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Sex differences in pericardial adipose tissue assessed by PET/CT and association with cardiometabolic risk

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Abstract

Background: Recent studies suggest that pericardial adipose tissue (PAT) is associated with whole body adiposity and insulin resistance. Moreover, the incidence of cardiovascular disease (CVD) differs between men and women. Although CVD is more prevalent in men, women suffering from CVD have a higher mortality compared to men. Differences in PAT may account for some of the observed sex differences in manifestations of CVD.

Purpose: To assess pericardial adipose tissue (PAT) as a biomarker for cardiometabolic risk and to assess potential sex differences.

Material and Methods: We studied 303 subjects (151 women, 152 men, 57±17 yrs) across the weight spectrum. PAT and abdominal adipose tissue were quantified using clinical CTs obtained as part of a PET/CT. Cardiometabolic risk factors were assessed from medical records. Linear regression and ROC curve analyses were performed to evaluate associations between PAT and cardiometabolic risk.

Results: PAT was higher in overweight and obese compared to lean subjects and higher in men compared to women. PAT was positively associated with BMI, abdominal fat ($p<0.0001$), fasting glucose and serum lipids ($p<0.05$) with stronger associations in women than in men. PAT was accurate in detecting the prevalence of the metabolic syndrome with 74% sensitivity and 76% specificity (AUC=0.80).

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Declaration of Conflicting Interests

The authors have no conflict of interest to declare.

Conclusion: PAT is associated with measures of cardiometabolic risk and these associations are stronger in women compared to men. PAT could serve as a biomarker for opportunistic screening for cardiometabolic risk in patients undergoing chest CT.

Keywords

Pericardial adipose tissue; computed tomography; cardiometabolic risk; metabolic syndrome; opportunistic screening; obesity; biomarker

Introduction

Recent studies suggest that pericardial adipose tissue (PAT) is associated with whole body adiposity and insulin resistance. PAT is a unique fat depot as it surrounds the myocardium and coronary arteries and shares the coronary artery wall blood supply (1). In addition to storing lipids, PAT also secretes inflammatory cytokines (2, 3) which, given the proximity to the coronary arteries, may lead to acceleration of atherosclerosis (4, 5). Moreover, the incidence of cardiovascular disease (CVD) differs between men and women. Although CVD is more prevalent in men than women, women suffering from CVD have a higher mortality compared to men (6). Differences in PAT between men and women may account for some of the observed sex differences in manifestations of CVD.

PAT can be quantified using CT (7) and clinical chest CTs obtained for other purposes, such as for the evaluation of pulmonary nodules, emboli or during cancer surveillance could be used for opportunistic evaluation of PAT. The purpose of our study was to assess PAT using clinical CTs obtained for other purposes as a biomarker for cardiometabolic risk across the weight spectrum. We hypothesized that PAT increases with increasing BMI and that PAT correlates with markers of cardiometabolic risk. We furthermore aimed to assess sex differences in PAT and sex-specific association with cardiometabolic risk markers. We hypothesized that PAT is more strongly associated with cardiometabolic risk markers in women than in men.

Material and Methods

This study was approved by our Institutional Review Board and was Health Insurance Portability and Accountability Act (HIPAA) compliant, with exemption status for individual informed consent.

Subjects

We performed a retrospective search of subjects who had undergone whole-body ^{18}F -fluorodeoxy-glucose (FDG) positron emission tomography and computed tomography (PET/CT) examinations. We included adult subjects (≥ 18 years) across the weight spectrum (lean: BMI $<25 \text{ kg/m}^2$, overweight: BMI 25 to $<30 \text{ kg/m}^2$, obese: BMI $\geq 30 \text{ kg/m}^2$) who had undergone PET/CT for the work-up of benign etiologies or for surveillance of successfully treated malignancy and who had no history of active malignancy at the time of image acquisition. Exclusion criteria were active malignancy or FDG-avid lesions to suggest malignancy at time of PET/CT. Serum lipids, fasting glucose, blood pressure, the use of

medication to treat hypertension, type 2 diabetes mellitus (T2D) and hyperlipidemia were obtained from medical records. Fasting glucose was measured immediately prior to FDG-PET/CT. The time interval between PET/CT and measurement of blood pressure was 1.7 ± 2.3 months and measurement of serum lipids was 4.3 ± 3.5 months. Data on neck fat compartments, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and parameters to determine the metabolic syndrome were reported previously (8, 9), however, no data on PAT and its association with cardiometabolic risk factors have been reported.

Computed Tomography (CT)

Whole-body attenuation correction non-contrast CTs from a whole body PET/CT were used for this study. Briefly, all PET/CT studies were performed on an integrated scanner (Siemens Biograph 16 or 64, Siemens, Erlangen, Germany or GE Healthcare discovery, Milwaukee, Wisconsin, USA), with a 16- or 64-slice CT and a full-ring HI-REZ lutetium oxyorthosilicate PET. Examinations were performed after a 6-h fast, and blood glucose levels were measured prior to injection of radiotracer. Attenuation correction CT was obtained in the mid-expiration phase without intravenous contrast with the following parameters: slice thickness 5 mm, table feed per rotation 18 mm, time per table rotation 0.5 s, tube voltage 120 peak kilovoltage, tube current 11 mA and field of view 20 cm.

Quantification of adipose tissue

PAT cross sectional area (CSA) was measured on axial non-enhanced CT images at the level of the sagittal mid-point of the pericardial sac using semiautomated methods (Supplemental Figure). Predefined thresholds were set at -190 to -30 Hounsfield Units (HU) to identify adipose tissue (10).

Abdominal subcutaneous (SAT) and visceral adipose tissue (VAT) CSA and abdominal circumference were assessed at the mid-portion of the 4th lumbar vertebra. Analyses were performed using Osirix software version 3.2.1 (www.osirix-viewer.com/index.html). Automated thresholding methods were applied to identify adipose tissue CSA (cm^2) using a threshold set for -50 to -250 Hounsfield units (HU) as described by Borkan et al. (11).

Cardiometabolic risk factors

Data on the following cardiometabolic risk factors were collected from the patients' medical records: systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, fasting serum triglycerides, and total, LDL, HDL cholesterol. The presence of the metabolic syndrome was defined by the National Cholesterol Education Program criteria (NCEP Adult Treatment Panel III) if 3 or more parameters were present: abdominal circumference, >88 cm in women and >102 cm in men; fasting triglycerides, ≥ 150 mg/dL; fasting HDL cholesterol, <50 mg/dL in women and <40 mg/dL in men; blood pressure, $\geq 130/85$ mm Hg; and fasting glucose, ≥ 110 mg/dL (12). The use of medication to treat hypertension, T2D and hyperlipidemia were assessed from medical records.

Statistical analyses

JMP Statistical Discoveries (version 12; SAS Institute, Cary, NC) and MedCalc (version 9.2.1.0; Mariakerke, Belgium) were used for statistical analyses. Variables were tested for

normality of distribution by using the Shapiro-Wilk test. Variables that were not normally distributed were log transformed (BMI, glucose, serum lipids, PAT, VAT, SAT). Differences between men and women were assessed using an independent-samples t-test. The Tukey-Kramer test was used to adjust for multiple comparisons of PAT measurements across BMI groups. Linear regression analyses were performed between PAT, body composition, and cardiometabolic risk factors. Standard least squares regression modeling was performed to control for age, BMI, history of prior malignancy and medication use for hypertension, T2D, or hyperlipidemia. Receiver operating characteristic (ROC) curve analysis of PAT was performed to detect the metabolic syndrome. Sensitivity, specificity, area under the ROC curve, and confidence intervals (CI), as well as cutoff values for PAT to detect the metabolic syndrome were determined. $p < 0.05$ was used to denote significance. Data are presented as mean $\pm$ SD unless indicated otherwise.

Results

Subjects

Clinical characteristics of study subjects are shown in Table 1. We identified 303 subjects, 151 women and 152 men, with a mean age of 55 ± 17 years (range 18 – 91 years). Subjects were equally distributed across the weight spectrum with 101 subjects in the normal-weight group, 101 subjects in the overweight and 101 subjects in the obese group. Ninety-three subjects were taking medication to treat hypertension, 27 subjects were taking medication to treat T2D and 61 patients were taking medication to treat hyperlipidemia. The metabolic syndrome was present on 103 subjects (53 men and 50 women). There was no significant difference in age between men and women. Men had a higher mean BMI but the difference did not reach statistical significance (Table 1).

PET/CT was performed for benign etiologies in 94 subjects (work-up of lung nodules, $n=19$; unexplained adenopathy/ to rule out neoplasm, $n=66$; Ollier's disease, $n=1$; multiple sclerosis, $n=1$; neurofibromatosis type 1, $n=1$; vasculitis $n=1$; infection, $n=3$; encephalitis, $n=1$; cardiomyopathy, $n=1$) and for surveillance of successfully treated malignancy in 209 subjects. None of the subjects with a history of malignancy had FDG-avid lesions on PET/CT to suggest malignancy. Serum cardiometabolic risk markers and body composition are shown in Table 1. Men had higher fasting glucose and women had higher serum cholesterol. Men had more VAT while women had more SAT (Table 1).

Pericardial Adipose Tissue

Pericardial adipose tissue (PAT) was successfully quantified in all subjects. Men had significantly more PAT compared to women (Table 1). In men and women combined and within the male group, there was a significant increase in PAT across the weight spectrum between the lean, overweight, and obese subgroups, while there was no significant difference in PAT between overweight and obese women (Fig. 1). There was no significant sex difference in PAT between normal weight and overweight men and women ($p=0.5$ and $p=0.4$, respectively), while obese men had significantly more PAT compared to obese women ($p=0.02$).

Association between pericardial adipose tissue and cardiometabolic risk

Associations between PAT and body composition and cardiometabolic risk factors are shown in Table 2. In men and women combined, PAT was positively associated with BMI, markers of cardiometabolic risk, including diastolic blood pressure, serum lipids, and fasting glucose as well as VAT, SAT, and abdominal circumference, independent of age, history of prior malignancy and use of cardiometabolic associated medication. The associations between PAT and glucose, serum lipids, abdominal circumference, and abdominal fat remained significant after also controlling for BMI. When examining women and men separately, the associations between PAT and glucose, HDL cholesterol and triglycerides were significant in women but not in men (Table 2).

ROC curve analysis was performed to determine the accuracy of PAT to detect the metabolic syndrome. PAT was accurate in detecting the metabolic syndrome in men and women, and the accuracy was higher in women compared to men (Table 3 and Fig. 2).

Discussion

Our study shows that PAT, assessed by a simple single-slice method using clinical CTs performed for other purposes, was positively associated with markers of cardiometabolic risk and accurately detected the presence of the metabolic syndrome. Moreover, PAT was higher in men than in women but was more strongly associated with cardiometabolic risk measures and the metabolic syndrome in women compared to men.

Prior studies have suggested that PAT may represent a risk factor for cardiometabolic disease (13–17). In our study, PAT was associated with higher fasting glucose, serum triglycerides, and lower HDL cholesterol, and abdominal fat compartments, independent of age, BMI, history of prior malignancy, and use of medication to treat hypertension, T2D or hyperlipidemia. We also observed inverse associations between PAT and diastolic blood pressure in women and LDL cholesterol in men, however, these associations only became significant after controlling for medication use and lost significance after controlling for BMI, suggesting that the use of medication in subjects with obesity might be able to ameliorate some of the damaging effects of PAT.

A potential mechanism for the unique role of PAT in cardiometabolic risk may be its proximity to the coronary arteries and myocardial wall and the secretion of inflammatory cytokines which may lead to accelerated atherosclerosis (1–5). A study from the Framingham Heart Cohort examined the relationship between PAT and atrial conduction as measured by P wave indices. In multivariable models that adjusted for BMI and thoracic fat, PAT was associated with P wave indices, consistent with impaired atrial conduction (1). In a study from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, PAT was positively associated with parameters of arterial stiffness, independent of BMI, waist circumference and other risk factors and the effect size was larger in women than in men (13).

We found that although obese men had more PAT compared to obese women of similar age and BMI, PAT was associated with a more adverse cardiometabolic risk profile in women than in men. This is consistent with a study by Rosito et al (15) which showed a positive

association between PAT with cardiometabolic risk markers that were stronger in women compared to men. Indeed, there are known sex differences in CVD. Heart disease is more prevalent in men than women (6). However, women have a worse outcome and a higher mortality from CVD compared to men (18, 19). There are known sex differences in fat distribution with men having more VAT and women more SAT and these differences are partly determined by sex hormones (20). Estrogen promotes the accumulation of SAT and low estrogen contributes to VAT accumulation, as can be seen in postmenopausal women (21). A recent study has demonstrated increased epicardial adipose tissue in postmenopausal women and a significant association with left ventricular dysfunction in older women but not in men (22). The SWAN Cardiovascular fat Ancillary Study also demonstrated increased cardiac fat after menopause which was correlated with a decrease in estradiol levels, but not with androgen levels (23), indicating low estrogen levels as a mechanism of fat accumulation around the heart and associated CVD. Furthermore, a study in mice has demonstrated alterations of obesity-related genes in epicardial adipose tissue in aging females compared to males, suggesting that genetics might play a role in the sexual dimorphism of PAT and its pathophysiological role in CVD (24).

A unique feature of our study was the use of clinical chest CTs and quantification of PAT on single-slice with commercially available software, while the aforementioned studies used dedicated cardiac CTs or CT angiography and volumetric assessment requiring specialized software. In our study, PAT was quantified without difficulty in all cases using attenuation correction CTs obtained as part of a PET/CT. There has been increasing interest in using CTs obtained for other purposes for opportunistic screening, especially for osteoporosis (25–29). Our ROC curve analyses provided threshold values that were specific and sensitive for detecting the metabolic syndrome in men and women. Therefore, PAT could be used as a biomarker for cardiometabolic risk in patients undergoing chest CT for other purposes, such as the follow-up of pulmonary nodules or surveillance of malignancy.

Our study had the following limitations. First, the cross-sectional design limits our ability to determine causality. Second, in this retrospective study, we relied on medical records for clinical information. Third, the heterogeneous study population with the majority of subjects having a history of prior malignancy limits generalization of our results. Furthermore, prior malignancy and therapy can have effects on CVD. Fourth, we did not follow-up subjects to assess whether PAT can predict the development of CVD or T2D. Strengths of our study include the large number of men and women across the weight spectrum and detailed assessment of PAT and abdominal fat depots as well as cardiometabolic risk markers using clinical CTs obtained for other purposes.

In conclusion, PAT assessed by single-slice chest CT, is a marker of cardiometabolic risk and is accurate in detecting the presence of the metabolic syndrome. Moreover, although PAT was higher in obese men than in obese women, it was more strongly associated with measures of cardiometabolic risk and the metabolic syndrome in women compared to men. Our study suggests that PAT assessed on a single-slice chest CT could be used as a biomarker for opportunistic screening for cardiometabolic risk in patients undergoing chest CT for other purposes, such as the follow-up of pulmonary nodules or surveillance of malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1: Sex differences in pericardial adipose tissue across the weight spectrum.

Data are presented as mean±SEM. There was a significant increase in PAT across the weight spectrum between the lean, overweight, and obese subgroups, while the difference in PAT between overweight and obese women was not significant.

Figure 2: Receiver operator characteristic (ROC) curve of pericardial adipose tissue to detect the metabolic syndrome in women and men.

The area under the curve (AUC) was 0.85 with a cutoff value of $>16.8 \text{ cm}^2$ in women (**A**) and 0.77 with a cutoff value of $>18.2 \text{ cm}^2$ in men (**B**) ($p < 0.0001$ for both analyses).

Table 1

Clinical characteristics of study subjects. Data are presented as mean $\pm$ SD.

Variable	Women (n=151)	Men (n=152)	<i>p-value</i>
Age (years)	56 $\pm$ 17	54 $\pm$ 17	0.3
BMI (kg/m ²)	27 $\pm$ 6	28 $\pm$ 5	0.05
Systolic blood pressure (mm Hg)	126 $\pm$ 18	126 $\pm$ 15	0.9
Diastolic blood pressure (mm Hg)	75 $\pm$ 9	76 $\pm$ 10	0.4
Glucose (mg/dL)	109 $\pm$ 21	115 $\pm$ 28	0.04
Total cholesterol (mg/dL)	204 $\pm$ 61	175 $\pm$ 43	0.003
LDL cholesterol (mg/dL)	112 $\pm$ 50	95 $\pm$ 35	0.03
HDL cholesterol (mg/dL)	61 $\pm$ 21	42 $\pm$ 16	<0.0001
Triglycerides (mg/dL)	141 $\pm$ 105	176 $\pm$ 128	0.09
Abdominal circumference (cm)	94 $\pm$ 15	97 $\pm$ 13	0.03
Visceral adipose tissue (cm ²)	106 $\pm$ 70	138 $\pm$ 78	0.0002
Subcutaneous adipose tissue (cm ²)	268 $\pm$ 138	233 $\pm$ 117	0.02
Pericardial adipose tissue (cm ²)	15 $\pm$ 9	19 $\pm$ 10	0.0005

Table 2.

Associations between pericardial adipose tissue and cardiometabolic risk factors.

Variable	Pericardial Adipose Tissue		
	Combined	Women	Men
BMI	0.76 *	0.73 *	0.78 *
Diastolic blood pressure	NS	-0.57 [#]	NS
Glucose	0.56 ^{#†}	0.59 ^{#†}	NS
LDL cholesterol	-0.54 ^{#†}	NS	-0.56 ^{#†}
HDL cholesterol	-0.57 ^{*†}	-0.69 ^{*†}	NS
Triglycerides	0.58 *	0.62 ^{*†}	NS
Abdominal circumference	0.78 ^{*†}	0.74 ^{*†}	0.80 ^{*†}
Visceral adipose tissue	0.84 ^{*†}	0.83 ^{*†}	0.85 ^{*†}
Subcutaneous adipose tissue	0.67 ^{*†}	0.70 *	0.73 *

Analyses were controlled for age, history of prior malignancy, and use of medication.

Presented are r values.

* p<0.001,

[#] p<0.05, NS: non-significant,

[†] p<0.05 after controlling for BMI

Systolic blood pressure and total cholesterol were not significant in any category

Table 3:

Receiver operator characteristic (ROC) curve analysis of pericardial adipose tissue in detecting the metabolic syndrome.

Parameter	Threshold	Sensitivity	Specificity	ROC AUC	95% CI	p-value
PAT combined (cm ²)	>15.3	73.5%	75.7%	0.80	0.74 to 0.86	<0.0001
PAT women (cm ²)	>16.8	67.4%	88.9	0.85	0.76 to 0.91	<0.0001
PAT men (cm ²)	>18.2	66.0%	77.6%	0.77	0.67 to 0.84	<0.0001

PAT: pericardial adipose tissue; AUC: area under the curve, CI: confidence interval