Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables

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Submitted 14 November 2006; accepted in final form 1 March 2007

Jürimäe J, Jürimäe T. Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables. *Am J Physiol Endocrinol Metab* 293: E42–E47, 2007. First published March 6, 2007; doi:10.1152/ajpendo.00610.2006.—The aim of the current investigation was to determine the possible relationships of fasting adiponectin level with body composition, bone mineral, insulin sensitivity, leptin, and cardiorespiratory fitness parameters in 153 women. Subjects were classified as premenopausal (*n* = 42; 40.8 ± 5.7 yr) if they had regular menstrual periods, early postmenopausal (*n* = 49; 56.7 ± 3.6 yr) if they had been postmenopausal for more than >1 yr but < 7 yr (5.5 ± 1.3 yr), and postmenopausal (*n* = 62; 72.2 ± 4.5 yr) if they had been postmenopausal for ≥ 7 yr. All women studied had a body mass index (BMI) <30 kg/m². Adiponectin values were higher (*P* < 0.05) in middle-aged (12.0 ± 5.1 μg/ml) and older (15.3 ± 7.3 μg/ml) postmenopausal women compared with middle-aged premenopausal women (8.4 ± 3.2 μg/ml). Mean plasma adiponectin concentration in the total group of women (*n* = 153) was 12.2 ± 6.3 μg/ml and was positively related (*P* < 0.05) to age, indexes of overall obesity (BMI, body fat mass), and cardiorespiratory fitness (PWC) values. In addition, a negative association (*P* < 0.05) between adiponectin with central obesity (waist-to-hip and waist-to-thigh ratio), fat-free mass, bone mineral (bone mineral content, total and lumbar spine bone mineral density), and leptin and insulin resistance (insulin, fasting insulin resistance index) values was observed. However, multivariate regression analysis revealed that only age, fasting insulin resistance index, and leptin were independent predictors of adiponectin concentration. In conclusion, circulating adiponectin concentrations increase with age in normal-weight middle-aged and older women. It appears that adiponectin is independently related to age, leptin, and insulin resistance values in women across the age span and menopausal status.

adiponectin; leptin; age; menopausal status; insulin resistance

HUMAN ADIPOSE TISSUE has long been perceived predominantly as a storage depot for energy surplus. However, recent research in the biology of adipose tissue indicates that it is not simply an energy storage organ but also a secretory organ that synthesizes and secretes multiple cytokine proteins that modulate various biological functions (8, 15, 17). The number and range of identified adipocytokines is continuing to expand rapidly (28), but the exact role of them in the regulation of human metabolism is still unknown. These proteins include adipin, resistin, tumor necrosis factor-α (TNF-α), leptin, and adiponectin (8, 28). Adiponectin was first identified by Scherer et al. (26) and is one of the most abundant circulating adipose tissue-specific adipocytokines. Adiponectin is structurally similar to TNF-α and is produced in visceral, subcutaneous, and bone marrow fat depots (30).

Several studies have demonstrated that adiponectin increases insulin sensitivity (8, 14, 15, 30, 31) and may improve the lipid profile (6, 8, 22, 31). Circulating adiponectin concentrations are decreased in obesity, diabetes, and cardiovascular disease and increase after weight loss and negative energy balance (7, 9, 12, 24). In addition, plasma adiponectin concentrations are negatively correlated with parameters of overall obesity (4, 13, 14, 30) as well as measures of central obesity (13, 17, 22, 25). Central obesity is known to be associated with insulin resistance (1), and adiponectin may represent a link between central obesity and insulin resistance (13).

However, the entire spectrum of predictors of circulating adiponectin concentrations remains to be fully elucidated (13). For example, it has previously been proposed that age may have an influence on adiponectin concentration (4, 6, 13, 16, 29), although Ryan et al. (25) found that plasma adiponectin was not different in adult women with a wide range of age and obesity. In addition, menopause transition may have an influence on circulating adiponectin concentration (16), since menopause has been associated with a decrease in body fat-free mass (FFM) and a concomitant increase in body fat mass (FM), especially abdominal visceral adipose tissue (20). In contrast, increased body FFM in women during menopause transition has positively been linked with bone mineral density (BMD; see Ref. 17 and 23). Some of the cross-sectional studies observed no correlation between circulating adiponectin and BMD (21), whereas other studies found such a relationship (17, 23) in women at different ages. Taken together, studies that have focused on plasma adiponectin concentrations as a function of age in premenopausal and postmenopausal women have reported conflicting results.

To our knowledge, no studies have been performed to examine the possible association of several body composition, bone, cardiorespiratory fitness, and metabolic variables with adiponectin in healthy normal-weight women with wide range of ages and without a known history of diabetes or other major diseases. To date, previous studies have incorporated obese women (13, 22, 24, 25, 32), women with diabetes (12, 23, 25), and/or only middle-aged women (13, 17, 21). Accordingly, the purpose of the present investigation was to determine the possible relationships of fasting adiponectin level with body composition, bone, insulin resistance, leptin, and cardiorespiratory fitness parameters in 153 healthy normal-weight women across the adult age span and menopausal status.

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MATERIALS AND METHODS

Participants. One hundred and fifty-three women without a known history of diabetes, between the ages of 38 and 80 yr, were recruited for this study. All subjects were participating in 1-h gymnastics sessions two times a week for at least last two years. All participants signed an informed consent that was approved by the Medical Ethics Committee of the University of Tartu (Tartu, Estonia). Before study enrollment, volunteers completed a self-administered questionnaire on general health and present medications, including hormone replacement and oral contraceptive treatment. They were excluded if they reported current or previous conditions that might have interfered with bone metabolism (such as heart disease, long-term corticosteroid use, smoking, alcoholism, and long-term high levels of physical activity). None of the participants were receiving treatment such as calcium, vitamin D, calcitonin, bisphosphonates, and diuretics, which could influence BMD.

Subjects were classified as premenopausal (n = 42) if they had regular menstrual periods, early postmenopausal (n = 49) if they had been postmenopausal for >1 yr but <7 yr (5.5 ± 1.3 yr; see Refs. 17 and 20), and postmenopausal (n = 62) if they had been postmenopausal for >7 yr. All premenopausal women were not on oral contraceptives, and all postmenopausal women had gone through menopause naturally and were not on hormone replacement therapy. All women studied had a body mass index (BMI) <30 kg/m².

Study design. All women were asked to come for two visits to complete the testing. On the first visit, participants had a venous blood sample taken in the morning after an overnight fast. Anthropometric parameters were taken, and a functional test was completed 2 h after a light breakfast. In premenopausal women, the first measurement session was conducted during the early follicular phase of the menstrual cycle (17, 27). The second measurement session consisted of body composition and bone mineral assessments by dual-energy X-ray absorptiometry (DEXA). Measurement sessions were separated by ~1 wk dependent on the participant’s schedule and DEXA availability. In addition, all participants completed a 3-day energy expenditure questionnaire (5).

Body composition, bone mineral mass, and BMD. Height was measured using a Martin metal anthropometer to the nearest 0.1 cm with a standardized technique. Body mass was measured with minimal clothing to the nearest 0.05 kg using a medical electronic scale (A&D Instruments), and BMI was calculated as body mass (in kg) divided by height (in m²). Body fat distribution was defined by the waist-to-hip circumference ratio (WHR); waist circumference was divided by height (in m). Waist circumference was obtained as the minimum value between the iliac crest and the lateral costal margin, and hip circumference as the maximum area of the buttocks (17). The waist-to-thigh circumference ratio (WTR) was also calculated (19). BMI and body FM were used as markers of overall adiposity, whereas WHR and WTR were used as markers of central obesity (13).

Whole body FM, FFM, and bone mineral content (BMC) were measured by DEXA using a DXA-IQ densitometer (Lunar, Madison, WI) equipped with adult, proprietary software, version 3.6. Participants were scanned in light clothing while lying flat on their backs with arms at the sides. The fast scan mode and standard participant positioning were used for total body measurements and analyzed using the extended analysis option. BMC was determined as the total body BMD and at the site of posterior-anterior spine (L2–L4; see Refs. 17 and 23).

Cardiorespiratory fitness. Physical working capacity (PWC) was determined on a cycle ergometer (Tunturi T8) using three progressive workloads at the intensities of 50, 100, and 150 watts for a period of 6 min at each level (17, 18). Heart rate at the end of each workload was measured using a Polar Vantage NV (Kempele) heart rate monitor. Individual PWC was calculated at the level of predicted maximal heart rate (205 – ½ age) by extrapolation (17, 18).

Blood analysis. A 10-ml blood sample was obtained from the antecubital vein with the participant in the upright position in the morning (7:00–8:00 A.M.) after an overnight fast. The plasma was separated and frozen at −20°C for later analysis. Adiponectin was assessed in duplicate using a commercially available RIA kit (catalog no. HADP-61HK; Linco Research). This assay has intra- and interassay coefficients of variation (CVs) of <7%. Leptin concentrations were also measured in duplicate by RIA (Mediagnost, Germany). This assay has intra- and interassay CVs of <5%. Insulin was determined on an Immulite 2000 (DPC, Los Angeles, CA). The intra- and interassay CVs for insulin were 4.5 and 12.2% at an insulin concentration of 6.6 μIU/ml. Glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase method with a commercial kit (Boehringer, Mannheim, Germany), and insulin resistance was calculated using the fasting insulin resistance index (FIRI): [fasting glucose (mmol/l) × fasting insulin (μIU/ml)]/25 (11).

Statistical analysis. Statistical analysis was performed with SPSS 11.0 for Windows (Chicago, IL), and means and SDs were determined. An α value < 0.05 was considered statistically significant for all analyses. Adiponectin and leptin concentrations were log-transformed to normalize distribution (27). One-way ANOVA and an unpaired, two-tailed t-test were used to assess differences between groups. Associations are given as Spearman’s rank correlation coefficients. Bivariate and multivariate regression analyses were performed to evaluate potential associations of adiponectin with body composition, bone mineral, cardiorespiratory fitness, and metabolic variables. These analyses were controlled for potential confounding variables such as age, menopausal status, body FM, WHR, FIRI, and PWC (i.e., see Ref. 13). The sample size of 153 subjects provides >80% power to detect a correlation coefficient r of at least 0.21 at the conventional level of statistical significance of α = 0.05.

RESULTS

Mean ± SD values of the measured characteristics for the study population are presented in Table 1. There were 42 premenopausal women ranging in age from 38 to 52 yr (40.8 ± 5.7 yr); 49 postmenopausal women ranging in age from 45 to 62 yr (56.7 ± 3.6 yr), who had been postmenopausal for >1 yr and <7 yr (5.5 ± 1.3 yr); and 62 postmenopausal women ranging in age from 63 to 80 yr (72.2 ± 4.5 yr), who had been postmenopausal for a mean of 23.4 ± 4.2 yr (range 15–33 yr). Significant differences (P < 0.05) in age were observed between groups. In addition, significant differences in height, body mass, BMI, WHR, %FM, FM, FFM, mean daily energy expenditure, and adiponectin values were observed between premenopausal and postmenopausal women. However, total BMD was significantly lower in postmenopausal women compared with premenopausal women. No differences in these values were observed between women in two postmenopausal groups. BMC and lumbar spine BMD values were significantly lower in different groups of women with increasing age. PWC values were not different between middle-aged premenopausal and postmenopausal (<7 yr) women and were significantly higher compared with the older postmenopausal (≥7 yr) women. Leptin, insulin, glucose, and FIRI were not significantly different between different groups of women.

Mean plasma adiponectin concentration in the total group of women (n = 153) was 12.2 ± 6.3 μg/ml and was significantly related (P < 0.05) to age (r = 0.48; Fig. 1A). WHR (r = −0.26), FM (r = 0.25; Fig. 1B), FFM (r = −0.23), BMC (r = −0.25), total BMD (r = −0.26), lumbar spine BMD (r = −0.31; Fig. 1C), and PWC (r = 0.21) values. We then tested if the relationship between adiponectin and measured variables
was the same across the different age groups. A negative relationship of adiponectin with WHR (r greater than −0.42; P < 0.05) and leptin (r greater than −0.37; P < 0.05) was found in both postmenopausal groups, whereas no relationship in these parameters was found in premenopausal women (r less than −0.19; P > 0.05). All other correlations between adiponectin and measured parameters in different age groups of women were not significant (r < 0.20; P > 0.05). In addition, leptin was significantly related to body mass, BMI, %FM, and FM values in different age groups (r > 0.27; P < 0.05) and the total group (r > 0.32; P < 0.05) of studied women.

A strong association of plasma adiponectin with age was found (β = 0.916; P < 0.0001), which remained significant after controlling for menopausal status (P = 0.001), menopausal status, and FM (P = 0.004) as well as for WHR (P = 0.020), FIRI (P = 0.0001), or PWC (P = 0.048) values. A significant relationship of adiponectin with menopausal status was observed (β = 0.911; P < 0.0001). However, the association of adiponectin with menopausal status did not remain significant after controlling for age (P = 0.151), age and FM as well as for WHR, FIRI, or PWC values (P > 0.210). In addition, a strong association between plasma adiponectin concentration and parameters of central obesity (WHR, WTR), overall obesity (BMI, FM), bone mineral (BMI, total BMD, lumbar spine BMD), cardiorespiratory fitness (PWC), leptin and insulin resistance (insulin, FIRI) was found (Table 2). The association of adiponectin with WHR, WTR, BMC, total BMD, lumbar spine BMD, leptin, and FIRI remained significant after accounting for age and menopausal status separately. In addition, the association of adiponectin with BMI, FFM, BMC, total BMD, lumbar spine BMD, and PWC remained significant after controlling for menopausal status. However, the association between adiponectin with central and overall obesity indexes and cardiorespiratory fitness parameters did not remain significant after controlling for age. The association of adiponectin with parameters of central and overall obesity, FFM, and PWC did not remain significant after controlling for age and menopausal status, as well as for FM, WHR, FIRI, or PWC values. The negative associations between adiponectin with bone mineral values (BMC, total BMD, and lumbar spine BMD) remained significant after adjusting for age, menopausal status, and WHR or PWC but not when controlling for FM, WHR, and FIRI. In addition, a negative relationship of adiponectin with leptin and FIRI values was found, and these relationships remained significant after controlling for age and menopausal status, as well as for FM, WHR, FIRI, or PWC values (Table 2).

**DISCUSSION**

The results of our study demonstrate that age influences plasma adiponectin concentration in healthy normal-weight physically active women. Plasma adiponectin levels were significantly higher in postmenopausal middle-aged and older women compared with middle-aged premenopausal women. Indexes of overall (BMI, FM) and central (WHR, WTR) obesity, FFM, bone mineral (BMI, total BMD, and lumbar spine BMD), insulin resistance (insulin, FIRI), cardiorespiratory fitness (PWC), and leptin were associated with plasma adiponectin concentration in the total group of healthy women. However, multivariate analysis revealed that only age, FIRI, and leptin were significant independent predictors of adiponectin concentration. To our knowledge, this is the first complex study to investigate the possible influence of different body composition, bone mineral, insulin resistance, and cardiovascular fitness parameters on circulating adiponectin concentration in a large group of healthy normal-weight middle-aged and older adults.

The results of the present investigation demonstrated that adiponectin concentration was positively related to age in our subjects (see Fig. 1A). This is in accordance with the study by Gavrila et al. (13) with 121 middle-aged premenopausal and postmenopausal women (49.4 ± 9.2 yrs; BMI: 30.9 ± 5.5 kg/m2) and in contrast to the study by Ryan et al. (25) in 148 women.
women aged 18–81 yr (50 ± 1 yr) with a BMI range of 17.2–44.3 kg/m². It has previously been suggested that the significant association of adiponectin with age is the result of changes in body composition (6, 13). When our women were divided into three age groups, it appeared that the middle-aged premenopausal women (40.8 ± 5.7 yr) had the lowest adiponectin levels and the older postmenopausal women (72.2 ± 4.5 yr) had the highest adiponectin levels, but the differences in adiponectin concentration across the age were significant only between premenopausal and postmenopausal women. Adiponectin concentrations in middle-aged (56.7 ± 3.6 yr) and older postmenopausal women were not significantly different, demonstrating that menopausal status had a major influence on adiponectin concentration in healthy normal-weight women. Similar to our results, Gavrila et al. (13) found significantly higher adiponectin values in postmenopausal women compared with premenopausal women, whereas Ryan et al. (25) found no differences in adiponectin concentration between young (<40 yr), middle-aged (40–59 yr), and older (≥60 yr) women.

In addition, no differences in overall and central obesity indexes or FFM were observed between two groups of our postmenopausal women, whereas premenopausal women were significantly leaner and had less fat. Accordingly, menopausal status in addition to age appears to have a significant influence on adiponectin concentration and body composition values.

Several studies have found an inverse association between adiponectin concentration and different markers of central obesity (WHR, WTR; see Refs. 6, 17, 22, 25, 29) in women at different ages, health status, and body composition. The results of the present study confirm the established relationship between plasma adiponectin levels and different markers of central obesity (see Fig. 1B and Table 2). Interestingly, Yang et al. (32) reported an inverse association between adiponectin concentration and WHR in morbidly obese patients but not in overweight and moderately obese patients. In addition, current studies have also demonstrated that women after menopause have higher circulating levels of insulin and a greater propensity to store fat with increasing age (13, 20, 25), whereas insulin resistance (insulin, glucose, FIRI), overall (BMI, FM, %FM) and central (WHR, WTR) obesity values were not different in our middle-aged and older postmenopausal women (see Table 1). However, postmenopausal middle-aged (12.0 ± 5.1 µg/ml) and older (15.3 ± 7.3 µg/ml) women had significantly higher circulating adiponectin values compared with middle-aged premenopausal women (8.4 ± 3.2 µg/ml). This would imply that women with lower adiponectin values should also have higher body FM values (13, 14, 30), which was not the case in our study. These results could be explained by the fact that, since insulin sensitivity was not different between the specific groups of studied women (see Table 1), circulating adiponectin concentration was not decreased or, alternatively, the lack of a decrease in adiponectin concentration does not change insulin sensitivity.

Very few studies have examined the association between plasma adiponectin concentration and bone mineral values in women (17, 21). Jürimäe et al. (17) found an inverse association between adiponectin and measured BMDs, whereas Kontogianni et al. (21) failed to find such a relationship in perimenopausal women. It was argued that women in our previous study probably had more fat stored in the visceral abdominal area (17) compared with the women in Kontogianni et al. (21)
study. To our knowledge, this is the first study that demonstrates the association between adiponectin and bone mineral values in postmenopausal women (see Fig. 1C). However, the relationship between adiponectin concentration and measured bone mineral values was controlled by total FM and insulin resistance in addition to age and menopausal status (see Table 2). This is in accordance with the study by Berner et al. (3), who reported a link between adiponectin and bone homeostasis by demonstrating transcription, translation, and secretion of adiponectin as well as expression of its receptors, AdipoR1 and AdipoR2, in bone-forming cells. In another study, Berg et al. (2) demonstrated that adiponectin therapy in mice resulted in a decreased hepatic gluconeogenesis and muscle triglyceride content, suggesting that adiponectin carries signals from adipose tissue to muscle and liver. Taken together, the results of the present study suggest that adiponectin may also carry signals from adipose tissue to bone, since adiponectin had a negative association with bone mineral values in our healthy normal-weight middle-aged and older women.

In the current study, adiponectin concentration was negatively and independently related to plasma leptin levels, which is similar to other studies with women at different ages (6, 24, 25) and in contrast to the study by Gavrila et al. (13) in middle-aged premenopausal and postmenopausal women with a wide range of BMI values. Gavrila et al. (13) suggested that adiponectin and leptin may represent two different and independent pathways that control insulin sensitivity. However, the different results of the present study with a relatively homogeneous group of middle-aged and older women (BMI <30 kg/m²) and that of Gavrila et al. (13) could be explained by the differences in overall adiposity values and/or fat distribution characteristics.

In our study sample, plasma adiponectin concentration was also negatively and independently related to insulin resistance (FIRI) in healthy normal-weight middle-aged and older women. Many studies have reported significant negative associations between fasting adiponectin concentration and different markers of insulin resistance in obese subjects and subjects with type 2 diabetes (12, 14, 22, 30), whereas other recent studies with healthy normal-weight premenopausal women have found no relationship of fasting adiponectin concentration with insulin, glucose, or calculated FIRI (10). At present, the exact mechanism by which higher adiponectin levels may improve insulin sensitivity at the cellular level are poorly understood (8, 15), and further longitudinal studies are needed to investigate the effect of adiponectin on insulin sensitivity.

In accordance with previous investigations (17, 25), adiponectin demonstrated a significant association with the measured cardiorespiratory fitness parameter, whereas leptin was not related to PWC value in middle-aged and older women. In contrast, Ferguson et al. (10) found no relationship between adiponectin concentration and indexes of cardiorespiratory fitness in young women. Thus the results of our study suggest that, in addition to body compositional and bone mineral parameters, superior PWC, another important cardiovascular disease risk-reducing factor (18), increases adiponectin concentration in healthy normal-weight middle-aged and older women. In accordance with these results, Hulver et al. (15) suggested that adiponectin serves as a protective mechanism against the development of cardiovascular diseases. In summary, our data demonstrate that plasma adiponectin concentrations increase with age in healthy normal-weight middle-aged and older women. There is a complex interaction between specific body composition, bone mineral, cardiorespiratory fitness, and metabolic variables with adiponectin concentration in a relatively homogeneous group of healthy middle-aged and older women. Elucidation of the full spectrum of determinants of circulating adiponectin should be the focus of future studies, since it may have major physiological importance (13). It appears that adiponectin is independently related to age, leptin, and insulin resistance values across the age span and menopausal status. However, the cross-sectional nature of our study limits determinations of temporality or causality. Therefore, further interventional studies are necessary to evaluate the relationship of plasma adiponectin with specific body composition, bone mineral, and insulin resistance values.

**GRANTS**

This study was funded by Estonian Science Foundation Grant 6638.
REFERENCES


