Blood level of adiponectin is positively associated with lean mass in women without type 2 diabetes

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Abstract

Objective: The objective of this study was to evaluate the relationship between blood levels of adiponectin and leptin with lean body and trunk adipose mass in women with and without type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study analyzed baseline data from five previous clinical studies involving postmenopausal women (n = 95). Body composition was assessed by dual-energy x-ray absorptiometry, and appendicular lean mass was calculated based on body mass index (ALM_BMI). Adipokines and cytokines were measured by enzyme-linked immunosorbent assay. Linear mixed-effect models with a random study effect were used to investigate the relationship between predictors (eg, adiponectin, leptin), outcomes (eg, ALM_BMI, trunk adipose mass), and co-variables (T2DM status, age, interleukin-6, and C-reactive protein).

Results: Postmenopausal women with T2DM had lower ALM_BMI than those without T2DM. There was a positive association between blood adiponectin and ALM_BMI in postmenopausal women without T2DM, but no association in those with T2DM. Blood leptin was negatively associated with ALM_BMI for women regardless of T2DM diagnosis. Blood adiponectin was negatively associated, whereas blood leptin was positively associated with trunk adipose mass for the entire cohort.

Conclusions: T2DM status moderated the relationship between blood adiponectin and ALM_BMI, where blood adiponectin was positively associated with ALM_BMI in postmenopausal women without T2DM, but not those with T2DM. Dysregulated metabolism in T2DM may contribute to lower muscle mass in women with T2DM, but future research is required to elucidate this mechanistic link. The negative association between blood leptin and ALM_BMI was a novel finding. Future studies will need to more clearly define the relationship between these variables.

Key Words: Adiponectin – Adipose mass – Diabetes – Lean mass – Leptin.

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Leptin is an adipokine primarily produced in adipose tissue, circulating adiponectin levels are inversely related to adipose mass. Leptin is an adipokine that regulates energy balance by suppressing hunger and food intake. Circulating leptin levels are positively associated with adipose mass.

While the relationship between adiponectin, leptin, and adipose mass has been extensively studied, there is little research on the relationship between these adipokines and lean body mass in postmenopausal women. Additionally, it is unclear whether or not T2DM status impacts these relationships. The purpose of this study was to evaluate the relationship between blood levels of adiponectin and leptin with lean body mass and trunk adipose mass in postmenopausal women with and without T2DM.

METHODS

Participants

Women were recruited from the Columbus, OH area between 2004 and 2015. Analyses were restricted to only postmenopausal women from five studies (2 unpublished, Kiecolt-Glaser). The size of the cohorts from the five clinical studies were 3, 11, 16, 21, and 44 individuals (n = 95 total). Women were excluded for substance and tobacco use, gastrointestinal diseases and disorders, impaired cognitive function, immune-related conditions, or major inflammatory diseases. Inclusion criteria for this secondary analysis included women who were middle-aged or older (age 43-75 years old), with or without type 2 diabetes, with or without history of breast cancer, and no history of a major cardiovascular event. Other details for inclusion were reported earlier and are briefly described in Supplementary Tables 1 and 2, http://links.lww.com/MENO/A441.

Because of the combination of cohorts from five clinical studies, we controlled for clinical study as described in the “Statistical analysis” section.

Trial design

This is a cross-sectional study where all protocols were approved by the Institutional Review Board of The Ohio State University. Data were derived from the first clinical visit after consent and before any interventions. One study was a crossover intervention and data from this study were derived from the clinical visit before the first diet period intervention or the clinical visit after a 4-week wash-out period and before the second diet period intervention.

Body composition

Body composition was assessed via dual-energy x-ray absorptiometry (DEXA). One of three DEXA instruments were used for analysis: a Lunar iDEXA (GE Healthcare, Fairfield, CT), a Lunar DPX-NT (GE Healthcare, Fairfield, CT), and a Lunar iDEXA (Lunar Corp, Madison, WI). To assess the validity of the instruments used, two scans were performed on a subset of the women for the DEXA instruments to determine the coefficient of variation. The coefficient of variation for trunk adipose mass available for three studies was 1.63%. A half-body scan was used to predict whole-body composition for one obese woman who did not fit in the scanning area. Postmenopausal women with DEXAs that had appendicular regions missing due to inability to fit in the designated area were excluded from analysis. Appendicular lean mass (ALM) (the summation of arm and leg lean mass) adjusted for body mass index (BMI) (ALM\_BMI) as identified by The Foundation for the National Institute of Health Sarcopenia Project was used for data analyses for lean body mass. The average coefficient of variation for ALM\_BMI was 1.10% for the three available studies. Sarcopenic lean mass was defined as ALM\_BMI <0.512.

Biochemical assays

Cytokine and adipocytokine analyses were performed on blood samples collected after a minimum 10-hour fast. The samples were centrifuged, and the plasma or serum was extracted and then stored at −70°C or −80°C until analyses were performed. Biochemical analysis of cytokine and adipocytokines were carried out in two different laboratories by enzyme-linked immunosorbent assay according to the manufacturer’s instructions. Blood levels of adiponectin were measured using Meso Scale Discovery (Rockville, MD), Linco Research (St. Charles, MO), or Millipore (Burlington, MA) kits. Blood levels of leptin were measured using Meso Scale Discovery, Linco Research or R&D Systems (Minneapolis, MN) kits. Blood levels of interleukin (IL)-6 were measured using Meso Scale Discovery and Millipore kits. Blood levels of C-reactive protein (CRP) were measured using Meso Scale Discovery and Immunodiagnostik (Bensheim, Germany) kits. Sample values were extrapolated using a four-parameter logistic fit. A total of four samples were excluded from adiponectin analysis; three samples were excluded because blood adiponectin levels were outside the standard curve and one sample was excluded because the sample had a large coefficient of variation (>20%). A total of two samples were excluded from leptin analysis; one sample was excluded because blood leptin levels were outside of the standard curve and one sample was excluded because there was not enough sample to measure. A total of 10 samples were excluded from IL-6 analysis; five samples were excluded because blood IL-6 levels were below the standard curve, two samples were excluded because the sample had a large coefficient of variation (>20%), one sample was excluded because there was not enough sample to measure, and two samples were excluded as outliers. A sample was considered an outlier if the sample value was >3 standard deviations (SDs) away from the total mean.

Statistical analysis

To account for between-study heterogeneity, linear mixed-effect models with a random study effect were used to investigate the relationship between predictors (eg, adiponectin, leptin) and outcomes (eg, ALM\_BMI, trunk adipose mass).
Explanatory variables were added into the models as fixed effects including T2DM status, age, IL-6, and CRP. IL-6 and CRP values were right-skewed; therefore, all analyses for IL-6 and CRP used natural log-transformed values to better approximate normality of residuals. Of primary interest were the effects of adiponectin, leptin, and T2DM status on ALM BMI and trunk adipose mass. The interactions among adiponectin, leptin and T2DM status were also investigated. All models were first run without including any possible confounders, that is, with only the key predictor and T2DM included (“unadjusted model”), and then with age, IL-6 and CRP included (“adjusted model”). Data were analyzed using SAS software, version 9.4 (Cary, NC). P < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the women

Characteristics of the women are provided in Table 1. The cut-off for ALM BMI for sarcopenic mass for women is 0.512. In our cohort, 9% (n = 9/95) of women had sarcopenic muscle size. Unfortunately, we did not measure grip strength in some of our primary studies so a diagnosis of frank sarcopenia is not possible. The average BMI in our overall cohort was 30.4, where 85% (n = 81/95) of women were overweight or obese (BMI > 25). Average ALM BMI was significantly lower in postmenopausal women with T2DM compared with postmenopausal women without T2DM (Table 1; P < 0.0001). The average ALM BMI was 0.57 units in postmenopausal women with T2DM, compared with 0.66 units in postmenopausal women without T2DM. Blood levels of adiponectin tended to be lower in postmenopausal women with T2DM versus postmenopausal women without T2DM (Table 1; P = 0.09). The average blood adiponectin level was 9.14 ± 7.4 μg/mL in postmenopausal women with T2DM, compared with 16.5 ± 7.1 μg/mL in women without T2DM.

Adipokines and body composition in menopause

Table 2: Regression models predicting ALM BMI

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Effect</th>
<th>Estimate</th>
<th>Std Err</th>
<th>P</th>
<th>Estimate</th>
<th>Std Err</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>0.603</td>
<td>0.027</td>
<td>&lt;0.0001</td>
<td>0.66</td>
<td>0.094</td>
<td>&lt;0.0001</td>
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<tr>
<td>Adiponectin</td>
<td></td>
<td>0.0035</td>
<td>0.0001</td>
<td>0.02</td>
<td>0.0026</td>
<td>0.002</td>
<td>0.12</td>
</tr>
<tr>
<td>T2DM</td>
<td></td>
<td>0.0015</td>
<td>0.0037</td>
<td>0.97</td>
<td>-0.0017</td>
<td>0.0048</td>
<td>0.83</td>
</tr>
<tr>
<td>Adiponectin+T2DM</td>
<td></td>
<td>-0.0066</td>
<td>0.003</td>
<td>0.01</td>
<td>-0.0082</td>
<td>0.003</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>-0.0004</td>
<td>0.0001</td>
<td>0.79</td>
<td>0.0007</td>
<td>0.013</td>
<td>0.97</td>
</tr>
<tr>
<td>ln (IL-6)</td>
<td></td>
<td>-0.0017</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
<td>-0.0015</td>
<td>0.0004</td>
<td>0.001</td>
</tr>
<tr>
<td>ln (CRP)</td>
<td></td>
<td>0.0817</td>
<td>0.0017</td>
<td>0.18</td>
<td>0.0046</td>
<td>0.001</td>
<td>0.74</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td>-0.0007</td>
<td>0.001</td>
<td>0.67</td>
<td>-0.0078</td>
<td>0.017</td>
<td>0.44</td>
</tr>
</tbody>
</table>

P values from linear mixed-effects models with a random effect for study. Bolded values indicate statistical significance at P < 0.05.

ALM BMI, appendicular lean mass normalized to body mass index; CRP, C-reactive protein; IL-6, interleukin-6; SD, standard deviation; T2DM, type 2 diabetes mellitus.
ALM<sub>BMI</sub> (Table 2; \(P = 0.02\)), but for postmenopausal women with T2DM, this relationship tended in the opposite direction and was not significant (slope = −0.0030, \(P = 0.16\)). This interaction remained significant with models that included age, IL-6, and CRP (Table 2; \(P = 0.02\)).

Next, the relationship of leptin and T2DM status to ALM<sub>BMI</sub> was measured (Table 2). Blood leptin was negatively associated with ALM<sub>BMI</sub> for the total cohort (Table 2; \(P < 0.0001\)). A 1 ng/mL increase in leptin was associated with a 0.0017 unit decrease in ALM<sub>BMI</sub>. This relationship remained significant when adjusting for T2DM, age, IL-6, and CRP (Table 2; \(P = 0.001\)). In this adjusted model, T2DM status was not associated with ALM<sub>BMI</sub> (Table 2; \(P = 0.18\)). T2DM did not moderate the relationship of leptin with ALM<sub>BMI</sub> (\(P = 0.94\), data not shown).

Blood IL-6 was not associated with ALM<sub>BMI</sub> in either model controlling for adiponectin or leptin. Blood CRP was negatively associated with ALM<sub>BMI</sub> in the model that controlled for adiponectin (Table 2; \(P = 0.049\)); a 10% increase in CRP was associated with a 0.0020 unit decrease in ALM<sub>BMI</sub>. CRP was not associated with ALM<sub>BMI</sub> in the model that controlled for leptin.

### Interactions between adipokines, T2DM, and trunk adipose mass in postmenopausal women

The second objective of the study was to determine the relationships between adiponectin, leptin, and T2DM status with trunk adipose mass (Table 3). Blood adiponectin was negatively associated with trunk adipose mass for the entire cohort (Table 3; \(P = 0.02\)). A 1 \(\mu\)g/mL increase in adiponectin was associated with a 0.19 kg decrease in trunk adipose mass. However, this relationship was not significant when the model adjusted for T2DM, age, IL-6, and CRP (Table 3; \(P = 0.63\)). In this adjusted model, T2DM status was significantly associated with trunk adipose mass; postmenopausal women with T2DM had 5.0 kg higher trunk adipose mass on average than women without T2DM (Table 3; \(P = 0.0009\)). T2DM status did not moderate the relationship of adiponectin with trunk adipose mass (\(P = 0.64\), data not shown).

Next, the relationship of leptin and T2DM status to trunk adipose mass was measured (Table 3). Blood leptin was positively associated with trunk adipose mass for the entire cohort (Table 3; \(P < 0.0001\)). A 1 ng/mL increase in leptin was associated with a 0.15 kg increase in trunk adipose mass. This relationship remained significant when the model adjusted for T2DM, age, IL-6, and CRP (Table 3; \(P < 0.0001\)). In this adjusted model, T2DM status was significantly associated with trunk adipose mass (Table 3; \(P < 0.0001\)), but did not moderate the relationship of leptin with trunk adipose mass (\(P = 0.77\), data not shown).

Blood CRP was positively associated with trunk adipose mass in both the model that controlled for adiponectin (Table 3; \(P = 0.001\)) and the model that controlled for leptin (Table 3; \(P = 0.04\)). A 10% increase in CRP was associated with a 0.16 kg increase in trunk adipose mass when controlling for adiponectin, and a 0.10 kg increase in trunk adipose mass when controlling for leptin. Blood IL-6 was positively associated with trunk adipose mass in the model that controlled for leptin (Table 3; \(P = 0.04\)), but not for adiponectin (Table 3; \(P = 0.08\)). A 10% increase in IL-6 was associated with a 0.11 kg increase in trunk adipose mass when controlling for leptin.

### DISCUSSION

The first objective of this study was to determine the relationships between blood levels of adiponectin, leptin, and T2DM status with lean body mass in postmenopausal women. In our study, we found that postmenopausal women with T2DM had significantly lower ALM<sub>BMI</sub> than postmenopausal women without T2DM (Table 1). This finding is consistent with previous studies demonstrating lower ALM in people with T2DM than nondiabetic counterparts. Low blood adiponectin levels are consistently associated with an increased risk of developing T2DM across many diverse populations. In our study, we found that blood adiponectin levels were marginally lower in the postmenopausal women with T2DM, although this was not statistically significant (Table 1).

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**Table 3. Regression models predicting trunk adipose mass**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Effect</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate</td>
<td>Std Err</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Intercept</td>
<td>21.0</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Adiponectin</td>
<td>−0.19</td>
<td>0.081</td>
</tr>
<tr>
<td>T2DM</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ln(IL-6)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ln(CRP)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Leptin</td>
<td>Intercept</td>
<td>14.1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Leptin</td>
<td>0.15</td>
<td>0.022</td>
</tr>
<tr>
<td>T2DM</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ln(IL-6)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ln(CRP)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(P\) values from linear mixed-effects models with a random effect for study.

Bolded values indicate statistical significance at \(P < 0.05\).

CRP, C-reactive protein; IL-6, interleukin-6; Std Err, standard error; T2DM, type 2 diabetes mellitus.
To our knowledge, we are the first to investigate the interaction between adiponectin and T2DM status in relation to lean body mass as adjusted for BMI (eg, ALM_{BMI}) in postmenopausal women. While blood adiponectin was not associated with T2DM status in our total cohort, we found different relationships when comparing postmenopausal women without T2DM to those with T2DM. There was a positive association between adiponectin and ALM_{BMI} in postmenopausal women without T2DM; however, there was no association between adiponectin and ALM_{BMI} in postmenopausal women with T2DM. Dysregulated metabolism in T2DM may be a contributing factor in lower muscle mass in women with T2D; however, future research is needed to elucidate a causal link. In addition, insulin resistance is associated with increased inflammation, altered adipocyte secretions, dysregulated fatty acid metabolism, and lipotoxicity, all factors that may influence adiponectin and ALM_{BMI}. Using DEXA to measure lean mass, we report here that blood adiponectin is positively related to ALM_{BMI} in postmenopausal women. In contrast, Kosacka et al., who utilized bioelectrical impedance to estimate lean mass, found a negative correlation between adiponectin and percent muscle mass in men and women without T2DM but with obstructive sleep apnea syndrome. It is also possible that the relationship between blood adiponectin and ALM_{BMI} is different among postmenopausal women compared with other populations. Other studies have found no association between blood adiponectin and ALM in premenopausal women and total lean mass in aging Asian men and women, where ALM was not expressed per BMI unit. The lack of adjusting data with BMI is important because most of our cohort was overweight or obese. Differences in body composition between men and women, racial differences in adiponectin levels, and changes in body composition that occur during menopause may explain the differences between our findings and those in previous studies.

To our knowledge, we are the first to find a significantly negative relationship (P < 0.0001) between blood leptin and ALM_{BMI} in postmenopausal women, regardless of T2DM status (Table 2). Findings from previous studies evaluating the relationship between blood leptin and lean mass in postmenopausal women are conflicting. Several studies reported a positive relationship between leptin and total lean mass in adults. In contrast, at least one study reported no association. The difference in our finding compared with others may be due to a variety of reasons. First, adjusting for body size (eg, ALM_{BMI}), the influence of larger BMI on larger lean mass per se is minimized in our analyses. To our knowledge, no other studies have analyzed the relationship of adipokines with ALM when adjusted for body size (eg, ALM_{BMI}). Secondly, some prior studies used relatively healthy weight postmenopausal women, whereas our cohort was primarily overweight. Third, there may be a relationship between time after menopause and blood leptin; however, this is currently not well-characterized.

The second objective of this study was to determine the relationships between blood levels of adiponectin, leptin and T2DM status with trunk adipose mass in postmenopausal women. Despite the fact that adiponectin and leptin are both primarily produced by adipocytes, their blood levels have generally opposing relationships with total adipose mass. Adiponectin levels generally decrease with increasing adipose mass, whereas leptin levels generally increase with increasing adipose mass. When we evaluated trunk adipose mass as a marker of central obesity, we found that blood adiponectin was negatively associated, whereas blood leptin was positively associated with trunk adipose mass (Table 3). In these models, T2DM status was positively associated with trunk adipose mass. Leptin was also positively associated with both inflammatory markers that we measured (eg, IL-6 and CRP) in our postmenopausal women (Table 4), which is consistent with what is reported by others. Adiponectin was negatively associated with IL-6, while there was a marginal negative association between adiponectin and CRP (Table 4). These findings are similar to previous studies. However, some studies evaluating postmenopausal women did not find a relationship between adiponectin and IL-6 or CRP. Our findings provide more evidence of a positive relationship between lepentin inflammatory markers, and the relationship between leptin and inflammatory markers.

This study has a few limitations. First, this is a cross-sectional study looking at associations between measurements, so no causations can be inferred from these data. It is unclear how estrogen deficiency in postmenopausal women impacts blood adiponectin and leptin concentrations. Previous prospective studies evaluating the menopause transition in women (eg, pre vs postmenopause) have found conflicting results regarding the effect of menopause on these adipocytokines. While one study found increased blood adiponectin after women reached postmenopause, two studies found no differences between pre versus postmenopausal measurements. With regards to leptin, Lee et al. found no differences in blood leptin after postmenopause, whereas two studies found significantly increased leptin in postmenopause versus premenopause; however, this difference is likely related to adipose mass gain, not menopause per se. A future study should prospectively evaluate the congruent measurement of changes in blood

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Cytokine</th>
<th>n</th>
<th>Correlation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>IL-6</td>
<td>81</td>
<td>-0.37</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>91</td>
<td>-0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>Leptin</td>
<td>CRP</td>
<td>93</td>
<td>0.28</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Cytokines were natural log-transformed for calculating correlations. P values from linear mixed models with a random effect for study (outcome = adipokine, predictor = cytokine). Bolded values indicate statistical significance at P < 0.05.

CRP, C-reactive protein; IL-6, interleukin-6.
adiponectin and leptin levels, and changes in lean and adipose mass over time. Second, small cohort sizes may contribute to a type II error which may obscure significant relationships between adipokines and body composition. Third, total adiponectin, but not high-molecular-weight (HMW) adiponectin was measured. HMW adiponectin constitutes less than 1% of total adiponectin levels and has stronger affinity to AdipoR1, the prominent adiponectin receptor in skeletal muscle compared with medium or low molecular weight adiponectin forms. Measuring HMW adiponectin may be more relevant to biological activities for adiponectin if adiponectin changes are causally related to changes in \( \text{ALM}_{\text{BMI}} \).

CONCLUSIONS

In this study, we evaluated several relationships between adiponectin, leptin, T2DM status, and body composition (e.g., lean body and adipose mass) in postmenopausal women. We observed that T2DM status moderated the relationship between blood adiponectin and \( \text{ALM}_{\text{BMI}} \), where adiponectin was positively associated with \( \text{ALM}_{\text{BMI}} \) in postmenopausal women without T2DM, but not in those with T2DM. On the contrary, blood leptin and T2DM were negatively associated with \( \text{ALM}_{\text{BMI}} \) in postmenopausal women. In regard to trunk adipose mass, adiponectin was negatively associated, whereas leptin and T2DM status were both positively associated with trunk adipose mass. These findings provide evidence that blood levels of adiponectin and leptin may be useful biomarkers of health status in postmenopausal women with or without diabetes. Future studies will need to identify causal associations between adipokines and body composition so that mechanistic targets may be used to improve therapies to manage dysregulated metabolism and comorbidities.

REFERENCES