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Effects of menopausal status on circulating calcitonin gene-related peptide and adipokines: implications for insulin resistance and cardiovascular risks

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Key words: CALCITONIN GENE-RELATED PEPTIDE (CGRP), INSULIN, CARDIOVASCULAR RISK FACTORS, MENOPAUSE, LEPTIN, RESISTIN, ADIPONECTIN

ABSTRACT

Objectives To determine, first, the effects of menopausal status on circulating calcitonin gene-related peptide (CGRP) levels and, second, the correlation between circulating CGRP levels and biomarkers for cardiovascular disease.

Methods Cross-sectional study of healthy premenopausal and postmenopausal women volunteers and women admitted for elective benign abdominal surgery in a district general hospital. All women were non-smokers, had no history of endocrinological problems and were not receiving any hormone therapy. Fasting blood samples (premenopausal \( n = 45 \): follicle stimulating hormone (FSH) < 20 IU/l, estradiol (mean ± SEM) 440.33 ± 51.82 pmol/l; postmenopausal women \( n = 28 \): FSH > 20 IU/l, estradiol 93.79 ± 17.40 pmol/l) were analyzed for CGRP, resistin, leptin, adiponectin, insulin and lipids using ELISA and immunoassays.

Results Mean circulating CGRP levels were higher in the postmenopausal women compared with premenopausal women (pre: 41.79 ± 9.01 pg/ml, post: 138.14 ± 45.75 pg/ml; \( p = 0.047 \)). Among women who were experiencing hot flushes, the postmenopausal women had significantly higher CGRP levels than the premenopausal women (pre: 21.98 ± 4.95 pg/ml, post: 171.08 ± 61.80 pg/ml; \( p = 0.028 \)). Serum CGRP levels positively correlated with serum insulin levels \( (r = 0.652, p = 0.016) \) and HOMA index \( (r = 0.54, p < 0.001) \).

Conclusion These data show that circulating CGRP levels are influenced by menopausal status and suggest additional mechanisms through which increased risk of hyperinsulinemia and cardiovascular disease may arise in postmenopausal women.
INTRODUCTION

Menopausal transition is associated with increased risk of cardiovascular disease (CVD) in women\(^1\). Estrogen deficiency leads to an unfavorable lipid profile\(^2\), which until recently had been considered the main pathological phenomenon responsible for development of atherosclerosis and CHD. However, improvement in lipid profile with hormone replacement therapy (HRT) does not reduce cardiac disease events in clinical studies\(^3,4\). Furthermore, recent evidence has shown an increased risk of ischemic heart disease and stroke in HRT users, demonstrating the limited understanding of the pathogenesis of these diseases\(^5\).

Calcitonin gene-related peptide (CGRP) is a potent vasodilator and proinflammatory neuropeptide that plays an important role in maintaining microvascular homeostasis. CGRP has been linked to the development of CVD by promoting myocardial injury via its own proinflammatory properties, as well as by initiating or augmenting other endogenous inflammatory mechanisms\(^6,7\). Increased CGRP levels have been noted in subjects with hypertension and myocardial infarction\(^7,8\), but the exact mechanism for this is uncertain.

Elevated CGRP serum levels have been observed during hot flushes in postmenopausal women and in men, following castration\(^9-11\), linking acute release of CGRP with onset of vasomotor symptoms. We have recently demonstrated that CGRP is expressed in adipose tissue at mRNA and protein level and that CGRP expression is higher in adipose tissue from postmenopausal women, suggesting a potential mechanism by which adipose tissue may contribute to the increased prevalence and severity of vasomotor symptoms\(^12\). Previously, animal studies have shown higher tissue levels of CGRP in an estrogen-deficient state\(^13,14\) suggesting that secretion and activity of CGRP may be influenced by the sex hormones. However, to date, there have been no studies investigating the effect of natural menopause on serum CGRP levels and whether this is directly or indirectly associated with vasomotor symptoms and CVD risk.

Postmenopausal women have an increased tendency of visceral fat deposition, which, by virtue of its proinflammatory and prothrombotic properties, contributes to their risk of developing the metabolic syndrome and CVD\(^15\). Adipose tissue-derived proteins (adipokines), resistin, leptin and adiponectin, provide a potential link between obesity and the pathogenesis of CVD\(^15\).

Whilst studies have indicated sexual dimorphism with regard to serum levels of these adipokines\(^16,17\), reports as to the influence of menopausal status remain conflicting\(^18-20\). Murine studies have indicated resistin in obesity-associated insulin resistance and type 2 diabetes mellitus\(^21\), but current studies have been conflicting, with current suggestions highlighting a proinflammatory role in humans\(^22\). Leptin is also considered as a proinflammatory protein that may contribute to the development of CVD through adverse affects on vasculature\(^23\), by promoting arterial thrombosis\(^24\) and by stimulating production of reactive oxygen species (ROS)\(^25\). In contrast, adiponectin, the anti-inflammatory and antiatherogenic adipokine, is positively associated with increased insulin sensitivity\(^26\). Lower circulatory levels of adiponectin are associated with increased severity of CVD and can be used as a predictor for this\(^27\).

The combination of increased central obesity and chronic low-grade inflammation appears to be a mechanism for the pathogenesis of CVD\(^28\). This was supported by the results from the Women’s Health Initiative (WHI) study, demonstrating white cell count and C-reactive protein (CRP) as the strongest predictors for cardiovascular morbidity and mortality in postmenopausal women\(^29\). As such, this may have implications for postmenopausal women with an increase in CVD risk.

Therefore, the aim of this study was, first, to determine the effects of menopausal status on serum CGRP, resistin, leptin, adiponectin and anthropometric factors, through analysis of the differences in mean serum levels in premenopausal and postmenopausal women and, second, to determine the influence of CGRP on cardiovascular health in postmenopausal women, by examining the correlation between serum CGRP levels and known markers of CVD.

MATERIALS AND METHODS

Subjects

For these studies, fasting blood samples were obtained from premenopausal and postmenopausal women \((n = 73\): premenopausal 45, postmenopausal 28\). The postmenopausal status was defined as amenorrhea for more than 12 months, with serum follicular stimulating hormone (FSH) levels > 20 IU/l. Subjects with any medical condition (i.e. hypertension, CVD, thyroid disorders, renal disorders, diabetes or chronic pain conditions) were excluded from the study. None of the subjects were on endocrine therapy (i.e. HRT, tamoxifen, steroids or antiglycemic agents) or any
medication that might have influenced CGRP secretion. All samples were collected in accordance with the research protocol approved by the Solihull Local Research Ethics Committee.

**Collection of clinical data**

Anthropometric data were collected to calculate body mass index (BMI) and waist/hip ratio (WHR). Women with a BMI between 18 and 24.9 kg/m² were classified as normal, 25–29.9 kg/m² as overweight and a BMI of ≥30 kg/m² as obese. Systolic and diastolic blood pressures were recorded for each subject in the sitting position. The date of the last menstrual period, cycle length and regularity were recorded to determine the phase of the menstrual cycle in premenopausal women. Women who were within the last 2 weeks of their cycle were classified as being in the luteal phase (n = 17) and women who were in the earlier part of their cycle were classified as being in the follicular phase (n = 21). All women were asked if they were experiencing hot flushes and the average number of hot flushes experienced per week was recorded. The women experiencing hot flushes were asked to indicate the level of distress caused by hot flushes on a scale of 0–10, 0 being no distress at all and 10 being the most severe distress (10-point Likert scale). Data were analyzed as interval data.

**Collection, storage and analysis of blood samples**

Blood samples were collected after a minimum of 6 h fasting. The samples were immediately processed, the sera separated and stored at −70°C until required. All serum samples were analyzed for estradiol, FSH, glucose, insulin, total cholesterol, triglyceride, low density lipoprotein (LDL) and high density lipoprotein (HDL) and CGRP levels. Additionally, samples were analyzed for leptin (n = 56: premenopausal 31, postmenopausal 25), resistin (n = 61: premenopausal 35, postmenopausal 26) and adiponectin (n = 66: premenopausal 39, postmenopausal 27) levels.

Estradiol and FSH levels were determined using electrochemiluminescence immunoassays (Roche Diagnostics, USA) (estradiol reference range 18.4–15 781 pmol/l, coefficients of variation (CV) intra-batch 5.7%, inter-batch 6.2%; FSH reference range 0.1–200 IU/l, CVs intra-batch 2.8%, inter-batch 4.5%). The sample for serum glucose was collected into a fluoride oxalate tube and analyzed using an automated colorimetric method (Roche Diagnostics) (reference range 0.11–25 mmol/l, CVs intra-batch 0.9%, inter-batch 1.8%). Serum insulin levels were determined using a solid-phase enzyme amplified sensitivity immunoassay (Linco Research Inc. Missouri, USA) (sensitivity 2 μU/ml, range 2–200 μU/ml, CVs intra-assay 5.96%, inter-assay 10.3%). HOMA scores were calculated as fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5.

The total cholesterol, serum triglyceride and HDL levels were determined using an automated colorimetric method (Roche Diagnostics, USA) (triglyceride reference range 0.05–11.3 mmol/l, CVs intra-batch 1.5%, inter-batch 1.8%; total cholesterol reference range 0.08–20.7 mmol/l, CV intra-batch 0.8%, inter-batch 1.7%; HDL reference range 0.08–3.11 mmol/l, CVs intra-batch 0.9%, inter-batch 1.85%). The serum LDL cholesterol concentration was calculated using the Freidwald approximation: LDL cholesterol = total cholesterol - HDL cholesterol - (triglycerides/2.22) mmol/l.

The analysis for determination of CGRP (ALPCO Diagnostics, Windham, USA), estrone (ALPCO Diagnostics), leptin (LINCO Research, Missouri, USA), resistin (R&D Systems Abingdon, UK) and adiponectin (LINCO Research) was performed by solid-phase enzyme amplified sensitivity immunoassay (CGRP sensitivity 2 pg/ml, CVs intra-assay 2.7–25%, inter-assay 0.7–16.6%; estrone sensitivity 10 pg/ml, CVs intra-assay 6.7–9.1%, inter-assay 6.9–11.7%;; resistin sensitivity 0.5ng/ml, CVs intra-assay 2.6–4.6% inter-assay 2.6–6.2%; resistin sensitivity 0.026 ng/ml, CVs intra-assay 3.8–5.3%, inter-assay 7.8–9.2%.; adiponectin sensitivity 0.78 ng/ml, CV intra-assay 0.9–7.4%, inter-assay 2.4–8.4%). All samples were analyzed in duplicate and an equal number of pre- and postmenopausal samples were loaded onto each plate. Those results showing more than 10% intra-test variations were repeated.

**Statistical analysis**

Statistical analysis was performed using SPSS statistical software package 12.0.1 (SPSS Inc.). Student t tests have been performed to analyze differences in the mean between groups. A Pearson correlation coefficient was calculated for continuous variables. The data showing non-normal distribution were logged prior to calculating correlation coefficients. The significance threshold has been taken as p < 0.05. The data have been presented as mean ± standard equivalent of the mean, unless stated otherwise.
RESULTS

Baseline characteristics

Mean age, BMI, WHR, serum estradiol and FSH levels of pre- and postmenopausal groups are shown in Tables 1 and 2. As expected, the postmenopausal women were older, had lower serum estradiol levels, lower estrone levels and higher serum FSH levels. The two groups were comparable in terms of mean systolic blood pressure, diastolic blood pressure and fasting glucose and insulin levels (Table 1). There were more women in the normal-weight category in the premenopausal group. The mean BMI was comparable in the overweight and the obese categories in pre- and postmenopausal women (Table 2). Age was inversely correlated with WHR ($r = -0.236, p = 0.04$), i.e. a weak correlation was observed between central adiposity and increasing age. Age was negatively correlated with serum estradiol ($r = -0.407, p < 0.001$) and positively correlated with serum FSH levels ($r = 0.582, p < 0.001$), i.e. older women had lower estradiol and higher FSH levels.

Hot flushes

Among postmenopausal women, 60.7% reported having hot flushes, with an average distress score of 3.72, whilst 15.6% of premenopausal women reported having hot flushes with a similar distress score (3.71). All except one of the premenopausal women, who reported hot flushes, were above the age of 43 years. All premenopausal women had serum FSH < 20 IU/l (mean 6.89 ± 1.06 IU/l) and serum estradiol levels within the normal range (mean 434.29 ± 146.88 pmol/l). The postmenopausal women had a significantly higher average number of hot flushes per week (premenopausal: 1.84 ± 1.1; postmenopausal: 12.1 ± 3.3, $p = 0.006$). Analyzing the study population as a whole, the women experiencing hot flushes had higher mean BMI and WHR compared with the women who were not experiencing any hot flushes (Table 3). The mean estradiol level was lower and mean FSH level was higher in women experiencing hot flushes (Table 3). There was a positive correlation between the number of hot flushes experienced per week with the serum FSH ($r = -0.292, p = 0.013$). Similarly, a negative correlation was observed between the number of hot flushes and serum estrone levels ($r = -0.268, p = 0.022$).

Table 1  Baseline characteristics of premenopausal and postmenopausal groups of women. Results are shown as mean ± standard equivalent of the mean unless stated as standard deviations (SD). Independent Student $t$ tests were used to compare groups

<table>
<thead>
<tr>
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<th>Premenopausal (n=45)</th>
<th>Postmenopausal (n=28)</th>
<th>$p$ Value</th>
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<tr>
<td>Age (years) ± SD</td>
<td>41.22 ± 6.58</td>
<td>57.00 ± 9.24</td>
<td>&lt;0.001</td>
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<tr>
<td>Waist/hip ratio</td>
<td>0.81 ± 0.01</td>
<td>0.82 ± 0.01</td>
<td>0.191</td>
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<td>Body mass index (kg/m²) ± SD</td>
<td>26.81 ± 5.02</td>
<td>27.82 ± 3.91</td>
<td>0.370</td>
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<tr>
<td>Mean systolic BP (mmHg)</td>
<td>123.51 ± 2.54</td>
<td>127.71 ± 3.04</td>
<td>0.299</td>
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<tr>
<td>Mean diastolic BP (mmHg)</td>
<td>73.40 ± 1.35</td>
<td>76.21 ± 1.86</td>
<td>0.216</td>
</tr>
<tr>
<td>Serum estradiol (pmol/l)</td>
<td>440.33 ± 51.82</td>
<td>93.79 ± 17.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum estrone (pg/ml)</td>
<td>338.77 ± 28.07</td>
<td>233.61 ± 36.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estrone/estradiol ratio</td>
<td>1.12 ± 0.120</td>
<td>3.51 ± 0.70</td>
<td>0.001</td>
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<tr>
<td>Serum FSH (IU/l)</td>
<td>6.08 ± 0.46</td>
<td>77.67 ± 7.28</td>
<td>&lt;0.001</td>
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<tr>
<td>Serum glucose (mmol/l)</td>
<td>4.89 ± 0.09</td>
<td>4.83 ± 0.08</td>
<td>0.689</td>
</tr>
<tr>
<td>Serum insulin (μU/ml)</td>
<td>7.39 ± 0.98</td>
<td>7.68 ± 1.29</td>
<td>0.855</td>
</tr>
<tr>
<td>HOMA index</td>
<td>1.64 ± 0.24</td>
<td>1.77 ± 0.31</td>
<td>0.853</td>
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BP, blood pressure; FSH, follicle stimulating hormone

CGRP and insulin in menopause

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not show any significant difference in mean CGRP levels with respect to BMI.

Serum CGRP levels correlated positively with fasting insulin levels ($r = 0.394$, $p = 0.002$) (Figure 2) and HOMA index ($r = 0.540$, $p < 0.001$). The correlation with insulin and HOMA index increased significantly ($r = 0.652$, $p = 0.016$; $r = 0.679$, $p = 0.011$, respectively) when age, BMI and menopausal status were adjusted for.

**Lipid profile**

As expected, the postmenopausal women had an unfavorable lipid profile compared with the premenopausal women. The postmenopausal women had higher mean serum total cholesterol, triglyceride and LDL levels (Table 4). Furthermore, total cholesterol, triglyceride and serum LDL levels were significantly higher in the obese women compared with the women with normal BMI ($p = 0.009$, $p = 0.007$, $p = 0.018$, respectively). Serum cholesterol correlated positively with age, BMI and WHR. Serum triglyceride and LDL levels also showed similar correlations. The mean serum HDL levels were comparable in the two groups and no significant correlation was observed between serum HDL and age or BMI. Serum cholesterol levels were negatively correlated with serum estradiol and positively correlated with serum FSH levels ($r = -0.358$, $p = 0.003$; $r = 0.475$, $p < 0.001$). Serum triglyceride levels showed similar trends.

**Leptin, resistin and adiponectin**

The leptin levels were two-fold greater in the obese women compared with the women with normal BMI (normal BMI: 19.68 ± 3.41 ng/ml; obese: 53.44 ± 6.06 ng/ml, $p < 0.001$). This effect was seen in both premenopausal and postmenopausal groups, although there were no significant differences in the mean leptin or resistin levels between premenopausal and postmenopausal subgroups (Table 4). Strong positive correlations were observed between serum leptin levels and BMI ($r = 0.625$, $p < 0.001$), serum cholesterol ($r = 0.325$, $p = 0.019$), serum triglyceride ($r = 0.301$, $p = 0.03$) and LDL levels ($r = 0.294$, $p = 0.038$). Serum leptin levels also correlated positively with serum insulin levels ($r = 0.468$, $p = 0.001$) and the HOMA index ($r = 0.398$, $p = 0.004$). In addition, serum adiponectin levels were strongly correlated with WHR ($r = -0.649$, $p = 0.016$) and serum HDL levels ($r = 0.925$, $p < 0.001$), when age, BMI and menopausal status were controlled for. However, there was no significant difference between serum adiponectin levels in premenopausal and postmenopausal groups (Table 4). The mean adiponectin level did not differ between women with normal BMI and the obese group.

**DISCUSSION**

The present study investigated the influence of menopausal status and adiposity on CGRP levels, in order to evaluate CGRP’s role in cardiovascular risk, postmenopause. The findings from these studies determined that postmenopausal status significantly increased circulating CGRP levels, whilst the state of insulin resistance also affected CGRP levels. As the first study to identify a positive correlation between serum CGRP and fasting insulin levels, our findings support the previously reported antagonistic effect of CGRP on insulin action and, thus, a potential mechanism by which CGRP may have an adverse influence on cardiovascular health in postmenopausal women.

The results of our studies demonstrating increased CGRP levels in postmenopausal women, especially those still experiencing hot flushes, are in accord with previous clinical data that demonstrated increased CGRP secretion during hot flushes. It is tempting to speculate that the increased serum CGRP levels are associated with the occurrence of hot flushes as there was no difference in the mean serum CGRP levels in pre- and postmenopausal women who did not have hot flushes. However, further work in a larger group of symptomatic women would be required to establish a causative effect. Furthermore, animal

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<th>Postmenopausal n (mean ± SD)</th>
<th>$p$ Value</th>
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<tr>
<td>18-24.9 kg/m²</td>
<td>16 (22.7 ± 1.45)</td>
<td>7 (24.24 ± 1.35)</td>
<td>0.03</td>
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<tr>
<td>25-29.9 kg/m²</td>
<td>18 (26.97 ± 1.61)</td>
<td>15 (27.03 ± 1.57)</td>
<td>0.98</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>10 (34 ± 4.22)</td>
<td>6 (33.98 ± 2.84)</td>
<td>0.92</td>
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</table>
studies have shown higher CGRP expression and secretion in the estrogen-deficient state\(^{13,14}\). Conflicting findings have also been reported in a previous study by Valentini and co-workers, where CGRP levels were shown to be lower in postmenopausal women. Such differences may have arisen due to the smaller number of participants in Valentini’s study (\(n = 15\))\(^{32}\) as well as differences in the study population in terms of time since menopause, presence of significant vasomotor symptoms and use of exogenous hormones – factors which may have affected the CGRP levels. All we can speculate is that the increased CGRP serum levels in postmenopausal women were related to hot flushes.

Within our study there was an apparent lack of linear correlation between serum CGRP and serum estradiol or estrone levels, or with the number of hot flushes. This finding was not unexpected as the majority of participants in this study were either asymptomatic or they were experiencing mild vasomotor symptoms, needing no treatment. Although 61% of postmenopausal women in this study group reported hot flushes, which is consistent with the general population\(^{33}\), a significant proportion (16%) of the premenopausal women also reported hot flushes, despite adequate serum estradiol and normal FSH levels. This suggests that circulating estradiol levels do not predict the occurrence or the severity of hot flushes. This may be due to the short circulatory half-life and rapid enzymatic degradation of CGRP, which may not allow circulatory levels to accurately reflect tissue levels\(^{34}\). Similarly, the serum estrogen levels in postmenopausal women may not be a valid indicator of the tissue bioavailability due to the varying level of its local production\(^{35}\). As such, the results indicate that
more than one mechanism is involved in the pathogenesis of hot flushes.

The results from this study support the recent findings of increased frequency and severity of hot flushes in women with higher BMI, thus challenging the common belief that obese women experience less vasomotor symptoms. Furthermore, the women with higher WHR, i.e., women with higher central adiposity, had worse symptoms, suggesting a possible role for visceral fat in the pathogenesis of hot flushes. However, to date, the mechanisms underlying this phenomenon remain undetermined.

From our studies, it is clear that the subjects, as previously noted, have shown an age-related increase in WHR, an unfavorable lipid profile in the postmenopausal group and increased total cholesterol, triglyceride and LDL serum levels with increasing BMI and WHR. All these factors support the known association of worsening metabolic syndrome with central adiposity in postmenopausal women. Previous longitudinal studies have shown a slight decrease in serum HDL levels during the menopausal transition, which remains unaffected by increasing age. However, the lack of this effect in our study is possibly due to the comparable BMI in the two groups, which has a strong influence on serum HDL levels. Our study shows that circulating leptin, resistin and adiponectin levels remained unaffected by menopausal status. Whilst adipokine secretion is strongly influenced by body fat content and distribution, the apparent lack of change in circulating levels in pre- and postmenopausal women remains unexplained.

Table 4 Serum lipid profile, adipokines and endotoxin levels in premenopausal and postmenopausal groups of women. Results are shown as mean ± standard equivalent of the mean (n). Independent Student t tests were used to compare groups.

<table>
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<th>Premenopausal</th>
<th>Postmenopausal</th>
<th>p Value</th>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.77 ± 0.14 (45)</td>
<td>5.97 ± 0.23 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.68 ± 0.12 (45)</td>
<td>3.49 ± 0.22 (28)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.70 ± 0.08 (45)</td>
<td>1.83 ± 0.09 (28)</td>
<td>0.276</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.87 ± 0.06 (45)</td>
<td>1.36 ± 0.17 (28)</td>
<td>0.009</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>31.52 ± 4.09 (31)</td>
<td>31.48 ± 4.28 (25)</td>
<td>0.995</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>14.37 ± 0.65 (35)</td>
<td>13.37 ± 0.58 (26)</td>
<td>0.276</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>11.86 ± 0.88 (39)</td>
<td>14.12 ± 1.07 (27)</td>
<td>0.108</td>
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LDL, low density lipoprotein; HDL, high density lipoprotein
subjects is not surprising, as the groups were BMI- and WHR-matched. In conclusion, these data highlight that circulating CGRP levels appear to be influenced by menopausal status and suggest additional mechanisms may contribute to the increased risk of hyperinsulinemia and cardiovascular disease in postmenopausal women.

ACKNOWLEDGEMENTS

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Conflict of interest Nil.

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References


