ORIGINAL RESEARCH

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The relationship between adiponectin and blood pressure in premenopausal and postmenopausal women

Abstract

Purpose: Menopause can affect the reportedly inverse association between adiponectin and blood pressure (BP); however, this relationship is still poorly understood. The present study cross-sectionally compared the relationship between adiponectin and BP in pre- and postmenopausal women.

Methods: Healthy, asymptomatic women on no medication ($n = 262$) were divided into a premenopausal group ($n = 125$, mean age 44.7 years) and a postmenopausal group ($n = 137$, mean age 65.6 years). Fasting values of serum adiponectin and BP were measured, in addition to body mass index (BMI), blood glucose and lipids. The correlation between the levels of adiponectin/BMI and mean BP (MBP) was analyzed with a linear regression model for the respective groups.

Results: The median adiponectin/BMI did not significantly differ between the pre- and postmenopausal groups (0.37 and 0.42, $P = 0.08$), and the premenopausal group had a significantly lower level of mean MBP than the postmenopausal group (87.6 and 100.7 mmHg, $P < 0.001$). In an unadjusted analysis, adiponectin/BMI was found to be significantly and inversely correlated with MBP in the premenopausal group ($r = -0.499$, $P < 0.001$) and the postmenopausal group ($r = -0.203$, $P < 0.01$), respectively. In a stepwise multivariate-adjusted analysis, adiponectin/BMI remained significantly, inversely and independently correlated with MBP in the premenopausal group ($\beta = -0.383$, $P < 0.001$), while no significant correlation was found between adiponectin/BMI and MBP for the postmenopausal group.

Conclusions: The adiponectin-BP relationship appears to be associated with premenopausal state.

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Hypertension is an important health problem worldwide because of its high prevalence and associated risk for cardiovascular disease [1]. Increased blood pressure (BP) is frequently interrelated with increased body mass index (BMI) and obesity [2]. Adiponectin, a major adipocytokine, has anti-inflammatory and anti-atherosclerotic functions, and is reportedly associated with cardiometabolic disorders including obesity, dyslipidemia and hypertension [3,4].

Menopause is known to compound cardiovascular disease risk factors, including body fat distribution change and BP increase, because estrogen withdrawal influences systemic cardiometabolic functions [5,6]. Higher concentrations of circulating adiponectin have been found in women in comparison with men [7], and the 'menopausal metabolic syndrome' in postmenopausal women has also been proposed as a new concept [5]. In fact, the menopausal state is suggested to significantly affect the association between low adiponectin concentrations and the increased prevalence of metabolic syndrome [8].

In contrast to many reports showing that adiponectin inversely correlates with increased BP and hypertension [9-19], several reports have not supported this association [20-24]. Furthermore, many studies have examined the association between adiponectin and BP/hypertension only in male subjects [12] or without a complete separate analysis between the two sexes [9,11,13,14,16-23]. In addition, there are no studies that have included menopausal information in the analysis on the association between adiponectin and BP/hypertension [10, 15,24]. The objective of the present study was to investigate the

relationship between adiponectin and BP in premenopausal and postmenopausal women. Considering that adiponectin is derived specifically from adipose tissue, the level of BMI-adjusted adiponectin (adiponectin/BMI) was used as a measure of adiponectin in this study, as reported previously [25-27].

Methods

A total of 262 healthy, asymptomatic female subjects, on no medication, ranging from 40–70 years of age, were recruited during health check-ups in community-based health education classes and outpatient clinics. The study population was composed of a premenopausal group ($n = 125$) and a postmenopausal group ($n = 137$) (Table 1). The eligible subjects were identified as follows: 1) non-smoking, 2) non-diabetic (defined as a fasting plasma glucose < 6.1 mmol/L), 3) absence of hypercholesterolemia (defined as a fasting serum total cholesterol < 5.7 mmol/L), 4) absence of hypertriglyceridemia (defined as a fasting serum triglyceride (TG) < 1.7 mmol/L), 5) absence of hypocholesterolemia of high-density lipoprotein (HDL) (defined as a fasting serum HDL-cholesterol ≥ 1.3 mmol/L), 6) no apparent dysfunction of kidney (defined as a fasting serum creatinine < 11.3 mmol/L), and 7) no apparent history of cardiovascular, thyroid, hematological or liver diseases. The study was approved by the Jichi Medical University ethics committee and all subjects gave their informed consent.

Postmenopause was self-reportedly determined as cessation of menses for a period of 12 months or longer [28]. The body height was measured to the nearest 0.1 cm and weight

TABLE 1. Clinical characteristics of the pre- and postmenopausal groups

Variables	Premenopausal ($n = 125$)	Postmenopausal ($n = 137$)	P-value
Age, years	44.7 ± 4.9	64.6 ± 4.4	$< 0.001^{**}$
BMI, kg/m ²	23.4 ± 4.3	24.0 ± 3.5	0.207
Systolic blood pressure, mmHg	119.8 ± 14.3	140.3 ± 19.2	$< 0.001^{**}$
Diastolic blood pressure, mmHg	71.6 ± 10.8	80.9 ± 12.4	$< 0.001^{**}$
Mean blood pressure, mmHg	87.6 ± 11.0	100.7 ± 13.7	$< 0.001^{**}$
Total cholesterol, mmol/L	5.08 ± 0.48	5.06 ± 0.57	0.534
Triglyceride, mmol/L	0.84 (0.62-1.15)	1.03 (0.81-1.31)	$< 0.001^{**}$
HDL-cholesterol, mmol/L	1.67 ± 0.29	1.61 ± 0.40	0.163
Plasma glucose, mmol/L	4.92 ± 0.42	5.10 ± 0.46	0.001 [*]
Adiponectin, $\mu\text{g/mL}$	8.8 (5.6-12.7)	9.9 (6.5-15.0)	0.015 [*]
Adiponectin/BMI	0.37 (0.23-0.62)	0.42 (0.26-0.63)	0.084

BMI: body mass index, HDL: high-density lipoprotein. The values are expressed as the mean $\pm$ standard deviation in parametrically distributed variables or median (interquartile range) in non-parametrically distributed variables. The values of triglyceride, adiponectin and the adiponectin/BMI were analyzed after log-transformation because of their skewed data distributions. Significance level (calculated using an unpaired t-test): * $P < 0.05$, ** $P < 0.01$.

FIGURE 1. Correlations between the adiponectin/body mass index and the mean blood pressure in the pre- and postmenopausal groups.

Left panel: the premenopausal group ($n = 125$; correlation coefficient = -0.499 , $P < 0.001$). Right panel: the postmenopausal group ($n = 137$; correlation coefficient = -0.203 , $P = 0.018$).

was measured to the nearest 0.1 kg with digital scales using a body analyzer system (OMRON Healthcare Co. Ltd., Kyoto, Japan), while subjects wore light indoor clothes and no shoes. The BMI was calculated as body weight (kg) divided by the square of height (m). Sampling blood required a prohibition against alcohol consumption and exercise the preceding day, and an overnight 10-12 hour fast. The serum total cholesterol, TG, HDL-cholesterol and fasting plasma glucose levels were measured enzymatically methods (reagents: Sekisui Co. Ltd., Tokyo, Japan) as well as serum creatinine levels were measured enzymatically (reagent: Wako Pure Chemical Ind. Ltd., Tokyo, Japan) using an autoanalyzer system (Hitachi High-Technologies Co. Ltd., Tokyo, Japan). The serum total adiponectin concentrations were measured with an enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) with intra- and inter-assay coefficients of variation of 3.3% and 7.4%, respectively [29]. Systolic BP (SBP) and diastolic BP (DBP) were measured in the seated subject's right arm with an appropriate cuff size using a mercury sphygmomanometer after 5 minutes of rest, as recommended previously [30]. The BP measurements were taken twice, and then were averaged for the analysis. The mean BP (MBP), calculated by the formula: $DBP + (SBP - DBP)/3$, was used as a variable of the overall BP in multivariate-adjusted analyses.

The data were expressed as the mean $\pm$ standard deviation (SD) or the median plus interquartile range. The data between the groups were compared using an unpaired t-test. A simple and stepwise multiple linear regression model was utilized to observe the correlation between adiponectin/BMI (as a dependent variable) and other variables including BP (as independent variables) as well as between MBP (as a dependent variable) and other variables (as independent variables). All of the measured variables were entered for multivariate-adjusted analyses into the stepwise regression model. Because of a close correlation between SBP and DBP in this study (correlation coefficient: > 0.7 in both groups), MBP was entered into the model, instead of the simultaneous analysis of SBP and DBP. The values of TG, adiponectin and adiponectin/BMI were log-transformed for all of the analyses because of their skewed distributions. A P-value of less than 0.05 was considered to be statistically significant.

Results

Clinical characteristics of the premenopausal and postmenopausal women are outlined in Table 1. The premenopausal group had significantly lower age and levels of SBP, DBP, MBP, TG, glucose and adiponectin than the postmenopausal group. While the premenopausal group tended to have a lower

TABLE 2. Correlations between anthropometric and cardiometabolic variables (independent variables) and adiponectin/BMI (as a dependent variable) in the pre- and postmenopausal groups

Variable	Premenopausal		Postmenopausal	
	r (P-value)	β (P-value)	r (P-value)	β (P-value)
Age, years	0.002 (0.981)	not determined	0.181 (0.034)*	not determined
Systolic blood pressure, mmHg	-0.381 (<0.001)**	-	-0.172 (0.044)*	-
Diastolic blood pressure, mmHg	-0.515(<0.001)**	-	-0.197 (0.021)*	-
Mean blood pressure, mmHg	0.499 (<0.001)**	0.383 (<0.001)**	0.203 (0.018)*	not determined
Total cholesterol, mmol/L	0.202 (0.024)*	not determined	0.172 (0.045)*	not determined
Triglyceride, mmol/L	0.459 (<0.001)**	0.244 (0.005)**	0.309 (<0.001)**	0.200 (0.016)*
HDL-cholesterol, mmol/L	0.356 (<0.001)**	0.182 (0.026)*	0.404 (<0.001)**	0.339(<0.001)**
Plasma glucose, mmol/L	0.106 (0.241)	not determined	0.038 (0.657)	not determined

BMI: body mass index, HDL: high-density lipoprotein. -: variable not entered into the stepwise multivariate-adjusted analysis model. The values of triglyceride and the adiponectin/BMI were analyzed after log-transformation because of their skewed data distributions. Significance level (r: correlation coefficients in a simple linear regression analysis, β : correlation coefficients in a stepwise multiple linear regression analysis):

*P < 0.05, **P < 0.01.

adiponectin/BMI than the postmenopausal group, there were no significant difference in the adiponectin/BMI between the groups.

In the premenopausal group, simple linear regression analysis of the adiponectin/BMI (as a dependent variable; Table 2) indicated that adiponectin/BMI was significantly and inversely correlated with SBP, DBP, MBP, total cholesterol and TG, as well as significantly and positively correlated with HDL-cholesterol. In the postmenopausal group, the adiponectin/BMI was significantly and inversely correlated with SBP, DBP, MBP and TG, as well as significantly and positively correlated with age, total cholesterol and HDL-cholesterol. In the premenopausal group, subsequent multivariate-adjusted analysis (Table 2) indicted that adiponectin/BMI was significantly, inversely and independently correlated with MBP, while adiponectin/BMI was significantly and independently correlated and TG (inverse) and HDL-cholesterol (positive). In the postmenopausal group, adiponectin/BMI was found to be significantly and independently correlated with TG (inversely) and HDL-cholesterol (positively), similar to the results of the premenopausal group, while there was no significant correlation between adiponectin/BMI and MBP.

In the premenopausal group, simple linear regression analysis of MBP (as a dependent variable; Table 3) showed that MBP was significantly and positively correlated with SBP, DBP, total cholesterol, TG and glucose, as well as significantly and inversely correlated with adiponectin/BMI. In the postmenopausal group, MBP was significantly and positively correlated with SBP, DBP and TG, as well as significantly and inversely correlated with adiponectin/BMI. In the premeno-

pausal group, subsequent multivariate-adjusted analysis (Table 3) indicated that MBP was significantly, inversely and independently correlated with adiponectin/BMI, while the positive correlation between MBP and total cholesterol and between MBP and glucose remained. In the postmenopausal group, MBP was significantly, positively and independently correlated with TG, while a correlation was no longer observed between the MBP and adiponectin/BMI

Discussion

The present study showed a significant and independent inverse correlation between adiponectin/BMI and MBP in premenopausal, but not postmenopausal, women. While the present study also showed a significant and independent correlation between adiponectin/BMI and TG (inverse) and HDL-cholesterol (positive), these results were consistent with a previous study [25]. The finding of a significant inverse correlation between adiponectin/BMI and MBP only in premenopausal women suggests that menopause can affect the adiponectin-BP relationship; namely, premenopause may be a relatively specific condition during which this relationship exists. It is worth noting that the extension of this finding to menopause provides new insight into the current knowledge regarding the association between adiponectin and BP/hypertension.

The mechanism of the association between adiponectin and BP levels remains to be established. While this appears to be complex association, there are several possible explanations: for example, nitric oxide-mediated endothelial dysfunction, an activation of the renin-angiotensin system and an increase in the sympathetic nervous activity in a reduction of adiponectin [3]. One study reported that estrogen inhibits adiponect-

TABLE 3. Correlations between anthropometric and cardiometabolic variables (independent variables) and the mean blood pressure (as a dependent variable) in the pre- and post-menopausal groups

Variable	Premenopausal		Postmenopausal	
	r (P-value)	β (P-value)	r (P-value)	β (P-value)
Age, years	0.170 (0.058)	not determined	0.113 (0.187)	not determined
Systolic blood pressure, mmHg	0.883 (<0.001)**	–	0.908 (<0.001)**	–
Diastolic blood pressure, mmHg	0.950 (<0.001)**	–	0.945 (<0.001)**	–
Total cholesterol, mmol/L	0.264 (0.003)**	0.174 (0.026)*	0.072 (0.400)	not determined
Triglyceride, mmol/L	0.348 (<0.001)**	not determined	0.291 (0.001)**	0.291 (0.001)**
HDL-cholesterol, mmol/L	-0.169 (0.059)	not determined	-0.091 (0.288)	not determined
Plasma glucose, mmol/L	0.245 (0.006)**	0.198 (0.010)*	0.165 (0.054)	not determined
Adiponectin/BMI	-0.499 (<0.001)**	-0.443 (<0.001)**	-0.203 (0.018)*	not determined

BMI: body mass index, HDL: high-density lipoprotein. –: variable not entered into the stepwise multivariate-adjusted analysis model. The values of triglyceride and the adiponectin/BMI were analyzed after log-transformation because of their skewed data distributions. Significance level (r: correlation coefficients in a simple linear regression analysis, β : correlation coefficients in a stepwise multiple linear regression analysis): *P < 0.05, **P < 0.01.

in [31], while other studies have reported that there were no overt clinical effects of estrogen on adiponectin [21,32]; thus, the changes in several sex hormones that occur with the onset of menopause may influence circulating adiponectin concentrations. Although an earlier study did not include information regarding menopause [21], that study demonstrated that, in a somewhat different pattern in male subjects, serum adiponectin concentrations sharply increased with convex-curved behavior until the subjects reached 50 years of age (which is the average menopausal age in Japanese women [33]) and then gradually increased in female subjects [21]. The sharp increase in adiponectin until the subjects reached 50 years of age may be related to a clear direct correlation between adiponectin and BP in the menopausal group observed in our present study.

A limitation of this study is that sex hormones were not measured. Due to the cross-sectional study design, a cause-effect relationship between adiponectin and BP cannot be shown. Unfortunately, data on waist circumference or other parameters of abdominal adiposity and fat distribution (i.e., based on the dual-energy X-ray absorptiometry and computed tomography scans) were not measured in this study. Future studies using a longitudinal design with a greater sample size and more informative data on obesity are warranted.

In summary, a significant inverse correlation between adiponectin/BMI and MBP was found among premenopausal women but not postmenopausal women. These data indicate that the adiponectin-BP relationship may have an important role in the premenopausal state as compared to the postmenopausal condition. Experiments to clarify the effects of menopause on the association between adiponectin and MBP are therefore planned for further studies.

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