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# Zależności między adiponektyną i leptyną a zespołem metabolicznym u kobiet przed i po menopauzie

*Lucyna Siemińska[1], Celina Wojciechowska[2], Wanda Foltyn[1], Dariusz Kajdaniuk[1], Beata Kos-Kudła[1], Bogdan Marek[1], Maja Nasiek[3], Mariusz Nowak[1], Janusz Strzelczyk[1], Anna Zemczak[1]*

[1]*Katedra Patofizjologii i Endokrynologii Śląskiej Akademii Medycznej, Zabrze*
[2]*II Katedra i Klinika Kardiologii Śląskiej Akademii Medycznej, Zabrze*
[3]*Poradnia Endokrynologiczna, Gliwice*

**Streszczenie**

**Wstęp:** U kobiet po menopauzie częściej występuje zespół metaboliczny (ZM) i choroby układu krążenia. Adiponektyna i leptyna produkowane przez tkankę tłuszczową odgrywają rolę w patogenezie ZM.

**Cel pracy:** Ocena wpływu menopauzy na powiązania między adiponektyną oraz leptyną i różnymi czynnikami ryzyka.

**Materiał i metody:** Do badania włączono 56 kobiet po menopauzie i 75 młodych kobiet. Oceniano: ciśnienie tętnicze, wskaźnik masy ciała (BMI, *body mass index*), obwód w talii, WHR, stężenie triglicerydów (TG), cholesterolu frakcji HDL (cHDL), stężenie glukozy na czczo i w teście obciążenia glukozą 75 g. Badane kobiety podzielono na podgrupy w zależności od liczby stwierdzonych czynników ryzyka. Przy obecności co najmniej 3 czynników rozpoznawano zespół metaboliczny. Stężenie adiponektyny i leptyny oceniano metodą RIA.

**Wyniki:** Stężenie adiponektyny malało wraz ze wzrostem liczby czynników ryzyka w grupie przed- i pomenopauzalnej. W porównaniu do młodych kobiet z ZM, u kobiet po menopauzie i z ZM stwierdzono istotnie niższe stężenia adiponektyny. W przeciwieństwie do przedmenopauzalnych kobiet, w grupie pomenopauzalnej wraz z rosnącą liczbą czynników ryzyka obserwowano wzrost stężenia leptyny. Porównując młode kobiety z ZM i kobiety pomenopauzalne z ZM, obserwowano wyższe stężenia leptyny w tej ostatniej podgrupie. Stwierdzono zależności między leptyną i różnymi składowymi ZM, zwłaszcza u kobiet po menopauzie. W analizie wieloczynnikowej, adiponektyna i leptyna stanowiły niezależne czynniki powiązane z ZM.

**Wnioski:** Potwierdzono istotną rolę patofizjologiczną adiponektyny w rozwoju ZM. Leptyna jest powiązana z różnymi czynnikami ryzyka, ale wydaje się, że odgrywa ona rolę w patogenezie ZM jedynie u pomenopauzalnych kobiet.

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***Słowa kluczowe:*** *adiponektyna, leptyna, menopauza, zespół metaboliczny*

Dr med. Lucyna Siemińska
Katedra Patofizjologii i Endokrynologii, ŚAM
plac Traugutta 2, 41–800 Zabrze
e-mail: lusiem@poczta.onet.pl

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# The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause

*Lucyna Siemińska[1], Celina Wojciechowska[2], Wanda Foltyn[1], Dariusz Kajdaniuk[1], Beata Kos-Kudła[1], Bogdan Marek[1], Maja Nasiek[3], Mariusz Nowak[1], Janusz Strzelczyk[1], Anna Zemczak[1]*

[1]*Department of Pathophysiology and Endocrinology, Silesian Medical University, Zabrze*
[2]*II Department and Clinic of Cardiology, Silesian Medical University, Zabrze*
[3]*Endocrinological Clinic Gliwice*

**Abstract**

**Introduction:** It is well known that there is a higher prevalence of cardiovascular risk factors and metabolic syndrome (MS) in postmenopausal women. Recently it has become evident that adiponectin and leptin secreted by adipose tissue may be involved in the pathophysiology of MS.

**The aim of the study:** was to assess the effects of the menopause on the relationships between adiponectin and leptin and different cardiovascular and metabolic risk factors.

**Materials and methods:** A total of 56 postmenopausal women and 75 premenopausal subjects were enrolled in this study. We measured blood pressure, BMI, waist circumference and WHR, triglycerides (TG), high density lipoprotein cholesterol (cHDL) levels and fasting glucose and applied the oral glucose tolerance test (OGTT). Women were categorised as having 0, 1, 2, 3 or more risk factors. The presence of at least 3 abnormalities was defined as MS. Serum was assayed for adiponectin and leptin by the radioimmunoassay (RIA) method.

**Results**: A decline in adiponectin was related to an increased number of MS variables in postmenopausal and premenopausal women. Postmenopausal women with MS had significantly lower adiponectin concentrations than premenopausal women with MS. Serum adiponectin concentrations were inversely correlated to leptin in postmenopausal women. In premenopausal women no clear relationships were found between serum leptin and the number of metabolic disturbances. In contrast to young women, postmenopausal women showed an increase in leptin secretion with a growing number of MS elements. Compared to premenopausal women with MS, postmenopausal women with MS had higher levels of leptin. We found associations between leptin and different risk factors, mainly in the postmenopausal group. When the presence of MS was used as a dependent variable (yes/no) and adiponectin, leptin and menopause status as independent factors, adiponectin and leptin remained significant variables related to MS.

**Conclusion:** The significant role of adiponectin in the pathophysiology of MS in premenopausal and postmenopausal women is confirmed in this study. Leptin is correlated with several MS components but this adipocytokine appears to play a role only in postmenopausal women.

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***Key words***: *adiponectin, leptin, menopause, metabolic syndrome*

Lucyna Siemińska, M.D.
Department of Pathophysiology and Endocrinology,
Silesian Medical University
plac Traugutta 2, 41–800 Zabrze, Poland
e-mail: lusiem@poczta.onet.pl

## Introduction

It is well known that there is a higher prevalence of cardiovascular risk factors and metabolic syndrome (MS) in postmenopausal women [1]. This is caused by increased obesity, redistribution of the fat mass and insulin resistance. It has been shown that an excess of fat mass and insulin resistance are two independent factors that contribute to an unfavourable metabolic profile in women after the menopause [2]. The occurrence of both these factors simultaneously creates the conditions that are most detrimental to the metabolic profile [2].

The exact mechanisms mediating the relationship between the accumulation of visceral fat after the menopause and metabolic disturbances remain unknown. Recently it has become evident that the adiponectin and leptin secreted by adipose tissue and free fatty acids (FFA) may be involved in the pathophysiology of MS [3].

Previous research has shown a relationship between obesity and decreasing adiponectin and increased leptin production [4–8]. It is still unclear whether the menopause influences the synthesis of adipocytokines. Only limited data are available with regard to this matter

and results vary. Some studies have shown decreased adiponectin and increased leptin levels in postmenopausal women [9, 10], while others have not [11, 12]. In our previous study we compared overweight postmenopausal and premenopausal women matched for body mass index (BMI) and failed to find any difference in adiponectin levels between the groups [13]. However, some reports have described elevated levels of adiponectin [14] and a decreased concentration of leptin in women after the menopause [7]. Discrepancies can be attributed to differences in the body composition of the subjects. Therefore, in order to reduce any bias due to confounding variables, we analysed postmenopausal women in relation to premenopausal women according to the number of MS components.

The objective of the present study was to assess the effects of the menopause on the relationships between adiponectin and leptin and various cardiovascular and metabolic risk factors, to determine whether there is an independent relationship between adiponectin, leptin and MS and to assess whether the number of MS components is associated with adiponectin and leptin concentrations in postmenopausal and premenopausal women.

## Materials and methods

We studied 56 postmenopausal (age 48–64) and 75 premenopausal women (age 21–40 years) recruited from women visiting the endocrinological and gynaecological clinics for routine check-up. The premenopausal women had regular menstrual cycles and none had recognised diabetes, ischaemic heart disease or any other chronic disease. Postmenopausal status was defined by amenorrhoea for at least 1 year. The exclusion criteria were the same as for young women.

MS is characterised by a clustering of the following abnormalities: abdominal obesity, insulin resistance, impaired glucose tolerance, dyslipidaemia, and hypertension. Since WHO, the American Association of Clinical Endocrinologists (AACE) and the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) have recommended slightly differing criteria for diagnosis of MS [15], for the purposes of this study we have taken into account parameters that include parts of the lists of each of these organisations. For each woman we evaluated the following risk factors: blood pressure, BMI, waist circumference and waist-to-hip ratio (WHR), triglycerides (TG), cHDL levels, fasting glucose and the results of the oral glucose tolerance test (OGTT). Following the WHO, ATP III and AACE guidelines, we considered the following cut-off limits for MS abnormalities: 1. TG > 1.7 mmol/l; 2. cHDL < 1.29 mmol/l; 3. hypertension if blood pressure ≥ 130/85 mm Hg; 4. BMI ≥ 25; 5. (a) impaired fasting glucose (IFG) (fasting glucose ≥ 6,1 mmol/l and < 7.0 mmol/l) or (b) impaired glucose tolerance (IGT) (glucose ≥ 7.8 mmol/l and < 11.1 mmol/l in 120 minutes after OGTT); 6. (a) waist circumference (ATP III takes 88 cm as the upper limit) and (b) WHR (the WHO has established the upper limit of the WHR as 0.85). These were evaluated in view of the fact that abdominal obesity shows a high degree of correlation with metabolic risk factors. Women were then categorised as having 0, 1, 2, 3 or more of the above 6 metabolic disturbances.

Serum adiponectin and leptin levels were determined by radioimmunoassay using commercial kits (Linco Research, St. Charles, MO).

The study was approved by the Ethics Committee of the Silesian Medical University (Katowice, Poland).

Statistical analysis was performed using the Statistica 7.1 package by StatSoft Inc., Tulsa, OK. The postmenopausal and premenopausal women were tested separately. Concentrations are presented as means ± SD for normally distributed data or medians plus ($25^{th}$; $75^{th}$) percentiles for abnormal distribution in the Shapiro-Wilks W test. For comparisons between groups the t test or the Mann-Whitney U test were used. Spearman's correlation coefficients were used to estimate linear relationships between variables. Comparisons of values in multiple groups were tested using one-way ANOVA. Fisher's exact probability test was used to investigate the proportion of MS variables in the postmenopausal women to those in the premenopausal women. Multiple regression analysis was performed in different models as described in the "Results" section. It was assumed that the difference was significant at $p < 0.05$.

## Results

Of the 131 women studied, 56 were in postmenopausal and 75 were in the premenopausal group. Table I characterises the subjects. Groups were differentiated with regard to age, BMI, WHR and waist circumferences. Previous studies have shown that adiponectin and leptin concentrations depend on BMI, WHR and waist circumference and are related to MS [3–9]; therefore, we analysed the groups separately according to the number of MS components. The postmenopausal and premenopausal women were divided into four subgroups with 0, 1, 2 and 3 or more abnormalities respectively. The criteria for the anthropometric measurements, lipid and carboxyhydrate metabolism, as well as the values for blood pressure, are described in "Material and methods". In this study MS was defined the presence of at least three abnormalities.

The prevalence of MS was 9% in premenopausal women and 30% in postmenopausal women. Most

**Table I**
*Physical and clinical characteristics of the postmenopausal and premenopausal women studied*

**Tabela I**
*Charakterystyka grup badanych kobiet przed i po menopauzie*

| Variable | Postmenopausal women, n = 56 | Premenopausal women, n = 75 | p |
|---|---|---|---|
| Age [years] | 53.9 ± 3.2 | 28.2 ± 4.1 | < 0.001 |
| BMI [kg/m$^2$] | 27.2 ± 3.1 | 23.3 ± 2.0 | < 0.001 |
| WHR | 0.84 ± 0.03 | 0.76 ± 0.05 | < 0.001 |
| Waist circumference [cm] | 89.0 [84; 94.5] | 78.0 [76.0; 85.0] | < 0.001 |
| TG [mmol/l] | 1.8 ± 0.40 | 1.44 ± 0.21 | < 0.001 |
| CHDL [mmol/l] | 1.4 ± 0.15 | 1.57 ± 0.49 | < 0.001 |
| Hypertension | 17 [30%] | 5 [7%] | < 0.001 |
| Disturbances of glucose metabolism | 31 [55%] | 10 [13%] | < 0.001 |
| Adiponectin [mg/ml] | 15.1 [9.8; 17.4] | 17.4 [14.5; 21.0] | < 0.001 |
| Leptin [ng/ml] | 14.7 [10.7; 17.3] | 11.0 [8.3; 12.0] | < 0.001 |
| 0 factors of MS | 6 [11%] | 53 [71%] | < 0.001 |
| 1 factor of MS | 15 [27%] | 9 [12%] | < 0.05 |
| 2 factors of MS | 18 [32%] | 6 [8%] | < 0.001 |
| ≥ 3 factors of MS | 17 [30%] | 7 [9%] | < 0.001 |

Skewed data are given as median plus [25$^{th}$; 75$^{th}$] percentiles. Normally distributed data are given as mean ± SD. The significance tests used are the Mann-Whitney U test for the variables that are not normally distributed and the unpaired t-test for the normally distributed variables. Fisher's exact probability test was used to compare disparities between the groups in the frequency of the markers of metabolic syndrome. Disturbances of glucose metabolism include IFG or IGT

premenopausal women (71%) had a healthy metabolic profile (0 features). Most postmenopausal women were characterised by 1 to 2 components of MS (59%).

For both groups lower serum adiponectin levels were present, as the greater number of MS components were clustered (Fig. 1). However, adiponectin concentration in the postmenopausal women with MS was significantly lower than in young women with MS. No differences in serum adiponectin were found between the postmenopausal and the younger women when these were compared to women with no disturbances. Similar results were obtained for subjects with one or two abnormalities.

There was a stepwise increase in serum leptin as the number of MS elements increased in postmenopausal women (Fig. 2). Postmenopausal women with MS were found to have higher levels of leptin when compared to younger women with MS.

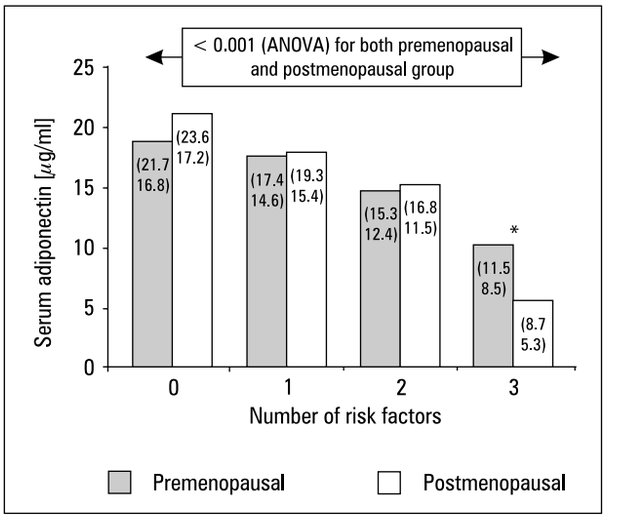


***Figure 1.*** *Dependence of serum adiponectin on the numbers of risk factors in premenopausal and postmenopausal women. The columns indicate the median, with percentyles (75th, 25th) in brackets; * p < 0.001 premenopausal vs. postmenopausal women*

***Rycina 1.*** *Zależność stężenia adiponektyny od liczby czynników ryzyka u kobiet przed i po menopauzie. Słupki przedstawiają mediany; w nawiasach umieszczono percentyle (75, 25); *p < 0,001 u kobiet przed* vs. *po menopauzie*

## Simple correlations and multiple regression analyses

When analysis was conducted for all postmenopausal women, serum adiponectin correlated with all risk factors: BMI ($p < 0.001$), WHR ($p < 0.001$), waist circumference ($p < 0.001$), TG ($p < 0.001$) and cHDL ($p < 0.001$). We observed negative associations between adiponectin and leptin in postmenopausal women ($p < 0.01$).

The stepwise regression analysis performed on the postmenopausal group with MS abnormalities as independent variables showed that WHR, leptin, disturbances

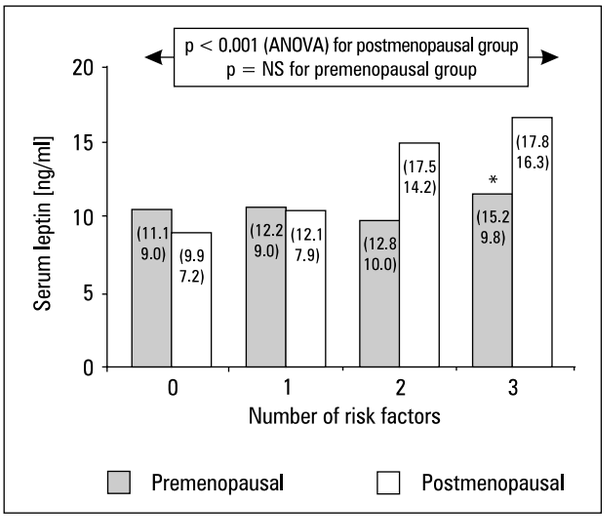


***Figure 2.*** *Dependence of serum leptin on the numbers of risk factors in premenopausal and postmenopausal women. The columns indicate the median, with percentyles (75th, 25th) in brackets; * p < 0.001 premenopausal* vs. *postmenopausal women*

***Rycina 2.*** *Zależność stężenia leptyny od liczby czynników ryzyka u kobiet przed i po menopauzie. Słupki przedstawiają mediany; w nawiasach umieszczono percentyle (75, 25); *p < 0,001 u kobiet przed* vs. *po menopauzie*

in glucose metabolism and the presence of hypertension were independent predictors for serum adiponectin (R2 = 0.71, p < 0.001, Tab. II).

In the premenopausal women, linear regression analysis showed that serum adiponectin levels were significantly associated with BMI (p < 0.01), WHR (p < 0.001), waist circumference (p < 0.001) and TG (p < 0.001). Stepwise regression analysis using the same independent variables as for the postmenopausal group showed that waist circumference, TG, IFG/IGT and hypertension emerge as independent predictors of adiponectin concentration in premenopausal women (R2 = 0.47, p < 0.001, Tab. II).

In postmenopausal women leptin was positively correlated with BMI (p < 0.001), WHR (p < 0.001), waist circumference (p < 0.001), TG (p < 0.001), cHDL (p < 0.001) and adiponectin (p < 0.01). In premenopausal women leptin was associated with BMI (p < 0.01), waist circumference (p < 0.01) and WHR (p < 0.01). In this group no association was demonstrated between leptin and lipid or glucose disturbances and no relationship was found between serum leptin and the number of metabolic disturbances (Fig. 2). In multiple stepwise regression analysis performed in the postmenopausal group BMI and adiponectin remained independent predictors for leptin (R2 = 0.66, p < 0.001, Tab. II). The following variables were entered into the model: BMI, WHR, waist circumference, TG, cHDL, adiponectin, hypertension (yes/no) and IFG/IGT (yes/no). In contrast, in the premenopausal group BMI and WHR were related independently to leptin concentration (R2 = 0.39; p < 0.01).

When the presence of MS was used as a dependent variable (yes/no), and adiponectin, leptin, and menopause status as independent factors, adiponectin and

**Table II**

***Multiple linear regression analysis using serum adiponectin or leptin as dependent parameters. The analysis was performed separately for premenopausal and postmenopausal subjects***

**Tabela II**

***Stężenia adiponektyny lub leptyny jako parametry zależne w analizie modelu liniowej regresji wielorakiej. Osobno rozpatrywano wyniki badań w grupach przed i po menopauzie***

| | Adiponectin as a dependent variable | | | | Leptin as a dependent variable | | | |
|---|---|---|---|---|---|---|---|---|
| | Premenopausal women | | Postmenopausal women | | Premenopausal women | | Postmenopausal women | |
| Independent parameter | Regression coefficient beta | p | Regression coefficient beta | p | Regression coefficient beta | p | Regression coefficient beta | p |
| BMI | –0.03 | NS | –0.1 | NS | 0.37 | < 0.001 | 0.46 | 0.001 |
| WHR | –0.12 | 0.NS | –0.20 | 0.04 | 0.35 | 0.001 | 0.16 | NS |
| Waist circumference | –0.22 | 0.04 | –0.14 | NS | 0.16 | NS | 0.16 | NS |
| TG | –0.31 | 0.001 | –0.13 | NS | 0.19 | NS | 0.17 | NS |
| CHDL | 0.11 | NS | 0.01 | NS | 0.04 | NS | 0.01 | NS |
| Leptin | –0.02 | NS | –0.27 | 0.01 | | | | |
| Adiponectin | | | | | 0.03 | NS | –0.32 | < 0.01 |
| Disturbances of glucose metabolism (yes/no) | –0.32 | 0.001 | –0.24 | < 0.001 | 0.13 | NS | 0.11 | NS |
| Hypertension (yes/no) | –0.29 | <0.01 | –0,20 | < 0.01 | –0.15 | NS | –0.04 | NS |
| | R2 = 0.47, p < 0.001 | | R2 = 0.71, p < 0.001 | | R2 = 0.39, p < 0.01 | | R2 = 0.66, p < 0.001 | |

Disturbances of glucose metabolism include IFG or IGT

**Table III**
*Stepwise regression analysis for independent predictors of the presence of MS in premenopausal and postmenopausal women taken together*

**Tabela III**
*Niezależne czynniki rokownicze wystąpienia zespołu metabolicznego w analizie modelu regresji krokowej rozpatrywane łącznie u kobiet przed i po menopauzie*

| Independent parameter | Regression coefficient beta | p |
|---|---|---|
| Adiponectin | –0.53 | 0.001 |
| Leptin | 0.29 | 0.001 |
| Menopause yes/no | –0.2 | 0.001 |
| | $R2 = 0.54$, $p < 0.001$ | |

leptin remained significant and independent variables related to MS. Table III presents a summary of the model ($R2 = 0.54$, $p < 0.001$).

## Discussion

The menopause is associated with obesity and with an increased risk of MS developing [1, 16]. In our study the prevalence of MS in postmenopausal women was indeed found to be high.

The aetiology of postmenopausal obesity is not fully known but it has become apparent that decreased physical activity, a reduced resting metabolic rate, an increase in fat intake and a decrease in fat oxidation all play a role [17]. The accumulation of visceral fat in postmenopausal women suggests that hypo-oestrogenism arising from ovarian failure may be responsible for fat redistribution. Many investigators have demonstrated that visceral fat significantly correlates with insulin resistance [18]. However, the hypothesis that increased FFA release into the portal vein leads to hepatic insulin resistance has recently been questioned [19]. Some studies have demonstrated a strong correlation between insulin sensitivity and subcutaneous fat mass [20] and between both visceral and subcutaneous fat and insulin resistance [21]. It is possible that subcutaneous truncal fat influences peripheral insulin sensitivity by releasing large amounts of FFA to the systemic circulation. In contrast, leg fat mass seems to be a significant protective factor, associated with a more favourable metabolic profile [22]. Low subcutaneous thigh fat is considered to be a risk factor for carboxyhydrate and lipid disturbances [23].

Adipose tissue produces various amounts of adiponectin and leptin at different body sites. Adiponectin is derived from visceral fat mass, while leptin is secreted mainly by subcutaneous adipose tissue [6]. Serum adiponectin is decreased in abdominal obesity [3, 4], although serum leptin levels are related to the subcutaneous fat of the lower leg [24]. The proportions of leptin release from visceral and subcutaneous compartments change after the menopause and increased secretion from visceral fat is observed [7]. Adipocytokines affect carbohydrate and lipid metabolism and, therefore, play a role in the pathogenesis of hypertension, atherosclerosis and diabetes [3–5, 25]. This hormone appears to have an impact on glucose and lipid metabolism in skeletal muscle, liver and in adipose tissue and has an anti-inflammatory effect on the vascular wall. Adiponectin inhibits monocyte adhesion to endothelial cells, suppresses macrophage-to-foam cell transformation and attenuates proliferation of smooth muscle cells [26]. Since it has become evident that inhibition of adiponectin production occurs during the development of obesity, hypoadiponectinaemia appears to be a link between obesity, insulin resistance and vascular disease. In our study a decline in adiponectin was related to an increased number of MS variables. These results are in agreement with previous reports [27]. Our results also demonstrate that postmenopausal women with MS have significantly lower adiponectin concentrations than premenopausal women with MS. This finding suggests that there is another factor that influences the associations between MS and adiponectin levels in postmenopausal women. In this study we demonstrated that serum adiponectin concentrations were inversely correlated to leptin in postmenopausal women. These associations remained statistically significant after multiple stepwise regression analysis. The mechanism underlying the observed associations is unknown. The observation has recently been made that hyperleptinaemia and hypoadiponectinaemia work together to accelerate atherosclerosis in obese subjects [28] and Satoh et al. suggest that the high leptin-to-adiponectin ratio is a marker of accelerated atherogenesis [29]. Recently the connections between lipoprotein lipase and adiponectin as well as leptin have been actively investigated; examples are studies by von Eynatten et al. [30] and Maingrette et al. [31]. Unfortunately, the direct relationship between adiponectin and leptin with respect to lipoprotein lipase remains uncertain. The other possible mechanism linking low adiponectin and high leptin involves the increased risk of insulin resistance after the menopause [32]. Adiponectin has been shown to be suppressed in states of insulin resistance [4, 5]. Leptin also contributes to the deterioration of insulin sensitivity [6–8]. Furthermore, the postmenopausal status is characterised by higher TNF-alpha levels [33] which reduce adiponectin levels. Positive associations between TNF-alpha and leptin have also been reported [34]. Unfortunately, these parameters were not measured in the present study and this hypothesis needs to be confirmed.

Leptin has been shown to be linked to adiposity and insulin resistance. Leyva et al. [8] have demonstrated the relationships between hyperleptinaemia and obesity, increased pressure, insulin resistance, hyperinsulinaemia and hypertriglyceridaemia. The effect of leptin on the development of MS is not fully understood. The leptin receptor has been identified on endothelial cells and leptin has been shown to promote atherogenic processes [35]. Elevated levels of leptin induce fatty acid oxidation, which plays a role in the progression of atherosclerosis [36]. Moreover, leptin enhances lipoprotein lipase secretion from macrophages contributing to monocyte adhesion to the endothelium and to the transformation of macrophages into foam cells [29]. In many studies leptin has been shown to be a marker of coronary events. Leptin increases sympathetic nervous activity and the administration of leptin in animal models causes a rise in blood pressure.

In our study serum leptin in premenopausal women correlated with BMI and WHR but no association was found with lipid, glucose abnormalities and adiponectin. No clear relationships were found between serum leptin and the number of metabolic disturbances. In contrast to young women, postmenopausal women showed an increase in leptin secretion with a growing number of MS elements and in stepwise regression analysis leptin remained an independent factor related to MS. A possible reason for the difference between premenopausal and postmenopausal women is that leptin secretion after the menopause is due to increased visceral fat [7]. This may contribute to the metabolic deterioration that occurs in women during this period. In our study the median concentration of leptin was significantly higher in postmenopausal women when compared with the premenopausal group.

In conclusion, the significant role of adiponectin in the pathophysiology of MS in premenopausal and postmenopausal women was confirmed in this study. Leptin is correlated with several MS components but this adipocytokine only appears to play a role in postmenopausal women.

The main factor determining the occurrence of MS in women is a depressed level of adiponectin. However, a high degree of leptin concentration also emerges as a factor contributing to the pathophysiology of MS. The precise role of adiponectin and leptin is probably complex and future studies in this matter are needed.

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