Original Investigations

Chest CT Measures of Muscle and Adipose Tissue in COPD:

Gender-Based Differences in Content and in Relationships with Blood Biomarkers

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Rationale and Objectives: Computed tomography (CT) of the chest can be used to assess pectoralis muscle area (PMA) and subcutaneous adipose tissue (SAT) area. Adipose tissue content is associated with inflammatory mediators in chronic obstructive pulmonary disease (COPD) subjects. Based on gender differences in body composition, we aimed to assess the hypothesis that in subjects with COPD, the relationships between PMA, SAT, and blood biomarkers of inflammation differ by gender.

Materials and Methods: We compared chest CT measures of PMA and SAT on a single slice at aortic arch and supraesternal notch levels from 73 subjects (28 women) with COPD between genders. The relationships of PMA and SAT area to biomarkers were assessed using within-gender regression models.

Results: Women had a lesser PMA and a greater SAT area than men (difference range for PMA, 13.3–22.8 cm^2; for SAT, 11.8–12.4 cm^2; $P < .05$ for all comparisons) at both anatomic levels. These differences in PMA and SAT remained significant after adjustment for age and body mass index. Within-gender regression models adjusted for age showed that SAT was directly associated with C-reactive protein (for aortic arch level, $P = .04$) and fibrinogen (for both anatomic locations, $P = .003$) only in women, whereas PMA was not associated with any biomarkers in either gender.

Conclusions: It appears that in subjects with COPD, there are gender-based differences in the relationships between subcutaneous adipose tissue and inflammatory biomarkers.

Key Words: CT; pectoralis muscle; adipose subcutaneous tissue; biomarkers; CRP; IL-6; fibrinogen; COPD.

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Chronic obstructive pulmonary disease (COPD) affects approximately 28.9 million people in the United States [1]. It is increasingly recognized that altered body composition is common in COPD and represents a clinically relevant process in patients suffering from this condition [2–4]. For example, a low body mass index (BMI) is associated with increasing mortality [4]. Furthermore, dissecting the components of body composition in COPD subjects gives additional understanding of extrapulmonary features of the disease. Prior investigation has demonstrated that the prevalence of low fat free mass (FFM) was higher than that of low BMI [5]. Together these findings suggest that characterizing distinct body components beyond BMI is of clinical importance.

There are several methods available for the determination of body composition including skinfold thickness, bioimpedance, and dual-energy x ray absorbance (DXA) [6]. However, measures of skinfold thickness have been found to underestimate FFM [6], and both bioimpedance and DXA

are not widely available. Prior investigations (7,8) have suggested that computed tomographic (CT) measures may provide additional insight into the body composition of smokers. Marquis et al. found that mid thigh muscular cross-sectional area was a stronger predictor of mortality in COPD than BMI (7). We also observed that mid thigh muscle loss is even present in smokers with mild COPD (9). We have demonstrated that CT measures of pectoralis muscle area (PMA) on a single-axial slice may be a more clinically relevant measure of COPD-related outcomes than BMI in the prediction of spirometric measures of lung function, symptoms, and exercise capacity. (10)

Subcutaneous adipose tissue (SAT) can also be assessed on axial CT images of the chest and can provide additional understanding of body composition in COPD. Chest CT measures of muscle area and fat area, however, may vary according to the anatomic location of the measurement and to gender differences in body composition, such as the presence of breast tissue in women in the anterior chest wall. Additionally, adipose tissue depots might be a source of inflammatory mediators and contribute to low-grade inflammatory state in COPD (11). Gender differences in adipose tissue metabolism and inflammatory biomarker levels have been documented (12,13). For example, smoking women have lower level of C-reactive protein (CRP) (13). Thus, exploring gender differences in the relationships between distinct body composition components and inflammatory mediators can further help in the understanding of extrapulmonary manifestations of COPD. In this study, we aimed to 1) assess the reproducibility of CT measurements of SAT area and PMA; 2) examine the association between these body composition metrics and blood inflammatory mediators; and 3) compare PMA and SAT and their association with inflammatory mediators in men versus women. We hypothesize that in COPD subjects, CT measures of PMA and SAT area are correlated with inflammatory mediators and that these correlations differ between genders. To test this hypothesis, we measured PMA and SAT area on CT scans of subjects from "The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) Study" (14) at two specific anatomic levels of the chest and correlated these findings with inflammatory mediators measured from peripheral blood.

MATERIALS AND METHODS

Population

The ECLIPSE Study is a noninterventional, multicenter, longitudinal study designed to identify factors that predict COPD progression as well as disease subtypes and biomarkers that may be useful as surrogate end points. ECLIPSE enrolled smokers (≥10 pack years) aged 40–75 years with chronic obstructive lung disease (GOLD) stage II–IV COPD ($n = 2162$) (14). All subjects provided informed
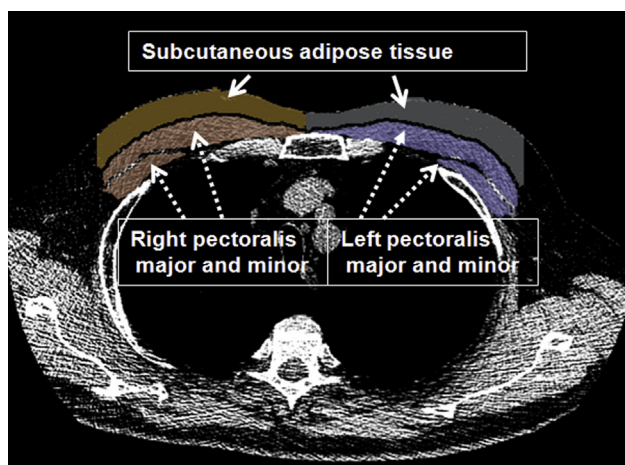
Figure 1. Axial slice at aortic arch level showing muscles and fat segmentation. The segmented pectoralis muscle major and minor (*dotted arrows*) and the subcutaneous adipose tissue (*solid arrows*) are shown. The pectoralis muscle area and subcutaneous adipose tissue area are computed as aggregate measures and reported in square centimeters.

consent to participate in the study. For this study, we used a convenience sample of 73 ECLIPSE subjects with COPD (28 women) who had FFM data collected. Body composition was assessed using bioelectrical impedance analysis as detailed elsewhere (3). Briefly, FFM was computed using sex-specific equations (15), and fat mass was calculated by subtracting FFM from weight. To take into account differences in body surface, fat mass index (FMI) was computed by dividing fat mass by squared height and expressed as kg/m^2.

Imaging Assessment

All subjects underwent a low-dose volumetric CT scan of the chest at baseline and at years 1 and 3 of follow-up with the following protocol: 120-kV peak, 40 mA, and 1.00- or 1.25-mm slice thickness at full inspiration. In this study, we used the baseline CT data to perform body composition measures. The radiation was estimated at 5 mSv for each subject for the entire ECLIPSE protocol (14).

PMA and SAT Area Measurements

Measures of PMA and SAT area were performed using custom software by a pulmonologist who was blinded to subjects' data. PMA and SAT area were measured on a single-axial slice of the CT scans as follows: The reader visually identified the superior aspect of the aortic arch and then scrolled toward the apex of the lungs to identify the first axial image above the arch and the first image above the supraesternal notch of the sternum. These slices were selected because they were easy to identify and could be replicated across a large cohort of subjects. The left and right pectoralis major and minor muscles were then identified on

TABLE 1. Baseline Characteristics of the 73 Selected Subjects by Gender

Variable	Female (n = 28)	Male (n = 45)	P
Age, years	64.5 (59.0–67.0)	62.0 (59.0–67.0)	.97
Pack years of smoking	43.5 (29.5–53.0)	44.0 (30.0–68.0)	.66
BMI, kg/m^2	24.3 (22.3–26.4)	28.6 (23.9–32.6)	.0045
Fat free mass, kg	37.3 (34.1–41.8)	59.4 (54.4–67.4)	<.0001
Fat mass index, kg/m^2	15.2 (14.1–16.3)	10.6 (10.1–12.4)	<.0001
FEV$_1$ % predicted	45.6 (34–53.5)	43.5 (31.2–54.9)	.84
Biomarkers			
C-reactive protein, μg/mL	4.2 (1.3–4.8)	5.1 (1.4–6.6)	.75
Fibrinogen, mg/dL	458.5 (425.0–507.0)	449 (386.0–485.0)	.226
Interleukin-6, pg/mL	2.6 (0.5–2.3)	6.6 (0.9–3.2)	.065

BMI, body mass index; FEV$_1$, forced expiratory volume in 1 second.

Continuous variables are presented as median (interquartile range) except for biomarkers (mean [interquartile range]). Missing data, BMI 7; fat mass index 7; C-reactive protein 3; interleukin-6 7.

the anterior chest, and their edges manually segmented using a predefined attenuation range of between −50 and 90 Hounsfield Units. The SAT area was defined as the region of interest between the pectoralis major muscles and skin surface on those same axial slices and, their edges were manually determined using a range between −200 and 0 Hounsfield Units. We used this limited subcutaneous fat region because the entire circumference of the chest was not available in many CT scans (Fig 1). Both PMA and SAT area are reported as the aggregate area in square centimeters of the right and left pectoralis major and minor and the right and left fat areas, respectively, assessed in those axial planes. To evaluate the intra- and inter-reader reproducibility of PMA and SAT area at these two locations, a second reader measured a random sample of 20 CT scans two times.

Lung Function Assessment and Biomarkers Collection

At baseline and each subsequent visit, patients underwent spirometric evaluation (Viasys MasterScope) before and 15 minutes after inhaling 400 μg of the bronchodilator salbutamol. Forced expiratory volume in 1 second (FEV$_1$) from spirometry is reported as percent predicted values (16). The following biomarkers in blood were collected at baseline and stored at −80°C until they were analyzed: CRP, interleukin-6 (IL-6), and fibrinogen (16). Biomarkers are reported as mean (interquartile range) as in a prior ECLIPSE report (16).

Statistical Analysis

The intra- and inter-reader agreements of PMA and SAT area were assessed with the concordance correlation coefficient (CCC) (17) and a Bland–Altman analysis (18). We used these tests because they provide complementary information on assessing agreement of CT measures between readers. Differences in subjects' characteristics at baseline and PMA and SAT area between genders were assessed using a Wilcoxon rank sum test because some of the variables did

not follow normality. Pairwise correlations of PMA and SAT area to anthropometric measures and biomarkers by gender were performed using a Spearman correlation. Liner regression models for PMA, SAT, and biomarkers were also performed. These three dependent variables were log transformed to normalize them. The models were adjusted for age and BMI. A P < .05 was considered significant. All the analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

## RESULTS

Clinical and Biomarker Data

Clinical and biomarker data by gender are shown in Table 1. Women had significantly lower stature, BMI, and FFM than men. In contrast, women had higher FMI than men. Women also had marginally significant (P = .065) lower levels of IL-6. No differences in age, dyspnea score, FEV$_1$ % predicted, CRP, and fibrinogen were found.

Intra- and Inter-Reader Assessment of PMA and SAT Area

The intrareader CCC of both PMA and SAT area at aortic arch level was 1.00, and corresponding values at supraesternal notch level were 0.697 and 0.981. The interreader CCC of PMA and SAT at aortic arch level were 0.985 and 0.994, respectively, and 0.818 and 0.979 at supraesternal notch level, respectively (Fig 2a). The Bland–Altman plots did not show a systematic bias across the range of PMA and SAT area values between readers (Fig 2b). The correlation between measures of PMA at aortic arch and supraesternal notch levels was 0.81, and the corresponding value for SAT area was 0.95.

Comparison of PMA and SAT Area by Gender

Regardless of the anatomic level of measurement, women had lower PMA than men (mean of 13.3 cm^2 and 22.8 cm^2 lesser
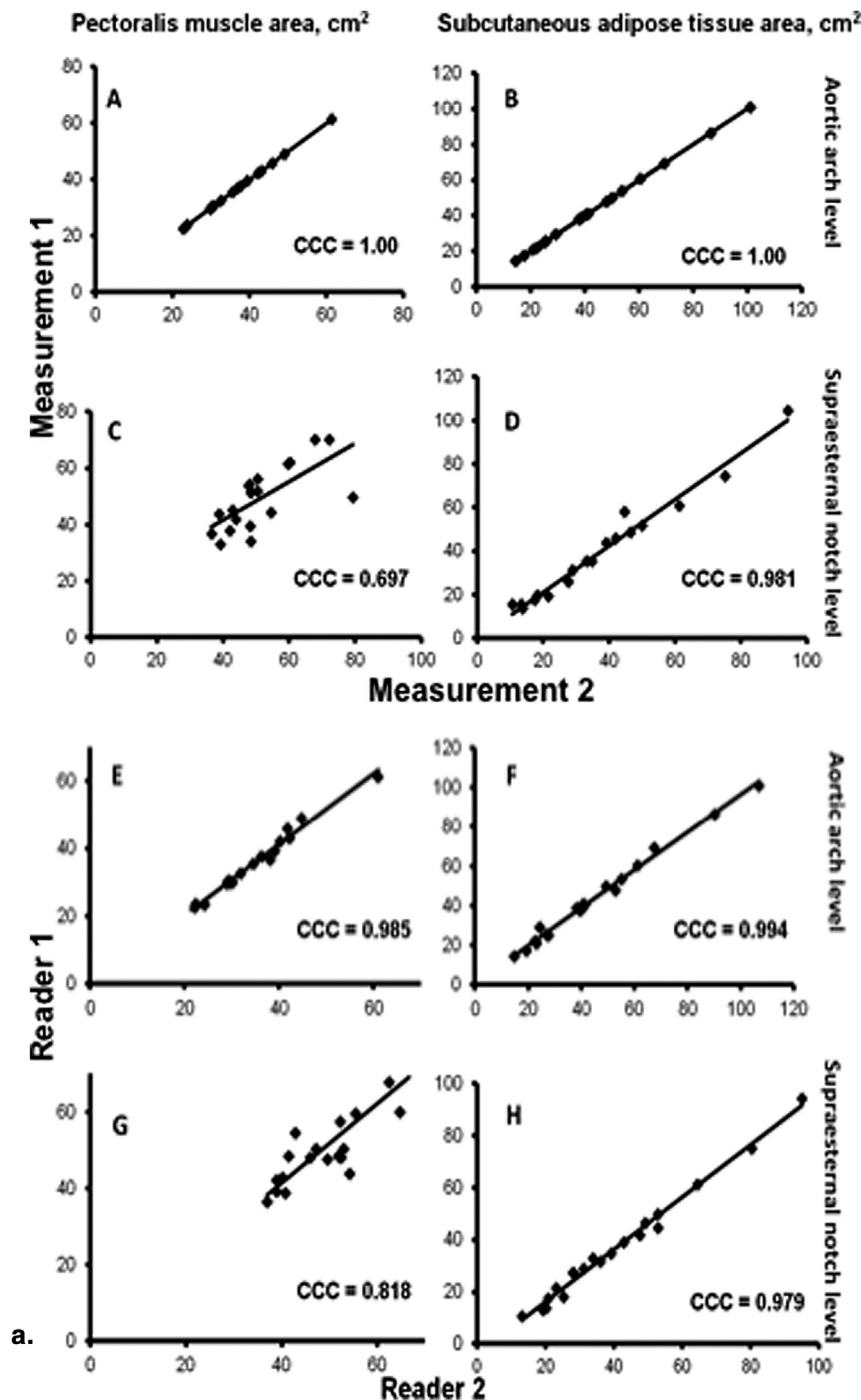
Figure 2. **(a)** Regression line plots and the concordance correlations coefficients (CCC) values of the reproducibility of pectoralis muscle area (PMA) and subcutaneous adipose tissue (SAT) area measurements between two readers. The intrareader reproducibility of PMA at aortic arch **(A)** and supraesternal notch levels **(C)** and that of SAT **(B, D)** are shown. Corresponding plots and CCC values for interreader reproducibility of PMA at aortic arch **(E)** and supraesternal notch levels **(G)** and that of SAT **(F, H)** are also shown. **(b)** Bland–Altman plots of the reproducibility of PMA and SAT area measurements. *Dotted lines* represent the 95% confidence intervals. Plots for intrareader reproducibility of PMA at aortic arch **(A)** and supraesternal notch levels **(C)** and that of SAT **(B, D)** are shown. Corresponding plots for interreader reproducibility of PMA at aortic arch **(E)** and supraesternal notch levels **(G)** and that of SAT **(F, H)** are also shown. (*continued*)

in women at aortic arch and supraesternal notch levels, respectively; for both $P < .0001$. An opposing significant difference in SAT area was observed in both locations (mean of 12.4 cm^2 and 11.8 cm^2 greater in women at aortic arch and supraesternal notch levels, respectively; Table 2). In regression models adjusted for age and BMI, the differences in PMA and SAT area between genders persisted (for all comparisons, $P < .0001$).
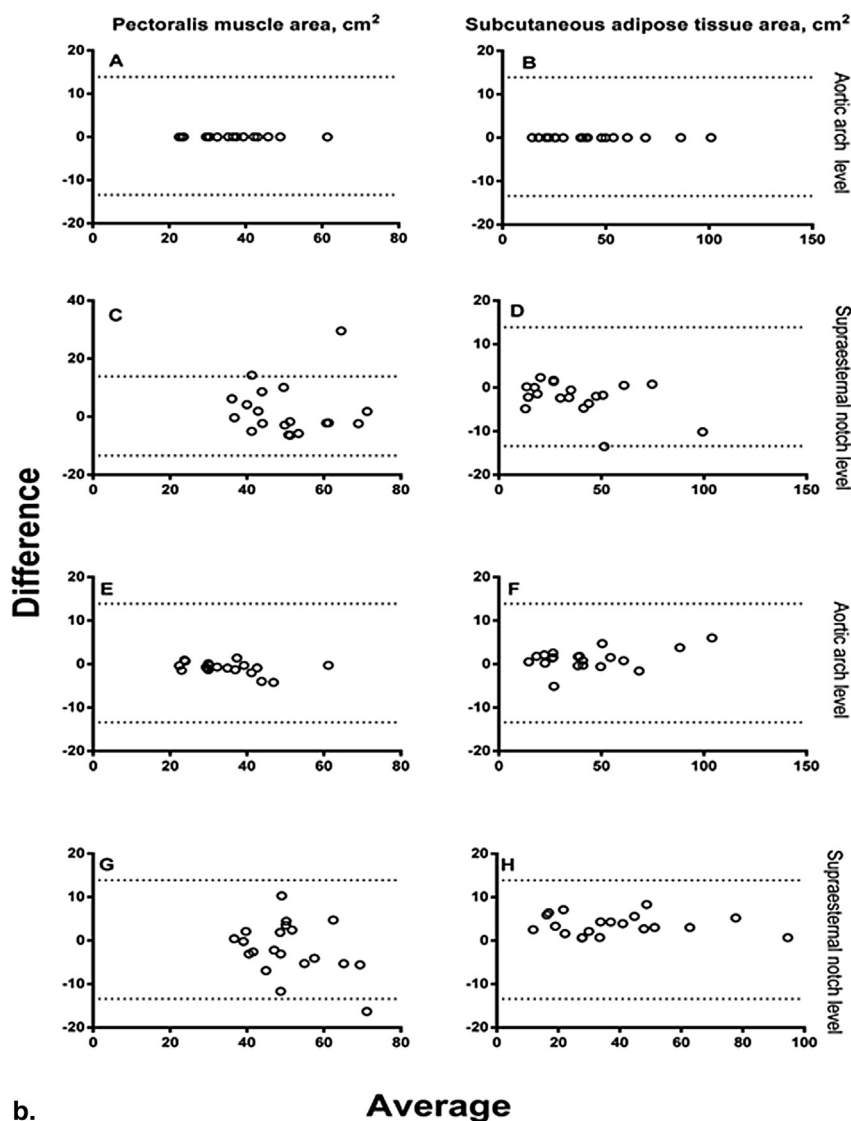
b.

Figure 2. (*continued*).

TABLE 2. Pectoralis Muscle Area (PMA) and Subcutaneous Adipose Tissue (SAT) Area in COPD Subjects by Gender

CT Measurement	Female, Median (interquartile range)	Male, Median (interquartile range)	P
PMA at aortic arch, cm²	24.2 (19.5–27.2)	37.0 (31.1–40.7)	<.0001
PMA at supraesternal notch, cm²	39.8 (33.7–42.9)	63.0 (52.3–70.8)	<.0001
SAT area at aortic arch, cm²	49.0 (35.2–68.7)	38.3 (24.9–49.9)	.03
SAT area at supraesternal notch, cm²	47.1 (28.2–64.3)	32.3 (23.0–51.3)	.04

CT, computed tomography.
Missing PMA and SAT area data at supraesternal notch level for one subject due to image truncation.

Relationships Between PMA, SAT Area, Anthropometric Variables, and Biomarkers

There was a significant correlation between both PMA and SAT area measured at both levels with BMI. These relationships were weaker in women. Similarly, the PMA and SAT area at both levels correlated positively with FFM in both genders

with the correlations coefficients being lower in women. SAT area but not PMA correlated directly with FMI, CRP, and fibrinogen only in women at both anatomic levels (Tables 3 and 4). The associations between SAT area and fibrinogen remained significant in within-gender adjusted models for age (for both anatomic levels, $P = .003$), whereas the association between SAT area and CRP was significant at aortic arch level only

TABLE 3. Spearman Correlation Coefficients (*r*) Between Pectoralis Muscle Area (PMA) and Subcutaneous Adipose Tissue (SAT) Area and Anthropometric and Biomarker Data in Women

	PMA		SAT Area	
Variable	Aortic Arch Level	Supraesternal Notch Level	Aortic Arch Level	Supraesternal Notch Level
Age	−0.33	−0.21	−0.07	−0.01
Body mass index, kg/m^2	0.44*	0.60**	0.62**	0.61**
Fat free mass, kg	0.41*	0.60**	0.40*	0.43*
Fat mass index, kg/m^2	0.25	0.30	0.59**	0.49*
Biomarkers				
C-reactive protein, μg/mL	0.20	0.12	0.40*	0.36*
Fibrinogen, mg/dL	0.03	0.29	0.54**	0.51**
Interleukin-6, pg/mL	0.25	0.18	0.28	0.32

*$P < .05$; **$P < .01$; $P > .05$ when the correlation coefficient has no asterisk.

TABLE 4. Spearman Correlation Coefficients (*r*) Between Pectoralis Muscle Area (PMA) and Subcutaneous Adipose Tissue (SAT) Area and Anthropometric and Biomarker Data in Men

	PMA		SAT Area	
Variable	Aortic arch level	Supraesternal notch level	Aortic arch level	Supraesternal notch level
Age	−0.12	−0.22	−0.15	−0.17
Body mass index, kg/m^2	0.58***	0.69***	0.89***	0.87***
Fat free mass, kg	0.44**	0.64***	0.77***	0.75***
Fat mass index, kg/m^2	0.04	−0.08	−0.04	−0.02
Biomarkers				
C-reactive protein, μg/mL	0.003	0.05	0.14	0.10
Fibrinogen, mg/dL	−0.07	−0.09	0.12	0.17
Interleukin-6, pg/mL	−0.2	−0.15	−0.21	−0.20

**$P < .01$; ***$P < .0001$; $P > .05$ when the correlation coefficient has no asterisk.

($P = .04$) and near significance at supraesternal notch level ($P = .11$). In contrast, BMI and FFM were not significantly associated with any above biomarkers within either gender ($P > .05$ for CRP, fibrinogen, and IL-6). FMI was correlated with CRP only in women ($r = 0.51$; $P = .009$).

DISCUSSION

In this study, we have demonstrated that chest CT scans can be used to assess body composition in subjects with COPD enrolled in the ECLIPSE study. We found that CT measurements of PMA at the aortic arch level, and SAT areas at both aortic arch and supraesternal notch locations were highly reproducible. PMA was lower in women compared to men, whereas it was the vice versa in SAT area. Additionally, SAT area was directly related to CRP and fibrinogen levels only in women, whereas PMA was not related with any biomarkers within either gender.

In this study, we used a simple approach to assess pectoralis muscle and subcutaneous fat content by measuring their cross-sectional areas on a single slice on existing chest CT scans. We found that the intra- and inter-reader agreement of PMA was high at aortic level and that of SAT area was high at both anatomic locations, respectively. The PMA agreement at aortic arch level was greater than that reported in COPDGene

subjects, (10) which may be due to readers' differences in experience with the task between the two studies. One explanation for the lesser intra- and inter-reader agreement in PMA at the supraesternal level is that structures such as vessels surrounding the pectoralis muscle look similar in density on noncontrast CT, making the identification of this portion of this muscle harder than at the aortic arch level. However, we think that with proper training, this CT technique is an easy-to-do, relatively fast assessment of the body composition making it usable in large-scale clinical and epidemiologic investigation.

CRP is a protein synthesized in hepatocytes, lymphocytes, and alveolar macrophages, and levels of CRP increase in response to acute and chronic infections (19). Fibrinogen is also an acute-phase reactant produced in the liver (19,20). Previous studies have shown that both systemic inflammatory mediators are elevated (12,19,21) and associated with relevant clinical outcomes (22,23) and mortality (24,25) in subjects with COPD. Moreover, adipose tissue depots including subcutaneous fat are associated with inflammatory mediators. For example, in COPD patients with high (vs. low) CRP had higher adipose tissue macrophages infiltration (11), and in the Framingham study, a positive association between SAT content measured at abdominal level and fibrinogen was observed (26). Consistent with these findings, we observed that in women, greater SAT area was linked to increased CRP and fibrinogen

levels. Although the reasons for these gender differences in the relationships of SAT and these biomarkers are unclear, it may involve differences in sex hormones regulation of these mediators, aging, and the interaction between these processes and COPD. Although the sample size of our study is small, our findings may suggest that SAT area has a sex-specific exacerbating effect on mediators of inflammation.

In this study, we also observed that PMA was lower in women than men, which is consistent with our data demonstrating lower FFM in women and with others' observations in peripheral skeletal muscles in patients with COPD (27). The magnitude of the observed difference in PMA at aortic level between genders was similar to that of COPDGene Study (10). In contrast, SAT area was greater in women than men at both anatomic locations suggesting that this measurement is not influenced by the breast in women. Together these findings are in agreement with the notion that the clinical assessment of body composition in COPD should take into account more factors than a simple measure of BMI (28).

Several limitations are worth of noting. We used a small convenient sample of subjects from a large study, so caution should be exercised to generalize our findings. Although CT measures of body composition were reproducible, they are likely dependent based on body position. For example, as one raises his/her hands above the head (the standard position for CT scanning), the pectoralis muscles become elongated and the PMA may be artificially decreased, and this factor might be important in subjects with severe COPD who may be limited to do this maneuver. Because the standard procedure for CT scanning in this study was with the hands above the head, we believe that this would not result in a specific gender bias. We used a CT cross-sectional area of muscle and adipose tissues on single slices as opposed to the gold standard measure of body composition (ie, DXA). However, FFM measured using bioelectrical impedance has been repeatedly shown to correlate with COPD-related traits demonstrating its utility in the research setting, (3,4,10) and we observed that FFM measured with bioelectrical impedance was directly associated with PMA in both genders. Therefore, we believe that our findings indicate that CT measures of muscle and adipose tissue are relevant to this disease although they do use the current reference standard.

It appears that there are gender differences in the relationships between CT measures of subcutaneous fat area and mediators of inflammation. Although these findings are preliminary, we believe that CT measures of muscle and fat are a valuable tool to assess body composition in COPD and warrant further investigation in larger cohorts and longitudinal studies.

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