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Genetics of metabolic syndrome and related traits

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Chapter 6

Menopause impacts the relation of plasma adiponectin levels with the metabolic syndrome

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Objective: Plasma adiponectin is negatively correlated with metabolic syndrome (MetS) components obesity and insulin sensitivity. Here, we set out to evaluate the effect of menopause on the association of plasma adiponectin with MetS.
Design: Data on plasma adiponectin and MetS were available from 2256 individuals participating in the Erasmus Rucphen Family study. Odds ratios for MetS were calculated by logistic regression analysis using plasma adiponectin quartiles. The discriminative accuracy of plasma adiponectin for MetS was determined by calculating the area under the receiver-operator curve (AUC). Analyses were performed in women and men, pre- and postmenopausal women and younger and older men.
Results: Virtually all determinants of MetS differed significantly between groups. Low plasma adiponectin showed the highest risk for MetS in postmenopausal women (OR = 18.6, 95% CI = 7.9 – 44.0). We observed a high discriminative accuracy of age and plasma adiponectin for MetS in postmenopausal women (AUC = 0.76), but also in other subgroups (AUC from 0.67 – 0.87). However, in all groups, the discriminative accuracy of age and BMI for MetS was not exceeded by age and plasma adiponectin.
Conclusions: Low plasma levels of adiponectin are associated with increased prevalence of MetS, especially in postmenopausal women. Age and BMI have similar discriminatory accuracies for presence of MetS when compared to age and plasma adiponectin. Thus, we conclude that the association of plasma adiponectin with MetS is significantly affected by menopause but challenge the additional value of adiponectin for the discriminatory accuracy for presence of MetS.

INTRODUCTION

The prevalence of obesity and the metabolic syndrome (MetS) is increasing dramatically in populations with a western lifestyle[1-3]. Central obesity, dyslipidemia, impaired fasting plasma glucose (FPG) and hypertension are important components of MetS[4]. Given the increased morbidity and mortality associated with MetS, research has focused on associations of specific biomarkers with the (early) onset and progression of MetS[2,5,6].

Obesity plays a key role in the aetiology of MetS and related diseases. Adipose tissue functions as an endocrine organ which responds to changes in metabolic conditions by secreting biologically active substances also known as adipocytokines or adipokines[7,8,9]. Specifically, the visceral fat depot, which has rapid access to the systemic circulation via the portal vein, is thought to play an important role in adipokine secretion and MetS and related disorders[10]. Many groups have suggested that plasma adipokines are potential biomarkers for MetS, in particular plasma adiponectin[11,12].

Adiponectin is secreted form adipose tissue and is present in plasma in various multimeric forms. Plasma adiponectin levels have been shown to differ largely between genders[13]. In humans, plasma adiponectin levels are negatively correlated with obesity and type two diabetes (T2D)[14,15,16]. In mouse models, adiponectin has been shown to play a role in energy homeostasis by regulating insulin sensitivity of the liver[17]. Adiponectin is suggested to have an important role in vascular endothelium as modifier of monocyte adhesion by affecting anti-inflammatory properties. In addition, adiponectin has also been implicated in regulation of vasodilatation, via the endothelial NO synthase (eNOS) pathway[18].

Gender and age effects in the expression of MetS have been previously demonstrated[19]. Furthermore, it was shown that MetS is more prevalent in men than in premenopausal women[19,20]. After menopause, women experience a substantial increase in dyslipidemia and other MetS related

risk factors, leading to a risk profile comparable with that seen in men[21,22]. Thus, differences between pre- and postmenopausal women with regard to the prevalence of MetS and plasma adiponectin have been reported independent from each other. It has been suggested that plasma adiponectin is a promising biomarker for MetS[11,12]. However, within the general population the effect of menopause on the association of plasma adiponectin with MetS is not clear. Furthermore, it is not clear to what extent menopause affects the association between plasma adiponectin and MetS.

The present study aims to elucidate the effect of menopause on the association of plasma adiponectin with MetS. In addition, we investigate the discriminatory accuracy of plasma adiponectin for presence of MetS as a measure for a MetS biomarker. Analyses were performed overall and in subgroups: pre- and postmenopausal women and younger and older men (stratified on the mean age at halt of menstruation of women).

METHODS

STUDY POPULATION

We used data of the Erasmus Rucphen Family (ERF) study. This population was embedded in an isolated population (Genetic Research in Isolated Populations, GRIP). The ERF population includes individuals who were not selected based on health information, but comprises living descendants of 22 couples, who had at least 6 children baptized in the community church between 1850 and 1900. Details about the genealogy of the population are described elsewhere[23,24,25]. The study protocol was approved by the medical ethics board of the Erasmus MC Rotterdam, the Netherlands. A written informed consent was obtained from each participant and all investigations were carried out in accordance with the Declaration of Helsinki.

DATA COLLECTION

Blood of participants was obtained in the fasted state. Total plasma insulin was analyzed with the INS-Irma kit of DIAsource ImmunoAssays (formerly Bio-Source; Nivelles, Belgium; cat #: KIP1254), total plasma adiponectin with the Human adiponectin RIA kit (cat#: HADP-61HK) of Linco Research (St. Charles, MO, USA) and total plasma CRP with the US C-reactive protein ELISA (cat.# DSL-10-42100) of Diagnostic Systems Laboratories (Webster, TX, USA), Inc. All measurements were performed conform the manufactures protocol. The distribution of plasma CRP level was skewed, therefore upper plasma CRP levels exceeding three times the standard deviation of the mean were removed from the analyses. Menopause was defined by halt of menstruation whether it be naturally, due to medication or due to surgical intervention. Insulin sensitivity was based on the homeostasis model assessment insulin resistance (HOMA-IR; glucose* insulin divided by 22.5). Assessment of the following study variables have been given earlier by others[26,23,27,19]: Medication use; glucose lowering, lipid lowering or anti-hypertension treatment, body mass index (BMI), MetS (International Diabetes Federation – 2006, europids); waist circumference (WC, men ≥ 94 cm, women ≥ 80), fasting plasma glucose (FPG, ≥ 5.6 mmol/L, previously diagnosed/treated type 2 diabetes patients included), HDL-cholesterol (HDL-C, men < 1.03 mmol/L, women < 1.29 mmol/L, treated patients included), total plasma triglycerides (TG, ≥ 1.7 mmol/L, treated patients included), systolic blood pressure (SBP, ≥ 130 mm Hg, treated patients included), diastolic blood pressure (DBP, ≥ 85 mm Hg, treated patients included).

STATISTICAL ANALYSES

Women were stratified in two groups according to menopause. The mean age of premenopausal -and postmenopausal women was 37.8 and 60.2 years respectively and the mean age at halt of menstruation was 46.8 years. In order to be able to exclude an age effect in our analyses, we divided the men in two groups, younger -and older men, using the mean age at halt of menstruation of women. Younger men were defined by an age limit of < 46.8 years, older men by an age limit of > 46.8 years. Continuous variables did show some deviation from a normal distribution. Analysis of mean differences between groups was tested using analysis of variance (ANOVA) statistics using log normal transformed continuous variables or chi-squared statistics (categorical variables). All further analyses were based on the log normal transformed trait values with exception of the correlation analysis, which was performed using Spearman's correlation method. Odds ratios (OR) were calculated using binary logistic regression analyses, using quartiles of plasma adiponectin level, age and BMI as independent variables. Plasma adiponectin cut off values for these quartiles were 18.3 mmol/L, 11.1 mmol/L, 7.9 mmol/L and 4.7 mmol/L for group 1 to 4 respectively. The group with highest plasma adiponectin levels (18.3 mmol/L) was taken as reference group. The discriminative accuracy for MetS was based on predicted probabilities (binary logistic regression) according four different models; model 1: age; model 2: age and BMI; model 3: age and plasma adiponectin; model 4: age, BMI and plasma adiponectin. Predicted probabilities were calculated in pre –and postmenopausal women, total women, younger –and older men and total men. The binary logistic regression in total women and total men included next to independent variables also interaction terms of the stratification component (menopause or younger and older men) with each independent variable within the respective model. For example, in the total female group the first model (1) included age and age*menopause, the second model (2) age, BMI, age*menopause and BMI*menopause, the third model (3) age, adiponectin, age*menopause and adiponectin * menopause and the final model (4) included age, BMI, adiponectin, age*menopause, BMI*menopause and adiponectin*menopause. The discriminating accuracy is the extent to which test results can discriminate between individuals who will develop the disease and those who will not[28]. The area under the receiver operating characteristic curve (AUC) is commonly used to quantify this discriminative accuracy of a predicting model[29]. The AUC is the probability that the test correctly identifies the diseased individual from a pair of whom one is affected and one is unaffected, and ranges from 0.5 (total lack discrimination) to 1.0 (perfect discrimination)[28]. Analysis of the data was performed using SPSS 14.01 software. Statistical tests were not independent, which was a equirement for multiple test correction (e.g. Bonferoni). However, as we performed a considerable amount of statistical tests, only P-values below 0.01 were assumed significant.

RESULTS

Characteristics of the study population are described in Table 1. Data on plasma adiponectin, insulin and CRP levels were obtained for 2256 individuals. The population included 695 premenopausal and 581 postmenopausal women and 418 younger and 549 older men (stratified on mean age of onset menopause in women). The prevalence of MetS was 17.0% in premenopausal women, 43.2% in postmenopausal women, 22.2% in younger men and 48.5% in older men. All measurements, with exception of age and HDL-cholesterol, differed significantly ($P < 0.05$) between women and men (data

Table 1: General characteristics of the study population

	Women		Men	
	Premenopausal (n=695)	Postmenopausal (n=581)	Younger (n=418)	Older (n=549)
Age (yr)	37.8 ± 9.6	60.2 ± 8.3 **	36.0± 7.8	59.5 ± 8.0 ***
Metabolic syndrome and its individual components				
Metabolic syndrome % (n)	17.0 (118)	43.2 (251) ***	22.2 (93)	48.5 (266) ***
Waist circumference (cm)	78.4 ± 11.3	86.1 ± 11.5 ***	90.5 ± 10.8	96.9 ± 11.2 ***
Glucose (mmol/L)	4.2 ± 0.8	4.7 ± 0.8 ***	4.5 ± 0.8	5.0 ± 1.1 ***
HDL-cholesterol (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	1.1 ± 0.3	1.2 ± 0.3
Triglycerides (mmol/L)	1.1 ± 0.6	1.4 ± 0.7 ***	1.4 ± 0.9	1.6 ± 0.9 *
Systolic blood pressure (mm Hg)	126.7 ± 15.2	147.4 ± 21.8 ***	136.9 ± 12.6	148.2 ± 20.0 ***
Diastolic blood pressure (mm Hg)	76.5 ± 9.6	80.9 ± 9.4 ***	78.8 ± 9.8	84.0 ± 9.2 ***
Metabolic syndrome related traits				
Body mass index (kg/m2)	25.5 ± 5.0	27.8 ± 4.7 ***	26.9 ± 4.1	27 .6 ± 4.0 ***
Insulin (_U/ml)	12.2 ± 5.5	13.6 ± 7.4 ***	13.9 ± 9.8	13.9 ± 8.1
HOMA-IR	2.3 ± 1.3	2.9 ± 1.9 ***	2.9 ± 2.5	3.2 ± 2.3
Adiponectin (mgl/L)	11.9 ± 5.3	12.9 ± 6.2 *	7.7 ± 3.8	8.2 ± 4.4 *
C-reactive protein (mg/L)	5.7 ± 4.6	6.3 ± 4.7 **	4.0 ± 3.6	5.9 ± 4.4 ***
Medication				
Glucose lowering % (n)	0.9 (6)	3.4 (20) ***	0.0 (0)	4.9 (27) ***
Lipid lowering % (n)	3.2 (22)	18.9 (110) ***	3.6 (15)	23.5 (129) ***
Blood pressure lowering % (n)	8.1 (56)	31.2 (181) ***	5.3 (22)	32.6 (179) ***

HDL: high density lipoprotein; HOMA-IR: Homeostatic model assessment-Insulin resistance. Values presented as mean ± SD for continuous variables and percent (number) for categorical variables. Plasma was taken in fasted state. Differences were calculated within gender group only, * P < 0.05, ** P < 0.01, *** P < 0.001. Significance of continuous variables based on ANOVA, for non-continuous variables based on Chi2.

not shown) and between pre- and postmenopausal women and between younger and older men.

Spearman's correlation coefficients between plasma adiponectin and MetS, MetS individual traits and MetS related traits are presented in Table 2. Correlation coefficients of plasma adiponectin level with MetS were -0.23, -0.37 in respectively pre- and postmenopausal women and -0.19, -0.22 in respectively younger and older men. We observed significant correlations of plasma adiponectin with each of the individual components of MetS with exception of diastolic blood pressure in all four groups. Correlation coefficients of plasma adiponectin level with MetS related traits: BMI, fasting plasma insulin level, HOMA-IR and plasma CRP level ranged from -0.11 to -0.34 ($P < 0.01$). Correlation coefficients differed in general more than 0.10 between pre- and postmenopausal women, whereas no difference was observed between younger and older men.

The presence of MetS was higher in subgroups with lower plasma adiponectin levels, indicated by the higher OR presented in Figure 1. The highest OR for the presence of MetS was observed for postmenopausal women in the lower plasma adiponectin quartile (OR = 18.6, 95% CI=7.9–44.0) which differed significantly from that seen in the premenopausal women (OR = 4.5, 95% CI=1.7–7.4). We did not observe such extreme differences in OR's between the two male groups.

To assess the value of adiponectin as biomarker for MetS, we analyzed the AUC as a measure of discriminative accuracy according to several models (Table 3). The AUC of age for MetS (model 1)

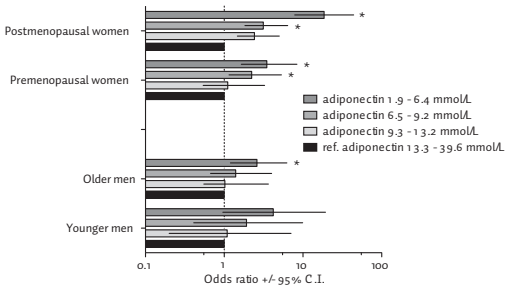

Fig.1. Odds ratio of adiponectin quartiles for presence of the MetS. Bars represent OR ± *95% confidence interval in pre- and postmenopausal women and younger men (<46.8 years old) and older men (>46.8 years old). * P < 0.01, Odds ratio based on logistic (binary) regression adjusted for age and body mass index.*

ranged from 0.55 (95% CI= 0.50 – 0.60) in older men to 0.71 (95% CI= 0.68 – 0.74) in total women. When the discriminatory accuracy for presence of MetS was based on age and BMI (model 2) AUC's ranged from 0.80 (95% CI= 0.76 – 0.83) in postmenopausal women to 0.92 (95% CI= 0.90 – 0.95) in younger men. In the third model, which included age and adiponectin (model 3), AUC's ranged from 0.67 (95% CI= 0.64 – 0.71) in older men to 0.87 (95% CI= 0.85 – 0.89) in the total female group. Finally, when age, adiponectin and BMI all (model 4) were included, we observed the largest AUC's, ranging from 0.84 (95% CI= 0.81 – 0.87) in postmenopausal women to 0.92 (95% CI= 0.90 – 0.95) in younger men.

Table 2: Spearman's correlation coefficients of plasma adiponectin levels with MetS, MetS individual components and MetS related traits.

	Women		**Men**	
	Premenopausal	**Postmenopausal**	**Younger**	**Older**
	(n=695)	(n=581)	(n=418)	(n=549)
Age	-0.03	0.07	-0.14 **	0.12 **
Metabolic syndrome and its individual components				
Metabolic syndrome	-0.23 ***	-0.37 ***	-0.19 ***	-0.22 ***
Waist circumference	-0.30 ***	-0.38 ***	-0.18 ***	-0.24 ***
Glucose	-0.09 *	-0.22 ***	-0.13 **	-0.07
HDL-cholesterol	0.33 ***	0.42 ***	0.29 ***	0.31 ***
Triglycerides	-0.19 ***	-0.34 ***	-0.18 ***	-0.17 ***
Systolic blood pressure	-0.03	0.00	-0.14 **	-0.08
Diastolic blood pressure	-0.01	0.01	-0.09	-0.06
Metabolic syndrome related traits				
Body mass index	-0.26 ***	-0.30 ***	-0.17 ***	-0.21 ***
Insulin	-0.27***	-0.33 ***	-0.18 **	-0.19 ***
HOMA-IR	-0.26 ***	-0.34 ***	-0.19 **	-0.18 ***
C-reactive protein	-0.11 **	-0.25 ***	-0.08	-0.14 **

HDL: high density lipoprotein; HOMA-IR: Homeostatic model assessment-Insulin resistance. Values presented as Spearman's correlation coefficient, * P < 0.05, ** P < 0.01, *** P < 0.001.

DISCUSSION

Low plasma adiponectin is associated with obesity and insulin resistance[15,30] and plasma adiponectin has been proposed as a biomarker for MetS[16,31]. Large differences in mean plasma adiponectin and correlation coefficients with Mets and MetS associated traits have been reported between genders[13,32,33]. Our observations confirmed a significant difference in plasma adiponectin level and

Table 3: Discrimanative accuracy (AUC) of age, BMI and plasma adiponectin in the prediction of MetS.

	Model 1 age	Model 2 age / BMI	Model 3 age / adiponectin	Model 4 age / BMI / adiponectin
Premenopausal women	0.61 (0.56 – 0.67)	0.87 (0.84 – 0.90)	0.72 (0.68 – 0.78)	0.88 (0.85 – 0.91)
Postmenopausal women	0.60 (0.55 – 0.65)	0.80 (0.76 – 0.83)	0.76 (0.72 – 0.80)	0.84 (0.81 – 0.87)
Total women	0.71 (0.68 – 0.74)	0.85 (0.83 – 0.88)	0.87 (0.85 – 0.89)	0.87 (0.85 – 0.89)
Younger men	0.66 (0.60 – 0.72)	0.92 (0.90 – 0.95)	0.71 (0.66 – 0.77)	0.92 (0.90 – 0.95)
Older men	0.55 (0.50 – 0.60)	0.84 (0.80 – 0.87)	0.65 (0.61 – 0.70)	0.85 (0.82 – 0.88)
Total men	0.67(0.64 – 0.71)	0.88 (0.86 – 0.90)	0.73 (0.69 – 0.76)	0.89 (0.87 – 0.91)

BMI: body mass index. Values presented as AUC (95% confidence interval). Detailed description of models see methods.

virtually all aspects of MetS between genders and within gender subgroups (Table 1). As large mean differences are also observed between the male groups (stratified on mean age of onset menopause in women), age seems significant contributor to variation in plasma adiponectin.

We further questioned whether menopausal status, independent from age, affects plasma adiponectin levels and its association with MetS and associated traits. The spearman's ρ correlation coefficients for plasma adiponectin levels with MetS, MetS individual components and associated traits were different in women before and after menopause (Table 2). Furthermore, we observed higher correlation coefficients in postmenopausal women and we observed that correlation coefficients varied to a much lesser extent between both male groups. These findings indicate that menopausal status, independent of age, had a large effect on the correlation of plasma adiponectin with MetS, MetS individual components and MetS associated traits (with exception of diastolic blood pressure).

The correlation of plasma adiponectin with MetS was further investigated by determining the OR for MetS in pre- and postmenopausal women and younger and older men. It is well known that age and body composition strongly influence the manifestation of MetS and that obesity is strongly associated with plasma adiponectin levels. Therefore, we included in addition to age, BMI as covariates in the logistic regression. Although an effect was seen in premenopausal women and both male groups, our analysis showed that the OR of MetS in the lowest adiponectin quartile was the highest in postmenopausal women (OR = 18.6 95% CI = 7.9 – 44.0, figure 1). Because in men such high OR was not observed, these data indicate that the risk for MetS was especially high for postmenopausal women, independently of age.

Our data showed a moderate discriminative accuracy for the presence of MetS, expressed as AUC, of age alone (Table 3, model 1). As obesity is an essential component of MetS, our data further confirmed the high discriminative accuracy for the presence of MetS of age and BMI (Table 3, model 2). As the AUC of age alone was lower compared to the AUC of age and plasma adiponectin (Table 3, models 1 and 3), plasma adiponectin contributed significantly to the discriminative accuracy for the presence of MetS. Including BMI in the model, this discriminative accuracy was even better (Table 3, model 4) and consistent between the genders and gender groups (AUC $\geq$ 0.84). Thus, the contribution of BMI in model 4 was substantial in the discriminative accuracy for the presence of MetS. Our findings further showed that age and BMI are more accurate in detecting the presence of MetS than age and adiponectin (Table 3, models 2 and 3). As measuring BMI is far more cost effective than measuring plasma adiponectin, the clinical utility of plasma adiponectin for the diagnosis MetS is questionable. Nevertheless, the logistic regression analyses indicated a high relative risk for MetS in particular in postmenopausal women with low plasma adiponectin. Since OR's are frequently used

in genetic studies, our data indicate that ignoring menopause may result in underestimation of effect size in genetic association analysis of plasma adiponectin.

The MetS can be diagnosed according to several different definitions[34]. In addition to the IDF MetS definition, a widely used MetS definition has been formulated by the National Cholesterol Education Pogram Adult Treatment Panel III (NCEP ATP III). The IDF and the NCEP ATPIII definitions differ slightly in MetS component threshold values[19,34]. Moreover, in contrast to the NCEP ATPIII, the obesity measure waist circumference is essential in the IDF definition. The Pearson correlation coefficient between IDF and NCEP ATPIII is 0.68 in our study cohort. To investigate whether the differences in MetS definitions affected the associations of plasma adiponectin with MetS or the discriminative accuracies for the presence the MetS, we recalculated all analyses using the NCEP ATPIII MetS definition. These analyses showed similar results obtained with regard to the IDF MetS definition. For example, postmenopausal women in the lower plasma adiponectin quartile showed for the IDF an OR of 18.6 (95% CI=7.9–44.0) and the NCEP ATPIII showed an OR of 16.8, (95% CI=7.8–36.4). In addition, the AUC analyses showed highly similar results (data not shown). These analyses demonstrated that our calculation of OR and the discriminative accuracies for the presence the MetS associated with plasma adiponectin were not determined by the
IDF MetS definition.

In conclusion, the present study confirmed gender differences in the association of plasma adiponectin with MetS and demonstrated that this association was significantly affected by menopause. We showed that adiponectin *per se* was strongly associated with MetS, in particular in postmenopausal women, but then its discriminative accuracy was overruled by the obesity measure BMI. Nevertheless, the strong effect of menopause on the association of plasma adiponectin with MetS and MetS components indicates that inclusion of menopause in genetic association studies of plasma adiponectin will increase statistical power.

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