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Adipocytokines and Associations with Abnormal Body Composition in Rheumatoid Arthritis

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Abstract

Purpose—We determined associations between adipokines and abnormal body composition in patients with rheumatoid arthritis (RA).

Methods—Combining data from three RA cohorts, whole-body dual-energy absorptiometry measures of appendicular lean mass and fat mass indices were converted to age, sex, and race-specific Z-Scores. Lean mass relative to fat mass was determined based on prior methods. Independent associations between body composition profiles and circulating levels of adiponectin, leptin, and fibroblast growth factor(FGF)-21 were assessed using linear and logistic regression models adjusting for demographics and study cohort. We also determined the improvement in the area-under-the-curve (AUC) for prediction of low lean mass when adipokines were added to predictive models that included clinical factors such as demographics, study, and body mass index (BMI).

Results—Among 419 participants, older age was associated with higher levels of all adipokines while higher C-reactive protein was associated with lower adiponectin levels and higher FGF-21 levels. Greater fat mass was strongly associated with lower adiponectin levels and higher leptin and FGF-21 levels. Higher levels of adiponectin, leptin, and FGF-21 were independently associated with low lean mass. The addition of adiponectin and leptin levels to regression models

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improved prediction of low lean mass when combined with demographics, study, and BMI (AUC 0.75 v. 0.66).

Conclusions—Adipokines are associated with both excess adiposity and low lean mass in patients with RA. Improvements in the prediction of body composition abnormalities suggest that laboratory screening could help identify patients with altered body composition who may be at greater risk of adverse outcomes.

Keywords

lean mass; fat mass; physical function; disability; rheumatoid arthritis

Sarcopenia is an important cause of functional impairment and contributes to poor long-term outcomes among the elderly (1–5). The assessment of body mass index (BMI) alone does not adequately characterize adverse metabolic changes to body composition, particularly in conditions where changes in muscle and fat compartments are likely to occur simultaneously in relationship to the disease and its severity. Low lean mass has been observed in patients with rheumatoid arthritis (RA) using methodologies such as whole-body dual X-ray absorptiometry (DXA). Low lean mass has also been associated with functional limitations in RA (6, 7) in which loss of lean mass often occurs in the setting of normal BMI, and thus is under-recognized.

Direct testing for low lean mass and other changes in body composition have not been a routine part of clinical care due to lack of availability of testing, flaws in the categorization of low lean mass based on body composition assessments, and lack of clear management algorithms once deficits are identified. We recently defined a construct of low lean mass relative to fat mass that overcomes limitations of prior methods that fail to account for the fact that lean and fat mass are tightly associated. These methods have provided an opportunity to evaluate factors associated with lean mass deficits, independent of the confounding effects of excess adiposity (8–11).

Adipocytokines are fat- and muscle-derived proteins that can serve as metabolic regulators and are hypothesized to become disrupted in the setting of cachexia, aging, and obesity. In addition, levels have been associated with adverse long-term outcomes in a number of studies. Levels of adiponectin, for example, have been linked to adverse health outcomes such as frailty and osteoporotic fracture in the general population (12, 13). Adiponectin has also been associated with radiographic progression in patients with RA, suggesting a link with severe disease (14). Few studies have evaluated adipokines as potential biomarkers of adverse body composition, though one study observed higher leptin and higher adiponectin levels in sarcopenic older adults (15). One prior study also found that greater adiponectin levels were associated with lower lean mass independent of adiposity in patients with RA (16). A better understanding of the relationships between adipokines and body composition could have implications in the understanding of the prognostic value of these biomarkers in RA and may have implications for screening for such changes in this and other at-risk groups.

We hypothesized that adipokines would be strongly associated with adverse body composition. The specific aims of the current study were 1) to determine whether circulating adipokines were associated with body composition abnormalities in RA and 2) to determine whether they might help to identify individuals with low lean mass identified by whole-body DXA assessments, the gold standard.

Methods

Study Sample

We combined and assessed three independent longitudinal cohorts of patients with RA. The internal review board at each institution approved each respective study and all subjects gave written informed consent.

1. **University of Pennsylvania (Penn) Cohort (N=113):** The Penn cohort was initiated in 2012 to evaluate alterations in body composition and bone structure in patients with RA. Subjects in the Penn cohort were recruited from the University of Pennsylvania Rheumatology practices and Philadelphia Veterans Affairs Medical Center and consisted of individuals aged 18–75 years who met 2010 American College of Rheumatology criteria for RA. Subjects with juvenile idiopathic arthritis (or another inflammatory arthritis), active cancer, a history of chronic diseases known to affect bone health (e.g. chronic kidney disease, liver disease, malabsorption syndromes), or pregnancy were excluded. One subject was excluded because her weight exceeded the limit for the DXA machine (300 pounds).

2. **Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in RA Study (ESCAPE RA) Cohort (N=190):** Subjects were men and women participating in the ESCAPE RA cohort study between October 2004 and May 2006 (17). Briefly, patients with RA followed at the Johns Hopkins Arthritis Center or referred from local rheumatologists were enrolled, all of whom met American College of Rheumatology 1987 classification criteria for RA, were 45–84 years of age, and did not report any prior pre-specified cardiovascular events or procedures. Subjects weighing >300 pounds were excluded due to weight limitations of the imaging equipment.

3. **University of California San Francisco (UCSF) Cohort (N=141):** Details regarding this study cohort have been previously published (18, 19). The majority of the research participants were drawn from the UCSF RA Panel Study between 2007–2009. RA Panel participants who lived in the greater San Francisco area were recruited for in-person assessments, including measurement of body composition. Exclusion criteria were non–English speaking, age <18 years, current daily oral prednisone dose >50 mg, current pregnancy, uncorrected vision problems that interfered with reading, and patients who had undergone joint replacement within 1 year.

Whole-Body DXA Assessment of Body Composition

The Penn cohort underwent whole-body DXA assessment using a Hologic densitometer (*Delphi Systems, Hologic, Inc., Bedford, MA*). For the UCSF subjects, a Lunar Prodigy DXA system (software version 9.3) was used. The ESCAPE-RA study also utilized a Lunar

Prodigy DXA system (Prodigy software, version 05.60.003) (*GE/Lunar Radiation, Madison, WI*). In vivo coefficients of variation for measurement of lean mass by the Lunar Prodigy have been estimated at 1% or less (20). Body composition measures for the UCSF subjects and ESCAPE RA subjects were adjusted based on the method by Shepherd et al. to facilitate comparison to NHANES data that were generated on Hologic equipment (21). The in vitro coefficient of variation for Hologic measurement of lean mass was less than 0.6% and the in vivo coefficient of variation in adults was less than 1% (22).

Measurement of circulating adipokines

In the Penn and UCSF cohorts, total adiponectin was measured on stored serum samples using a commercially available enzyme linked immunosorbent assay (ELISA) from R&D Systems. Leptin was measured using an immunoassay from *Meso Scale Discovery*. Fibroblast growth factor (FGF)-21 was measured in the UCSF and Penn cohorts using a commercially-available ELISA from R&D Systems. In the ESCAPE-RA study, adiponectin and leptin were measured by ELISA at the Laboratory for Clinical Biochemistry Research (*University of Vermont, Burlington, Vermont, USA*). In order to facilitate comparison to the Penn and UCSF cohorts, ten samples from ESCAPE-RA were also assessed using the R&D Systems and Meso Scale Discovery assays. Original levels were adjusted based on the comparison of these two assay results. The details of this adjustment and histograms showing the distribution of assay results by study can be found in Supplementary Methods, and Supplementary Figures 1 & 2. Adipokines were log-transormed to fit a normal distribution and the resulting values were standardized (so that a 1 unit change in the variable was equal to 1 standard deviation) when included in regression models or evaluated by quartile. All analyses were also both 1) adjusted for study and 2) performed separately within each individual study.

Clinical Measures

Detailed methods regarding data collection in the USCF (18), Penn (6), and ESCAPE RA cohort (17) have been published. Pain and patient global scores were assessed in all cohorts by visual analogue scale (VAS) (Range: 0–100). C-reactive protein (CRP, mg/dL) and ACPA status (positive or negative) were measured using standard clinical assays at each institution. The Health Assessment Questionnaire was used to assess disability in all three cohorts (23).

Statistical Analysis

Generation of ALMI, FMI and $ALMI_{FMI}$ Standard Deviation Scores—Appendicular lean mass index (ALMI) and fat mass index (FMI) were determined by dividing the respective estimate by height-squared, similar to the calculation of body mass index (BMI). Sex- and race/ethnicity-specific Z-Scores were generated for FMI relative to age using LMS (*Lambda, Mu, Sigma*) curves previously published by *Hologic Inc.*(6, 24) and for ALMI (not including bone mass) using LMS values provided by communication with the company. We defined lean mass based on a previous described method to generate adiposity-adjusted ALMI Z-Scores **($ALMI_{FMI}$)** by utilizing the residuals from the regression of ALMI Z-Score on FMI Z-Score within age, sex, and race categories (25). The $ALMI_{FMI}$ Z-Scores represent the number of SDs above or below the mean for a reference group of the same age, sex,

race/ethnicity, and FMI Z-Score. In basic terms, this method makes it possible to evaluate whether lean mass deficits are present when compared to what would be expected for that individual's level of adiposity. A negative value implies the value is below the reference population mean.

Categorization of Body Composition—Low lean mass and obesity were defined according to previously validated methods (8, 11, 26). Low lean mass was defined as an $ALMI_{FMI}$ Z-Score of less than or equal to −1 (15.9^{th} percentile for the NHANES population). Obesity was defined based on sex-specific FMI cut-point values developed by Kelly et al. in order to generate a prevalence of obesity that was the same as observed using a BMI cut point of 30 kg/m^2 in 25 year old participants in NHANES (FMI ≥13 for women; ≥9 for men) (24). These cutoffs performed similarly across racial groups.

Hypothesis Testing—We used linear regression models to evaluate associations between clinical factors and levels of each individual adipokine (log-transormed, per 1 SD). Multivariable models were derived by the inclusion of all factors found to be significantly associated with that adipokine ($p<0.05$) in bivariate analyses. Age, sex, race, body composition ($ALMI_{FMI}$, FMI) and study were forced into all models.

We assessed associations between adipokines and body composition parameters independent of age, sex, race, and study cohort. We evaluated adipokines as continuous variables and as quartiles to evaluate for non-linear trends. We used all available observations from baseline and follow-up visits, clustering on study participant to account for multiple observations per subject. We assessed the prediction of low lean mass and obesity in models that did and did not include adipokines in order to assess the added value of these tests in predicting altered body composition by assessing the area-under-the-curve (AUC). In the initial model, we incorporated only measures that would typically be available in clinic (age, sex, race, BMI, CRP) and study cohort. Then we tested the improvement in prediction with the addition of both adipokines to the model. For this we used the "roccomp" command in Stata, which tests the equality of two or more receiver-operating characteristics areas obtained from applying two or more test modalities to the same sample or to independent samples. We then determined the probability of low lean deficits for each patient and the threshold of probability with the highest accuracy (based on the Youden Index). We then determined the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the model at that threshold. We also determined the optimal threshold for adiponectin and leptin and evaluated diagnostic characteristics based on the implementation of these diagnostic thresholds. In sensitivity analyses, we stratified the analysis by study to evaluate for consistent effects across the three study cohorts.

Statistical analysis was performed using Stata 14.2 (*StataCorp, LP, College Station, TX)*.

Results

A complete description of these study cohorts has been previously published (Supplementary Table 1) and the characteristics of the study population by body composition category can be found in Supplementary Table 2 (10). A total of 424 of the

444 total participants had measures of body composition and adipokines available and were included in the analyses. A follow-up visit was not performed in approximately 20% of participants. Those with missing follow up data were more likely to be older, male, have lower lean mass, and to have longer disease duration at baseline (Supplementary Table 3).

Clinical Factors Associated with Adipokine Levels

Lower lean mass ($ALMI_{FMI}$ Z-Score) and lower fat mass (FMI Z-Score) were each associated with higher adiponectin levels (Figure 1). In adjusted models, the presence of low lean mass was associated with higher levels of adiponectin while obesity based on FMI was associated with lower levels (Figure 2). In multivariable models, higher adiponectin levels were also associated with older age, female sex, non-black race, and lower CRP levels at the baseline visit (Table 1).

Participants with higher fat mass (FMI Z-Score) and lower lean mass ($ALMI_{FMI}$) had higher leptin levels. This association was preserved in multivariable models (Figure 2). In multivariable models, older age, female sex and black race were each associated with higher leptin levels (Table 1).

Among the smaller cohort (UCSF and Penn only), higher fat mass and lower lean mass were each associated with higher FGF-21 levels. Both low lean mass and obesity were associated with significantly higher FGF-21 levels (Figure 2). Older age and higher CRP were each associated with higher FGF-21 levels in multivariable models (Table 1).

In each of these models, disease duration, smoking, HAQ, and current prednisone use were not associated with adiponectin, leptin, or FGF-21 levels.

Adipokines and Prediction of Low Lean Mass and Obesity

Over all study observations, in regression models adjusting for age, sex, race, BMI category, and study cohort, those with leptin levels in the highest quartiles had lower $ALMI_{FMI}$ Z-Scores and higher odds of low lean mass (Table 2). For example, the highest quartile of leptin had a much higher odds of low lean mass [OR: 7.55 (3.44, 16.53) $p<0.001$]. Higher adiponectin and FGF-21 levels were more modestly associated in similar models. Significant associations were also observed in models adjusting for FMI Z-Score instead of BMI (Supplementary Table 4). Associations per 1 SD and across the individual study cohorts can also be found in Supplementary Table 5. When both were included in regression models, higher leptin [β: −0.64 (−0.82, −0.47) $p<0.001$] and adiponectin [β: −0.21 (−0.34, −0.092) $p=0.001$] were each independently associated with lower lean mass (Supplementary Table 6).

Prediction of low lean mass was improved with the inclusion of adiponectin and leptin levels in regression models. In basic models that included age, sex, race, BMI, and study cohort, the AUC was 0.66 (95% CI 0.62, 0.71). The AUC improved to 0.75 (95% CI 0.71, 0.79) with inclusion of adiponectin and leptin (per 1 SD) into the model (Figure 3). The improvement in prediction in the overall cohort was statistically significant ($p<0.001$). A similar pattern of improvement in prediction was shown for each individual cohort (Supplementary Table 7). For example, in ESCAPE-RA, the inclusion of adiponectin and

leptin levels improved the AUC from 0.558 (95% CI 0.494, 0.621) to 0.701 (95% CI 0.643, 0.759) (p<0.001). The addition of CRP to the model slight improved overall prediction [OR (per 1 SD): 1.55 (95% CI 1.20–2.01) p=0.001; AUC=0.777 (95% CI 0.739, 0.815) ; N=413). Results were similar with further adjustment for diabetes.

For each study participant at enrollment, the predicted probability of low lean mass was defined based on the regression coefficients from models that included adipokines and CRP. The optimal threshold probability was 28.2% based on the Youden index [N=164 (39.7%) were above this threshold]. Using this threshold, the model was 73.7% specific and 77.1% sensitive at the baseline visit. In this population, the negative predictive value (NPV) was 90.0%, while the positive predictive value (PPV) was only 51.2% (Table 3).

Based on the Youden index for the identification of low lean mass, the optimal threshold for adiponectin was 21.9 mg/L for women and 22.3 mg/L for men. The optimal threshold for leptin was 17.9 ng/ml for women and 5.4 ng/ml for men. In regression models, a higher odds of low lean mass was observed when both adipokines were above these thresholds [N=89 (20.7%); OR 3.75 (95% CI 2.05, 6.85) p<0.001]. A much lower odds of low lean mass was observed when both adipokines were below these thresholds [N=122 (28.6%); OR 0.23 (95% CI 0.11, 0.46) p<0.001]. The sensitivity, specificity, PPV, and NPV for low lean mass when one or both adipokines were above noted thresholds are shown in Table 3.

Models incorporating age, sex, race, BMI, and study cohort were highly predictive of obesity by fat mass [AUC= 0.972 (95% CI 0.960, 0.980)]. This improved significantly but modestly with the inclusion of leptin and adiponectin levels [AUC= 0.978 (95% CI 0.968, 0.985)] (p for comparison 0.006; full models not shown). CRP was not associated independently in these models.

Discussion

In this study, we identified strong associations between adipokines and body composition abnormalities including deficits in lean mass among patients with RA. We found that the addition of adipokines to prediction models could help identify those with low lean mass. Since a major limitation to addressing adverse changes in body composition in patients with RA is their accurate identification and characterization, these findings help to support the potential use of circulating biomarkers to identify patients with lean mass deficits that might benefit from appropriate intervention. Importantly, these observations also have implications in our understanding of the role of adipokines in pathogenesis and severity of RA. Overall, the results suggest that a strong relationship between adipokines and body composition in an at-risk population may help to explain previously defined relationships between adipokines and adverse long-term outcomes such as fracture and mortality among older adults and with radiographic damage progression in patients with RA.

Adiponectin is a fat and skeletal-muscle derived adipocytokine that is higher in patients with lower BMI and increases dramatically in the setting of rapid weight loss (27–29). Leptin, in contrast, is strongly and positively associated with total adiposity and acts to modulate appetite and regulate fat stores. Given the role of adipokines as metabolic regulators,

adiponectin and leptin have been proposed as biomarkers that may help identify sarcopenia among at-risk patients (15). We previously demonstrated that higher adiponectin levels were associated with lean mass deficits in patients with RA from a smaller cohort (16). We also demonstrated associations between FGF-21, another metabolic regulator, and body composition abnormalities in patients with RA (30). This study builds on prior observations by confirming them in two additional independent cohorts and evaluating improvements in the identification of deficits by incorporating adipokine measurements.

These results support the hypothesis that adipokines provide important information about metabolic health that are not captured by BMI alone. Since DXA assessments of body composition are not available at all institutions nor are they covered by insurance, simple blood tests that could identify individuals with adverse body composition are potentially of value. The NPV in this population was sufficient to suggest that these measures may function well as an initial screening test. Further prospective studies are needed to evaluate the potential value of clinical application of such tools in this and other settings and in combination with other modalities. While measurement of adipokines improved the identification of those with lean mass deficits, the overall accuracy in model prediction remained modest, suggesting that additional testing would likely be needed to confirm the presence of body composition abnormalities in order to identify patients who might benefit from interventions. Further study is also needed to refine the clinical cut-points that could aid in screening and diagnosis. Physicians and patients currently have limited access to exercise therapies to address skeletal muscle loss, and targeted medical therapies are not currently available. However, a number of therapies are in the pipeline (31).

While not the primary focus, this study also described some clinical associations with adipokines. In addition to body composition, age, gender, and race were all associated with adipokine levels. Interestingly, CRP levels were also associated with lower adiponectin and higher FGF-21 levels, suggesting a potential relationship with systemic inflammation. However, the observed relationship between CRP, adiponectin, and FGF-21 might be hypothesized to be related to residual confounding related to fat distribution, since visceral fat may influence both CRP and adipokine levels. Evidence is conflicting as to whether adipokines are associated with disease activity in rheumatoid arthritis (32). However, systemic inflammation is a potential source of metabolic stress and a cause of cachexia in inflammatory diseases and therefore might be hypothesized to play an important role in influencing adipokine regulation.

Limitations of the current study include the lack of standardized measures for some variables including the adipokine assays across the three cohorts included. We also did not measure high molecular weight adiponectin, which may be the more biologically active form. In addition, it is difficult to determine the potential impact of missing follow-up data on some participants since any dropout from these studies could be related to the severity of illness. While the current study was aimed to determine associations between adipokines and body composition, it is important to acknowledge that the clinical entities of sarcopenia and cachexia are complex and may additionally described through the evaluation of muscle strength, muscle quality, and other assessments of skeletal muscle function, though these assessments may be difficult to obtain in a clinical setting.

Basic models with BMI accurately predicted excess adiposity such that adipokines added little. This maybe because of the high prevalence of obesity in the population. Future study may evaluate whether adipokines might add to prediction of excess adiposity in particular subgroups such as those with BMI 25–30 kg/m^2. Further, the predictive role for adipokines in identifying patients with sarcopenic obesity will require further study. Our study was not able to assess the impact of diet and nutritional deficiencies, which could play a role in the relationship between adipokines and body composition. Finally, the predictive value of adipokines might be expected to be lower among healthier individuals, those with particular comorbidities, or those who have lost weight rapidly through intentional means.

Strengths of the study include the large sample with body composition assessments, the use of a novel categorization methods, assessment of multiple adipocytokines, and the availability of longitudinal data.

In summary, in this study we observed that adipocytokines (leptin, adiponectin, and FGF-21) helped to identify low lean mass in patients with RA, suggesting that laboratory screening could help identify patients likely to benefit from exercise and strength training to promote skeletal muscle health. Methods to screen for body composition changes will be of increasing interest as therapies emerge to more effectively treat sarcopenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovation

1. While body composition abnormalities are common in patients with rheumatoid arthritis, few clinicians have access to clinical tools to identify them.
2. In this study, circulating adipokines were strongly associated with both excess adiposity and low lean mass in patients with RA.
3. Laboratory screening for abnormal body composition may help identify patients with abnormalities and who are at greater risk of adverse outcomes.

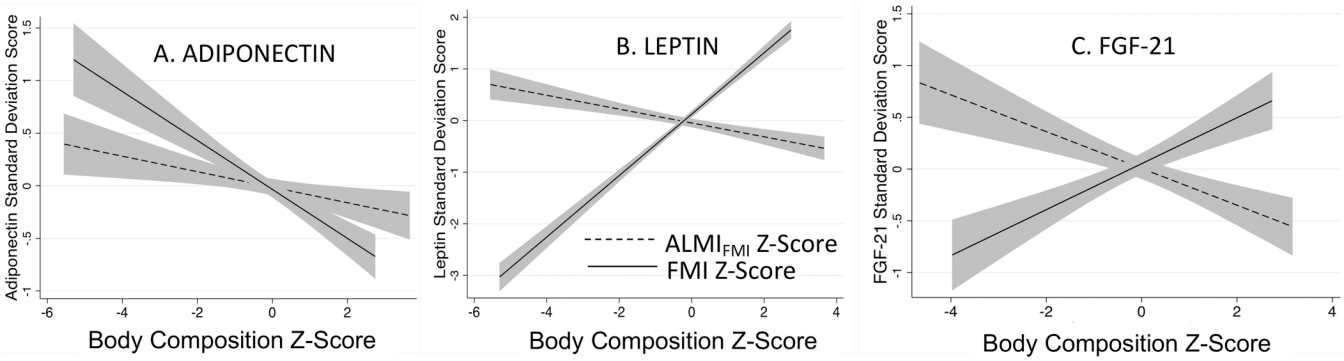

Figure 1:

Unadjusted associations between body composition Z-Scores [ALMI$_{FMI}$ (dashed line), FMI (solid line)] and levels of A) Adiponectin, B) Leptin, and C) FGF-21.

Abbreviations: ALMI$_{FMI}$= Appendicular Lean Mass Index adjusted for Fat Mass Index; FMI= Fat Mass Index

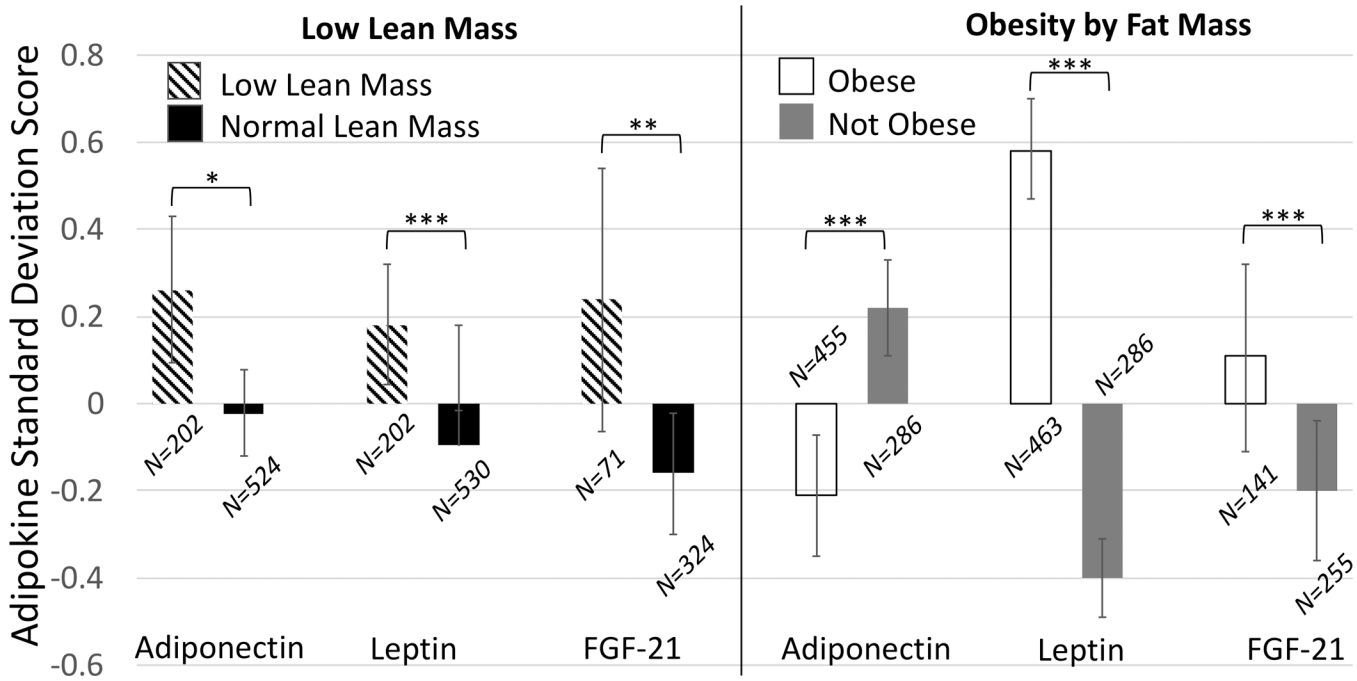

Figure 2:

Levels of adipokines (by standard deviation score) among patients with low lean mass v. normal (striped v. black) and obesity compared to normal (white v. gray) after adjusting for age, sex, race, and study over all study observations.

*p<0.05; **p<0.01; ***p<0.001

Abbreviations: FGF-21= Fibroblast Growth Factor-21

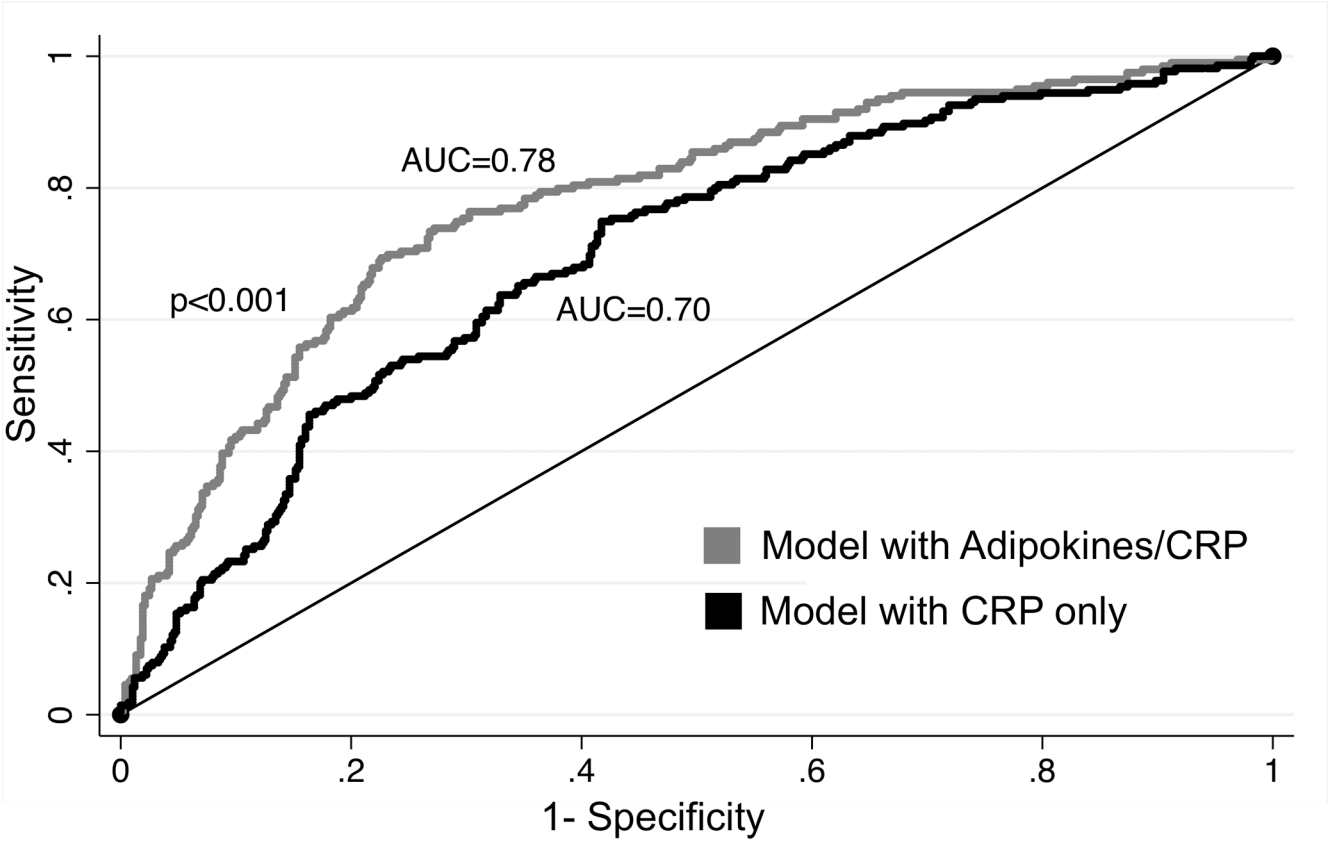

Figure 3:

Receiver operating characteristics of models including adipokines and CRP and not including CRP for predicting the presence of low lean mass relative to adiposity. All models additionally include age, sex, race, BMI, and study.

Abbreviations: AUC= Area-Under-the-Curve

Table 1:

Multivariable models assessing relationships between clinical variables at baseline and 1) adiponectin, 2) leptin, and 3) FGF-21 levels (per 1 SD of each adipokine). Final models included all variable associated in univariate analyses with age, sex, race, and body composition measure forced into each model.

	Adiponectin ***(per 1 SD)*** ***(N=410)***	**Leptin** ***(per 1 SD)*** ***(N=419)***	**FGF-21** ***(per 1 SD)*** ***(N=230)***
	β (95% CI)	β (95% CI)	β (95% CI)
Lean Mass Z-Score	−0.12 (−0.19, −0.043) **	−0.065 (−0.11, −0.019) **	−0.12 (−0.24, −0.012) *
Fat Mass Z-Score	−0.24 (−0.33, −0.16) ***	0.57 (0.52, 0.63) ***	0.19 (0.075, 0.31) **
Age (per yr)	0.020 (0.012, 0.029) ***	0.010 (0.004, 0.015) **	0.014 (0.003, 0.024) *
Female	0.77 (0.62, 1.00) ***	0.96 (0.84, 1.09) ***	0.049 (−0.25, 0.35)
Black	−0.47 (−0.77, −0.24) ***	0.24 (0.066, 0.42) **	−0.065 (−0.41, 0.28)
CRP (per 1 SD)	−0.16 (−0.27, −0.051) **	0.008 (−0.063, 0.080)	0.18 (0.007, 0.36) *
Current Smoking	--	--	0.27 (−0.093, 0.62)
Prednisone	--	--	--
Disease Duration (per yr)	--	--	--
Pain (per 1 unit)	--	−0.002 (−0.005, 0.000)	0.003 (−0.002, 0.008)
HAQ (per 1 unit)	0.12 (−0.016, 0.26)	−0.047 (−0.15, 0.059)	
Study			
ESCAPE	(reference)	(reference)	--
UCSF	−0.047 (−0.32, 0.23)	−0.14 (−0.32, 0.032)	(reference)
Penn	−0.42 (−0.66, −0.18) **	0.17 (0.012, 0.33) *	0.36 (0.049, 0.68) *

* p<0.05;

** p<0.01;

*** p<0.001

Lean Mass= $ALMI_{FMI}$ Z-Score

Fat Mass= FMI Z-Score

Table 2:

Association between adipokines and lean mass relative to fat mass in linear and logistic regression models adjusting for age, sex, race, BMI, and study. Each adipokine is assessed in a separate model. Analyses use all observations, clustered on study subject. All comparisons refer to Quartile 1 as the reference group.

	$ALMI_{FMI}$ Z-Score		Low $ALMI_{FMI}$ Z-Score	
	β (95% CI)	**P**	**OR (95% CI)**	**P**
Adiponectin Quartile (N=726)				
2	−0.66 (−0.97, −0.35)	<0.001	2.11 (1.17, 3.80)	0.01
3	−0.55 (−0.86, −0.22)	0.001	2.01 (1.06, 3.80)	0.03
4	−0.56 (−0.91, −0.22)_	0.002	1.91 (0.98, 3.72)	0.06
Leptin Quartile (N=734)				
2	−0.42 (−0.72, −0.12)	<0.001	2.13 (1.12, 4.06)	0.02
3	−0.95 (−1.33, −0.58)	<0.001	4.99 (2.49, 10.00)	<0.001
4	−1.22 (−1.65, −0.81)	<0.001	7.55 (3.44, 16.53)	<0.001
FGF-21 Quartile (N=395) *(Penn/UCSF only)*				
2	−0.20 (−0.51, 0.12)	0.22	0.89 (0.36, 2.19)	0.79
3	−0.47 (−0.84, −0.10)	0.01	2.24 (0.91, 5.48)	0.08
4	−0.72 (−1.16, −0.27)	0.002	2.87 (1.10, 7.46)	0.03

*adjusted for age, sex, race, BMI, and study.

Abbreviations; $ALMI_{FMI}$= Appendicular Lean Mass Index Adjusted for Fat Mass Index; FGF-21= Fibroblast Growth Factor-21; Penn= University of Pennsylvania; UCSF= University of California San Francisco; BMI= Body Mass Index.

Table 3:

Test characteristics for the identification of low lean mass from approaches based on 1) probability from regression models, 2) the presence of high levels of both adiponectin and leptin, and 2) the presence of high levels of either adiponectin or leptin.

	N (%)	Sensitivity	Specificity	PPV	NPV
Probability Based on Full Regression Model *	168 (39.7%)	70.9%	72.0%	47.9%	87.3%
Adiponectin and Leptin both Above Optimal Cut-point	89 (20.7%)	38.9%	85.8%	50%	79.3%
Either Adiponectin or Leptin Above Optimal Cut-point	304 (71.4%)	86.5%	34.6%	32.4%	87.6%

* Full regression model includes: age, sex, race, BMI, study cohort, adiponectin, and leptin levels.