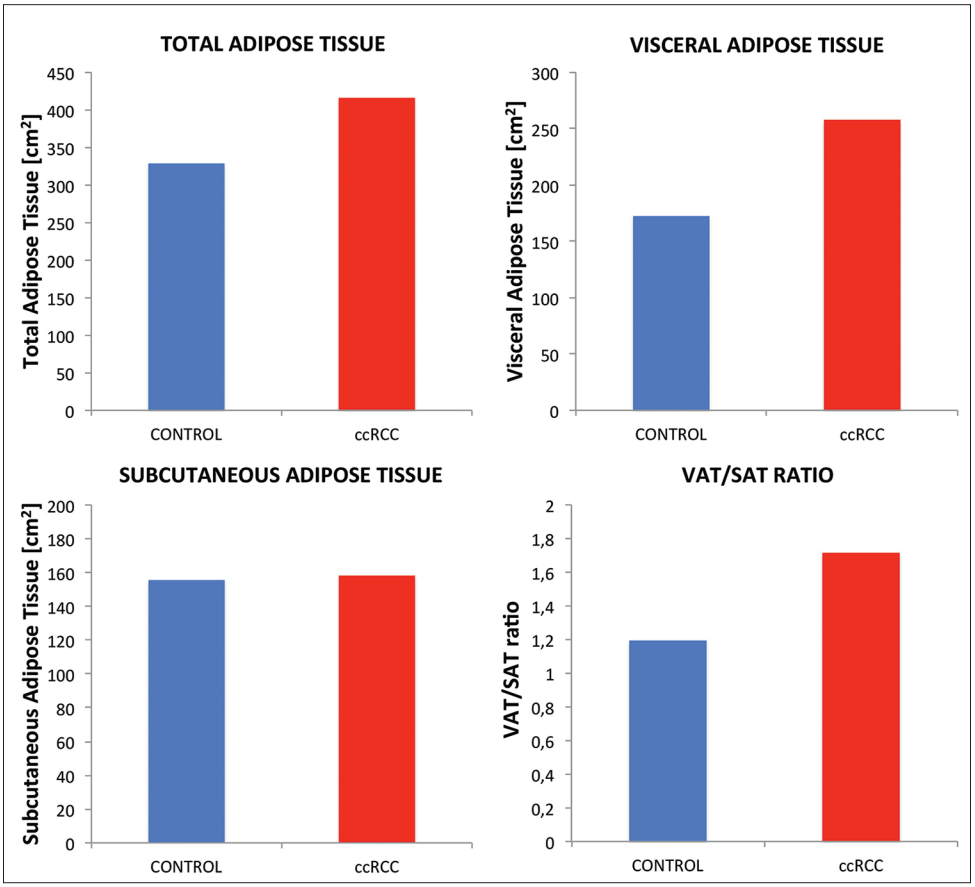

Figure 2: Mean value of total adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue areas and visceral adipose tissue/subcutaneous adipose tissue ratio in control and clear cell renal cell carcinoma groups

Wang *et al*. identified an association between lower plasma adiponectin concentrations and increased incidence of ccRCC, showing lower plasma levels of adiponectin and a greater VAT area in ccRCC patients compared to non-ccRCC patients. They also reported inverse linear correlation between VAT area and plasma adiponectin concentrations and high plasma leptin level in ccRCC obese patients and higher leptin and lower adiponectin in ccRCC patients with a VAT area ≥90 cm^2.[22]

Wang *et al*. found a significant difference in mean VAT area ($P = 0.001$) and TAT area ($P = 0.01$) between ccRCC and non-ccRCC patients, measured at the level of the umbilicus.[23]

Adiponectin is produced by adipocytes of VAT and its levels are reduced in obese subjects.[24,25] This adipokine is capable to stimulate insulin secretion and increase the fatty acids combustion and energy consumption.[26] It also acts by suppressing the growth of cancer cells and reducing the cancer risk.[19,27] In addition to RCC, an inverse association between adiponectin and breast and colon cancer levels was detected.[20-22,28]

Leptin is predominantly produced by adipocytes and it is elevated in obese individuals. Its principal functions are to set body weight, appetite, and energy homeostasis.[29-31] Leptin has an active role in carcinogenesis. it promotes cell proliferation and angiogenesis, inhibits cell apoptosis,

and has proinflammatory effects.[32-36] Lung cancer, breast cancer, and RCC patients show high levels of leptin, although some studies have shown an inverse correlation between serum leptin levels and the risk of RCC and others have not shown any significant association with RCC.[21,22,37-41]

Visfatin is associated with obesity and glucose regulation.[42] It controls mammalian cell growth and apoptosis.[43] Furthermore, visfatin determines novel blood vessel formation and migration.[44] Studies have reported a correlation of visfatin with different types of cancer, including breast, colorectal, and gastric cancer.[45-47]

Resistin is a product of macrophage infiltrate into adipose tissue and has been correlated with adiposity, inflammation and insulin resistance.[48,49] High levels of resistin are associated with cancer-associated chronic inflammation and plays a pivotal role in several malignancies such as breast and non-small cell lung cancer.[50,51]

The results of our study show significant differences in the mean VAT area and VAT/SAT ratio between ccRCC patients and control patients.

VAT area could be considered as a quantitative imaging parameter that might be linked to oncological risk of developing RCC. VAT area could be calculated in patients undergoing CT examination of the abdomen for other reasons or can be considered an additional feature in patients with undetermined/unclear renal lesions.

The retrospective nature of our study did not allow us to obtain further clinical information of the enrolled patients, such as BMI and hormonal status, to expand our analysis.

Further studies should be performed in larger series to confirm the association between VAT area and ccRCC risk and to explore it in female patients.

Conclusions

This study shows an increased VAT in male patients with ccRCC.

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Conflicts of interest

There are no conflicts of interest.

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