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Plasma adiponectin and insulin sensitivity in overweight and normal-weight middle-aged premenopausal women

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Abstract

Adiponectin has been reported to regulate systemic insulin sensitivity as a part of a broader control mechanism in energy balance. However, it is not clear whether adiponectin exerts its positive effects on insulin sensitivity equally in a wide range of obesity. We investigated the association of plasma adiponectin concentration with insulin resistance (IR) in a cross-sectional sample of 98 middle-aged premenopausal women with a wide range of obesity. In addition, we studied the relationship between adiponectin, body composition, and blood biochemical and cardiorespiratory fitness variables. Body composition and fat distribution were measured via dual-energy x-ray absorptiometry in normal-weight (NW) (n = 41, body mass index [BMI] <25 kg/m^2) and overweight (OW) (n = 57, BMI ≥25 kg/m^2) women. Fasting blood samples were obtained; adiponectin, leptin, insulin, glucose, and insulin-like growth factor–I were measured; and IR index was calculated. The IR index from fasting plasma insulin and plasma glucose levels was estimated using the homeostasis model assessment (HOMA), as follows: fasting plasma insulin (in microliter units per milliliter) × fasting plasma glucose (in millimoles per liter)/22.5. Adiponectin was significantly higher ($P = .0001$) in NW (14.7 ± 4.7 μg/mL) compared with OW (9.9 ± 3.1 μg/mL) women. Significant differences ($P < .003$) in body mass, BMI, percentage of fat mass, fat mass, trunk fat, trunk fat–leg fat ratio, leptin, insulin, and HOMA were also observed between NW and OW groups. Leptin was independently related to plasma adiponectin ($\beta = -.259$, $P = .001$) in the overall study group. Plasma adiponectin was only related to trunk fat–leg fat ratio ($\beta = -.242$, $P = .002$) among NW subjects, whereas plasma adiponectin was related to fat-free mass ($\beta = .182$, $P = .0001$) and HOMA ($\beta = -.576$, $P = .002$) among OW women. The inverse relationship between adiponectin and leptin concentrations suggests that leptin may be involved in the regulation of adiponectin in middle-aged premenopausal women. Our data also demonstrate that adiponectin may play an important role in sustaining insulin sensitivity only in OW middle-aged premenopausal women.

1. Introduction

Obesity is frequently associated with insulin resistance and abnormalities in glucose metabolism [1]. The pathophysiology linking obesity to type 2 diabetes mellitus is not well understood, but different adipocytokines are thought to be involved [2]. Adipocytokines are well known to substantially affect glucose and fat metabolism as well as energy homeostasis [3]. Adiponectin is a recently discovered adipocytokine that seems to be exclusively secreted by adipocytes and is the most abundant adipose tissue–derived protein [4]. Unlike other adipocytokines (eg, leptin, interleukin 6, resistin), adiponectin levels decrease with increased adipose tissue [5,6]. Lower circulating adiponectin concentrations relative to the normal controls have been observed in human subjects with obesity, type 2 diabetes mellitus, or cardiovascular disease in several studies [7-10]. Central obesity and visceral fat are known to be more associated with insulin resistance than subcutaneous or total fat [11], and it has been suggested that adiponectin may represent a link between central obesity and insulin resistance [12].

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Results from previous investigations suggest that high plasma adiponectin concentrations predict a lower incidence rate of type 2 diabetes mellitus [2,13,14], whereas low plasma adiponectin concentrations precede a decrease in insulin sensitivity and predict type 2 diabetes mellitus independently of obesity [2,15]. It is not entirely clear whether adiponectin is associated with insulin sensitivity equally in women with a wide range of obesity [2,13]. Kantartzis et al [13] found that plasma adiponectin concentration predicted insulin sensitivity in obese but not in lean women with a wide range of ages. To our knowledge, no studies have been performed to investigate the association between adiponectin and insulin sensitivity in a specific group of middle-aged premenopausal women of varying levels of adiposity. The spectrum of predictors of adiponectin levels remains to be fully elucidated in middle-aged women [12,16]. A physiologically significant relationship may exist between leptin and adiponectin, as these 2 hormones have additive effects in normalizing insulin sensitivity in animals [17]. However, conflicting results on the association between leptin and adiponectin have been reported in women [5,9,12,17].

The aim of the present investigation was to study possible differences in plasma adiponectin concentration associated with insulin sensitivity in overweight (OW) and normal-weight (NW) middle-aged premenopausal women. This study also explores the possible relationship of fasting plasma adiponectin level with various body composition, blood biochemical, and cardiorespiratory fitness variables in a group of women with a wide range of adiposity values and without a known history of diabetes.

2. Materials and methods

Ninety-eight middle-aged premenopausal women with a mean age 45.2 ± 4.3 years (range, 38-49 years) and body mass index (BMI) of 29.9 ± 6.2 kg/m^2 (range, 20.0-42.1 kg/m^2) volunteered to participate in the study. Subjects were divided according to the World Health Organization criterion into NW (n = 41) and OW (n = 57) groups based on whether their BMI was lower or higher than 25 kg/m^2, respectively. All subjects signed an informed consent that was approved by the Medical Ethics Committee of the University of Tartu, Tartu, Estonia. Before study enrollment, volunteers completed medical and physical activity questionnaires. They were excluded from the study if they reported current or previous (within 6 months) use of oral contraceptives, cortisone, antiepileptic drugs, cholesterol-lowering drugs, or binders; history of renal, gastrointestinal, or liver disease; alcohol intake/ethanol of more than 2 drinks per day; smoking; obesity secondary to endocrine disease; and participation in any regularly scheduled physical exercise.

All women were asked to come for 2 visits to complete the testing. On the first visit, we collected venous blood samples after a 10-hour fast. Anthropometric variables were determined and a functional performance test was completed 2 hours after a light breakfast [16,18]. The first measurement session was conducted during the early follicular phase of the menstrual cycle [16,18,19]. The second measurement session consisted of body composition assessment by dual-energy x-ray absorptiometry (DXA). The first and second measurement sessions were separated by approximately 1 week, which was dependent on the subject's schedule and DXA availability. In addition, the daily energy expenditure was calculated according to the method of Bouchard et al [20]. Briefly, a day is divided into 96 periods of 15 minutes each; and the subject had to fill each period with an activity intensity scale from 1 to 9. The scale and corresponding example activities were explained to the subjects before they filled out the response questionnaire instrument.

Height was measured using a Martin metal anthropometer to the nearest 0.1 cm using standard measurement techniques. Body mass was measured with minimal clothing to the nearest 0.05 kg using a medical electronic scale (A&D Instruments, Abingdon, United Kingdom), and BMI was calculated as body mass (in kilograms) divided by height (in square meters). Whole-body fat mass (FM) and fat-free mass (FFM) were measured via DXA using the DPX-IQ densitometer (Lunar, Madison, WI) equipped with adult, proprietary software, version 3.6. Participants were scanned in light clothing while lying supine with their arms at the sides. The standard participant positioning was used for total body measurements and analyzed using the extended analysis option. The standard manufacturer's skeletal landmarks were used to define trunk and leg fat. Body fat distribution was calculated as the ratio of trunk fat (in kilograms) to leg fat (in kilograms) [16,21,22].

Physical working capacity (PWC) was determined on a cycle ergometer (Tunturi T8, Turku, Finland) using 3 progressive workloads at intensities of 50, 100, and 150 W for a period of 6 minutes per increment [16,18,23]. Heart rate at the end of each workload was recorded using a Polar Vantage NV (Kempele, Finland) heart rate monitor. Individual PWC was calculated at the level of predicted maximal heart rate (205 − [age/2]) by extrapolation [16,18,23].

A 10-mL blood sample was obtained from the antecubital vein with the participant in the upright position in the morning (7:00 AM to 8:00 AM) after an overnight fast. The plasma was separated and frozen at −20°C for subsequent analysis. Adiponectin was assessed in duplicate using a commercially available radioimmunoassay kit (catalog no. HADP-61HK; Linco Research, St. Charles, MO). This assay has intra- and interassay coefficient of variation (CV) of less than 7%. Leptin concentrations were also measured in duplicate by a radioimmunoassay (Mediagnost, Reutlingen, Germany). This assay has intra- and interassay CV of less than 5%. The concentrations of insulin and insulin-like growth factor–I (IGF-I) were determined in duplicate on an Immulite 2000 (DPC, Los Angeles, CA). The intra- and interassay CVs were 4.5% and 12.2%, respectively, for

insulin at an insulin concentration of 6.6 μL U/mL and less than 7% for IGF-I . Glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase method with a commercial kit (Boehringer, Mannheim, Germany). The insulin resistance index from fasting plasma insulin and plasma glucose levels was estimated using the homeostasis model assessment (HOMA), as follows: fasting plasma insulin (in microliter units per milliliter) × fasting plasma glucose (in millimoles per liter)/22.5 [24]. The greater the HOMA value was, the greater was the level of insulin resistance.

Statistical analysis was performed with SPSS (Chicago, IL) 11.0 for Windows, and means and standard deviations were calculated. Adiponectin and leptin concentrations were log-transformed to normalize the distribution. An unpaired, independent 2-tailed *t* test was used to assess differences between groups. Association of plasma adiponectin concentration with other measured variables was assessed by Pearson correlations and partial correlation coefficient analyses. Multiple linear regression analysis was performed using plasma adiponectin concentration as the dependent variable and using BMI, FM, trunk fat, trunk fat–leg fat ratio, FFM, PWC, leptin, IGF-I, insulin, glucose, and HOMA as independent variables. A *P* value of less than .003 represented statistical significance after adjusting for multiple analysis.

3. Results

The mean (±SD), minimum, and maximum values of measured characteristics for study population are presented in Table 1. There were 41 NW middle-aged premenopausal women with BMI less than 25 kg/m^2 and 57 OW middle-aged premenopausal women with BMI of at least 25 kg/m^2. Significantly higher ($P < .003$) values for body mass, BMI, percentage FM (%FM), FM, trunk fat, trunk fat–leg fat ratio, leptin, insulin, and HOMA were observed in OW compared with NW women. In addition, adiponectin was significantly higher ($P = .0001$) in NW (14.7 ± 4.7 μg/mL) compared with OW (9.9 ± 3.1 μg/mL) women.

There was an inverse association ($P < .003$) of plasma adiponectin concentration with body mass ($r = -0.552$), BMI ($r = -0.600$), %FM ($r = -0.525$), FM ($r = -0.558$), trunk fat ($r = -0.491$), trunk fat–leg fat ratio ($r = -0.490$), leptin ($r = -0.553$), insulin ($r = -0.397$), glucose ($r = -0.292$), and HOMA ($r = -0.407$) in the overall study group. Partial correlation analysis revealed that plasma adiponectin concentration was significantly inversely related ($P < .003$) to body mass ($r = -0.580$), BMI ($r = -0.636$), %FM ($r = -0.580$), FM ($r = -0.596$), trunk fat ($r = -0.599$), trunk fat–leg fat ratio ($r = -0.528$), leptin ($r = -0.583$), insulin ($r = -0.398$), glucose ($r = -0.305$), and HOMA ($r = -0.411$) values after controlling for age. However, when adjusting for age and BMI, plasma adiponectin concentration was only related to plasma leptin level ($r = -0.293$, $P < .003$).

Using multiple linear regression analysis, leptin ($\beta = -.259$, $P = .001$) was significantly related to plasma adiponectin in the overall study group. The plasma adiponectin concentration was related to trunk fat–leg fat ratio ($\beta = -.242$, $P = .002$) among NW subjects, whereas adiponectin was related to FFM ($\beta = .182$, $P = .0001$) and HOMA ($\beta = -.576$, $P = .002$) among OW women in the regression analysis.

4. Discussion

In the present study, we investigated whether plasma adiponectin concentration is equally associated with insulin

Table 1
Subject characteristics of study population

Parameters	NW (n = 41)	OW (n = 57)	Total (N = 98)	Range
Age (y)	44.5 ± 4.9	45.7 ± 3.9	45.2 ± 4.3	38-49
Height (cm)	162.9 ± 5.0	159.9 ± 6.0	161.2 ± 5.8	150.0-172.9
Body mass (kg)	65.1 ± 8.1	87.8 ± 11.7*	78.1 ± 15.2	52.5-116.6
BMI (kg/m^2)	22.9 ± 2.4	34.4 ± 4.0*	29.9 ± 6.2	20.0-42.1
%FM	30.1 ± 8.1	43.5 ± 4.5*	37.8 ± 9.1	10.9-51.8
FM (kg)	19.1 ± 6.7	36.3 ± 6.7*	28.9 ± 10.9	5.4-47.7
Trunk fat (kg)	8.2 ± 2.9	16.7 ± 3.1*	13.0 ± 5.2	2.35-21.79
Trunk fat–leg fat ratio	1.19 ± 0.33	1.62 ± 0.21*	1.44 ± 0.34	0.71-2.06
FFM (kg)	44.1 ± 5.0	45.6 ± 4.1	45.0 ± 4.6	35.6-59.5
PWC (W)	163.3 ± 48.2	141.4 ± 41.8	150.7 ± 45.8	83.0-352.0
Daily energy expenditure (kcal)	1806.8 ± 354.3	1989.6 ± 366.6	1911.2 ± 329.9	1317.5-3041.5
Adiponectin (μg/mL)	14.7 ± 4.7	9.9 ± 3.1*	12.0 ± 4.7	4.2-32.7
Leptin (ng/mL)	10.5 ± 5.9	17.6 ± 4.3*	14.6 ± 6.2	1.9-31.3
IGF-I (ng/mL)	174.2 ± 69.8	143.7 ± 31.7	156.8 ± 53.5	68.5-365.3
Insulin (μL U/mL)	6.0 ± 2.9	9.6 ± 5.8*	8.1 ± 5.1	2.0-24.6
Glucose (mmol/L)	5.0 ± 0.9	5.6 ± 1.1	5.3 ± 1.1	4.1-8.2
HOMA	1.29 ± 0.72	2.45 ± 1.69*	1.96 ± 1.47	0.19-7.18

Values are mean ± SD.

* Significantly different from NW women; $P < .001$.

sensitivity in a specific age group in NW and OW middle-aged premenopausal women. The results of our investigation indicated that lower adiponectin concentration had an independent association with higher HOMA value in OW women only, whereas no relationship between adiponectin and HOMA value was detected in NW women. To our knowledge, this may be the first study reporting the relationship between plasma adiponectin concentration and insulin resistance that depends on the BMI level in a specific group of middle-aged premenopausal women. To date, similar results have been found in a group of men and women of wide range of age [5,13,16] and older men and women [2]. The results of the present study demonstrate an independent association between adiponectin and leptin concentration, suggesting that leptin may act in the regulation of adiponectin in this study population.

The main finding of the present investigation was that an independent association between circulating adiponectin concentration and insulin sensitivity was observed only in OW (BMI $\geq$25.0 kg/m^2) but not in NW (BMI <25.0 kg/m^2) middle-aged premenopausal women. In addition, OW women presented significantly lower values for adiponectin (9.9 ± 3.1 vs 14.7 ± 4.7 μg/mL) and higher values for HOMA (2.45 ± 1.69 vs 1.29 ± 0.72) compared with NW women. These results reveal that adiponectin is a unique adipocytokine in that its plasma concentration is markedly decreased in OW subjects [7-10], and this may contribute to an increase in insulin resistance. This association has also been demonstrated in many different populations, independently of overall adiposity variables (ie, BMI, FM), in study groups including NW and obese subjects with a wide range of ages [2,5,10,25]. It has been suggested that obesity-associated insulin resistance may represent a mechanism to counteract further expansion of adipose tissue and therefore limit obesity, despite the drawback of an increased risk of developing type 2 diabetes mellitus [26,27]. Hulver et al [28] suggested that adiponectin may improve insulin sensitivity by inhibiting the detrimental effects of tumor necrosis factor–α (TNFα) on insulin action. Specifically, adiponectin serves as a protective mechanism against the development of coronary artery disease [28], as TNFα-induced expression of endothelial molecules is inhibited by adiponectin [29]. Accordingly, the negative association between plasma adiponectin concentration and insulin resistance may be a result of decreased insulin sensitivity due to TNFα-induced defects in insulin signaling [28]. However, further investigations are required to study the effect of adiponectin on TNFα signaling and insulin sensitivity before any conclusions can be drawn.

In addition to confirming the association between plasma adiponectin concentration and different markers of overall adiposity (BMI, FM, %FM) [6,12] in middle-aged premenopausal women, measured central adiposity values (trunk fat, trunk fat–leg fat ratio) were also related to plasma adiponectin levels as reported in other studies [5,16,18,30]. These relationships were similar for measured overall and central obesity indices in the entire group of studied women, whereas other studies have indicated that central fat distribution is a better determinant of circulating adiponectin than total FM in heterogeneous groups of middle-aged women [5,12]. An interesting finding of the present investigation was that a significant association of plasma adiponectin concentration with central adiposity index was observed only in NW women. Trunk fat–leg fat ratio was an independent variable (β = −.242, P = .002) characterizing plasma adiponectin level in NW but not in OW women. These results suggest that the relationship between plasma adiponectin concentration and different adiposity values may depend on the degree of adiposity in middle-aged premenopausal women. This also implies that factors other than body adipose tissue may predominate in modulating the plasma adiponectin levels. It is interesting to note that FFM appears to be an independent variable (β = .182, P = .0001) characterizing plasma adiponectin concentration in OW women only. Accordingly, it may be postulated that FFM modulates circulating adiponectin concentrations only in middle-aged women who have experienced significant alterations in energy homeostasis. However, further studies are needed before any conclusions may be drawn.

Studies investigating whether adiponectin is secreted from visceral compared with subcutaneous adipose tissue have reported conflicting results [30,31]. However, it has been suggested that visceral fat tissue has a major role in reducing adiponectin concentration [27]. In contrast to adiponectin concentration, plasma leptin levels have been found to be positively and strongly associated with total and subcutaneous adipose tissue but less strongly with visceral fat tissue [18,30]. Another finding of the present study was an independent association between plasma adiponectin and leptin levels in the entire group of women. This association remained significant after controlling for age and BMI (r = −0.293, P < .003). According to our results, leptin is a negative predictor of circulating adiponectin levels independent of body composition variables in women of different ages and obesity levels [5,30]. In contrast, Gavrila et al [12] suggested that adiponectin and leptin may represent 2 different and independent pathways that control insulin sensitivity, as they did not find any relationship between adiponectin and leptin levels in middle-aged premenopausal and postmenopausal women. However, it has been proposed that adipocyte-generated endocrine signals, such as leptin and adiponectin, control systemic insulin sensitivity as a part of a broader control mechanism in energy balance [32]. Insulin may provide a mechanism by which adipose tissue detects changes in energy balance and, in turn, up-regulates or down-regulates *ob* gene expression accordingly [19]. This regulation occurs through endocrine feedback loop, in which pancreatic β-cell–derived hormone insulin and the adipocyte-derived hormone leptin signal the status of body energy stores to the hypothalamus [33]. Leptin and insulin depress the activity of excitatory neurons in the lateral

hypothalamus and affect energy expenditure, body mass control, and sympathetic activity [32,34]. Similar to the results of the present investigation, Huypens [32] suggested that adiponectin production is controlled in part by the hypothalamic actions of leptin.

In conclusion, these data support the hypothesis that adiponectin may play an important role in sustaining insulin sensitivity in OW middle-aged premenopausal women. The association of plasma adiponectin concentration with insulin sensitivity was found only in OW but not in NW middle-aged premenopausal women. However, further studies are required to fully elucidate the exact role of adiponectin in the pathogenesis of insulin-resistant states in this population of women with varying levels of adiposity. Furthermore, the adiposity level could be defined by more specific adiposity markers than BMI that was used in the present study. This is important because it may signify an inverse relationship between plasma adiponectin and leptin concentrations in middle-aged premenopausal women.

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