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Metabolism Clinical and Experimental 60 (2011) 180 – 185
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Serum concentrations of high–molecular weight adiponectin and their association with sex steroids in premenopausal women

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Received 24 July 2009; accepted 9 December 2009

Abstract

At present, the association between adiponectin and sex hormones in women is controversial. Recent studies suggest that it is high–molecular weight (HMW) adiponectin and the HMW to total adiponectin ratio rather than total adiponectin that are associated with antiatherogenic activities, insulin sensitivity, metabolic syndrome, and prediction of cardiovascular events. The present study aimed to investigate whether measuring HMW adiponectin and the HMW to total adiponectin ratio rather than total adiponectin might be more useful to detect an association between circulating female sex steroids and adipocytokines. In a clinical trial, we investigated the associations of total adiponectin, HMW adiponectin, and the HMW to adiponectin ratio with several androgens and estradiol in 36 healthy premenopausal women with regular cycles. No association between the investigated sex hormones and adiponectin was observed. The HMW adiponectin was negatively correlated with estradiol after adjustment for age and body mass index. The HMW to total adiponectin ratio was significantly negatively associated with testosterone, free testosterone, and androstenedione. The testosterone to estradiol ratio, as a parameter for the estrogen-androgen balance, was not associated with adiponectin or the HMW isoform. In conclusion, there is a negative association between estradiol and HMW adiponectin, and between testosterone, free testosterone, and androstenedione and the HMW to adiponectin ratio. Thus, one mechanism whereby female sex steroids may influence the cardiovascular risk of women could be alteration of the relationship between HMW and total adiponectin concentrations in plasma.

1. Introduction

Today, adipose tissue is viewed as an important endocrine organ secreting numerous biologically active molecules, termed *adipocytokines* [1]. Adiponectin is the most abundant adipocytokine and is expressed exclusively by adipose tissue [2]. It has been shown to possess anti-inflammatory and antioxidative properties [3]. Several studies describe its important role in the pathogenesis of insulin resistance, metabolic syndrome (MS), and cardiovascular disease [4-9]. In contrast to other adipokines, which increase as the fat mass increases, circulating levels of adiponectin are paradoxically decreased in obese subjects compared with lean subjects [7,10]. Three isoforms of circulating adiponectin have been described: a low–molecular weight (LMW) trimer, a medium–molecular weight (MMW) hexamer, and high–molecular weight (HMW) multimers [11-13]. In vitro data demonstrate the ability of HMW adiponectin to suppress apoptosis of endothelial cells [14]. In addition, there is considerable evidence that the HMW isoform is the major active form in plasma. Recent studies suggest that it is HMW adiponectin and the HMW to total adiponectin ratio rather than total adiponectin that are associated with antiatherogenic activities, insulin sensitivity, MS, and prediction of cardiovascular events [15-18].

Although there is evidence that adiponectin expression and secretion are regulated by tumor necrosis factor–α and glucocorticoids, sex differences in adiponectin levels support the view that sex hormones are involved in the expression of adiponectin [19]. These sex differences are of importance because they might contribute to the differences in the cardiovascular risk between women and men. Adiponectin plasma concentrations decline during progression of puberty,

The study has been approved by the local ethical committee. Participants gave their consent prior to inclusion.

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0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.12.010

and this decline is associated with the increase in testosterone [20,21]. Higher circulating adiponectin concentrations have been found in women compared with men [10,20,22-24]. In postmenopausal women, higher adiponectin concentrations have been described than in premenopausal women [23,25,26]. However, in terms of the relationship between circulating adiponectin concentrations and circulating ovarian steroids, data are conflicting [24,26-29]. The plasma concentration of adiponectin does not change during the menstrual cycle, and only a few studies found a correlation between adiponectin and circulating estrogen and testosterone [24,25,29,30]. This indicates that the mechanism responsible for the regulation of adiponectin by sex hormones is complex. Some authors have suggested that not only estrogen or androgen levels alone, but the estrogen-androgen balance might be of importance [24]. We hypothesize that in addition to estradiol, testosterone, and the estrogen-androgen balance, progesterone, androstenedione, and dehydroepiandrostenedione sulfate (DHEA-S) might be involved in the regulation of adiponectin. Adiponectin is differentially expressed in women and men, and differs between premenopausal and postmenopausal women [24,31,32]. To generate a homogenous study population, we therefore decided to include exclusively premenopausal women for the present project.

In contrast to stable concentrations of MMW and LMW adiponectin in women, HMW concentrations are higher during postmenopause and lower during pregnancy and premenopause [25]. Therefore, it can be speculated that mainly the HMW isoform of adiponectin is sensitive to female sex hormones. We further hypothesize that this isomer or the HMW to total adiponectin ratio might be better correlated with estrogen or androgen levels than total adiponectin [33].

To test this hypothesis, we conducted a study investigating the association between sex hormones and HMW adiponectin as well as the HMW to total adiponectin ratio in healthy premenopausal nonobese women.

2. Material and methods

Thirty-six volunteers were recruited from the Family Planning Centre of the University Hospital Zürich. Inclusion criteria were regular menstrual cycles in the 2 months preceding the start of the study, age between 18 and 40 years, and blood pressure within the reference range. Exclusion criteria were any regular use of medication, use of hormones, smoking, and body mass index (BMI) greater than 30 kg/m^2. Informed consent was obtained from all participants, and the study was approved by the local ethical committee.

Blood pressure, weight, and height were measured by well-trained staff. Body mass index was calculated from weight and height. Venous blood samples were collected between 8:00 AM and 10:00 AM after overnight fasting during the early phase of the menstrual cycle (days 2-5). This procedure was chosen to avoid any influence of physiologic fluctuations of sex hormones during the cycle on our results. Plasma was separated within 30 minutes and stored at −70°C until assayed. For each patient, samples from all visits were thawed and assayed in the same batch.

Serum levels of both HMW adiponectin and total adiponectin were determined by enzyme-linked immunosorbent assay (ELISA) detection (Multimeric Adiponectin ELISA Kit; Bühlmann Laboratories, Schönenbuch, Switzerland). In addition to total adiponectin, HMW adiponectin serum levels can be determined by this ELISA after protease treatment to digest LMW and MMW adiponectin. Sensitivity of the assay is 0.08 ng/mL. Intraassay coefficients variations (CVs) were 5.3% to 5.4% for total adiponectin and 3.3% to 5.0% for HMW adiponectin; interassay CVs were 5.0% and 5.7% for total adiponectin and for HMW adiponectin, respectively. The results are expressed as micrograms per milliliter. Serum controls for both total and HMW adiponectin were measured with each assay.

Estradiol, progesterone, testosterone, free testosterone (FT), androstenedione, DHEA-S, and sex hormone–binding globulin (SHBG) were analyzed by commercially available radioimmunoassays (estradiol—intraassay CV, 4.2%; interassay CV, 4.9%; sensitivity, 18 pmol/L; Sorin Biomedica Diagnostics, Saluggia, Italy; progesterone—intraassay CV, 3.6%; interassay CV, 3.9%; sensitivity, 0.06 nmol/L; Diagnostic Products, Los Angeles, CA; testosterone—intraassay CV, 4.5%; interassay CV, 5.1%; sensitivity, 0.1 nmol/L; CIS Diagnostic, Dreieich, Germany; androstenedione—intraassay CV, 2.7%; interassay CV, 4.8%-7%; FT—intraassay CV, 2.8%; interassay CV, 8.0%; sensitivity, 0.15 pg/mL; Diagnostic Products; DHEA-S—intraassay CV, 3.5%; interassay CV, 4.9%; sensitivity, 0.03 μmol/L; CIS Diagnostic; SHBG—intraassay CV, 2.8%; interassay CV, 7.9%; sensitivity, 0.04 nmol/L; Diagnostic Products).

3. Statistical analysis

Analyses were performed using SPSS 17.0 software (SPSS, Chicago, IL), and a P value < .05 was considered statistically significant. Demographic and biochemical data are expressed as mean (SD) or, when distribution was skewed, as median [range]. The testosterone to estradiol ratio and the ratio between FT and estradiol were calculated as parameter for the individual estrogen-androgen balance. Associations of sex hormones and sex hormone ratios with adiponectin, HMW adiponectin, and the HMW to adiponectin ratio were tested using linear regression analyses with and without adjustment for age and BMI. Parameters with skewed distributed (HMW adiponectin, adiponectin, HMW to adiponectin ratio) were log-transformed before analysis.

4. Results

The demographic and biochemical characteristics of the study group are presented in Table 1. Out of 36 women recruited, 32 blood samples were eligible for analyses. Four

Table 1
Demographic and biochemical characteristics of the study group

Variable (unit)	
n	32
Age (y)	35 (6.5)
Systolic blood pressure (mm Hg)	117 (9.8)
Diastolic blood pressure (mm Hg)	77 (6.3)
BMI (kg/m^2)	18.7 (1.4)
Estradiol (pmol/L)	116 (49)
Progesterone (nmol/L)	2.3 (0.8)
Testosterone (nmol/L)	1.4 (0.4)
FT (pmol/L)	4.0 (2.3)
Androstenedione (nmol/L)	7.1 (6.9)
DHEA-S (nmol/L)	4.4 (2.3)
SHBG (nmol/L)	58.66 (6.06)
Adiponectin (μg/mL)	6.5 [3.3;11.4]
HMW adiponectin (μg/mL)	4.6 [1.4;7.8]
HMW to adiponectin ratio	0.7 [0.4;0.9]
Testosterone to estradiol ratio	0.01 (0.006)
FT to estradiol ratio	0.031 (0.02)

Data are given as median [range] in case of skewed distribution and mean (SD) when normally distributed.

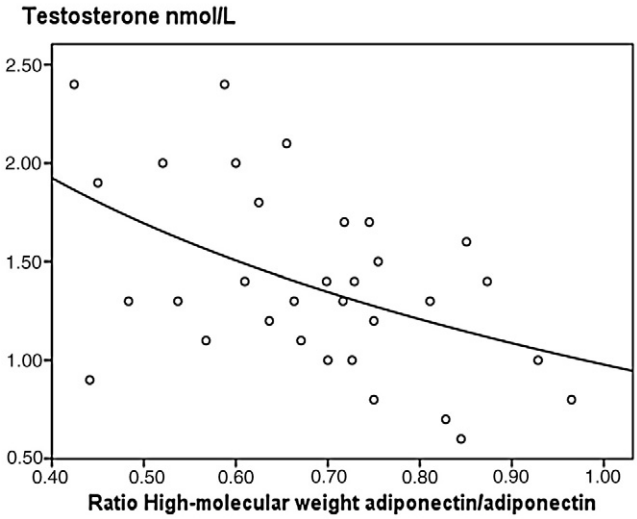

Fig. 1. Correlations between testosterone and HMW adiponectin to adiponectin ratio.

participants had to be excluded because they did not attend the clinic in the early phase of their cycle.

Table 2 presents the results of the univariate regression analysis before and after adjustment for age and BMI. No associations between adiponectin and sex hormones were found before and after adjustment for age and BMI. The HMW isoform was associated only with estradiol and only after adjusting for age and BMI. In contrast, the HMW to adiponectin ratio was significantly associated with androgens (testosterone, FT, and DHEA-S). After adjustment for age and BMI testosterone, FT and androstenedione were associated with the HMW to adiponectin ratio. Of all sex hormones, testosterone was found to be much more strongly associated in comparison with the other androgens or estradiol (Fig. 1). No associations were found between the adipocytokines and the testosterone to estradiol ratio or the FT to estradiol ratio.

5. Discussion

To our knowledge, this is the first human study investigating the association between the HMW adiponectin

Table 2
Linear regression analyses of sex hormones and sex hormone ratios (independent variables) vs serum adiponectin, HMW adiponectin, and HMW to adiponectin ratio

Sex hormones and ratios	Adiponectin	*P* value	HMW adiponectin	*P* value	HMW to total adiponectin	*P* value
Unadjusted						
Estradiol	−0.15	.40	−0.29	.10	0.28	.12
Progesterone	0.10	.58	0.24	.18	0.31	.08
Testosterone	−0.06	.72	−0.24	.18	−0.42	.02
FT	−0.08	.64	−0.19	.24	−0.35	.04
Androstenedione	−0.05	.76	−0.18	.32	−0.29	.11
DHEA-S	−0.16	.37	−0.26	.14	−0.36	.04
SHBG	0.12	.5	0.12	.5	0.09	.61
Testosterone to estradiol	0.08	.63	0.07	.70	0.021	.90
FT to estradiol	−0.12	.48	−0.12	.51	0.08	.65
Adjusted for age and BMI						
Estradiol	−0.36	.06	−0.42	.02	−0.325	.08
Progesterone	0.14	.46	0.22	.23	0.277	.14
Testosterone	0.01	.98	−0.25	.17	−0.50	.005
FT	−0.18	.34	−0.31	.09	−0.412	.024
Androstenedione	−0.09	.64	−0.25	.17	−0.37	.043
DHEA-S	−0.04	.83	−0.18	.32	−0.34	.06
SHBG	0.21	.26	0.18	.33	0.08	.65
Testosterone to estradiol	0.18	.32	0.01	.47	0.001	.99
FT to estradiol	−0.11	.54	−0.14	.45	−0.13	.49

Variables with skewed distributed were log-transformed before analysis.

isomer and androgens in healthy premenopausal women. In accordance with our hypothesis, the importance of the HMW isoform in the interaction with sex hormones was demonstrated not only in the significant negative association between estradiol and HMW adiponectin, but also in the negative association between the HMW to adiponectin ratio and FT, testosterone, DHEA-S, and androstenedione. Our data do not confirm the hypothesis that the estrogen-androgen balance is more associated with adiponectin concentrations than testosterone or estradiol alone. Furthermore, the androgen to estrogen ratio was not found to be associated with the HMW isoform or the HMW to adiponectin ratio.

Previous studies detected neither fluctuations of adiponectin during the menstrual cycle nor correlations of adiponectin with estradiol in the cycle [29]. Estradiol treatment of ovariectomized or postmenopausal women can result in an increase, no change, or a decrease in adiponectin [27,28,34]. Regarding the missing association between total adiponectin and estradiol, our data are in line with those of some, but not all, authors [24-27,29,32,35]. The following explanations may apply for some of the conflicting results. Most studies have been conducted in postmenopausal women or men with low estrogen levels and altered adiponectin levels as a consequence of diabetes, hypertension, or MS, whereas we investigated healthy premenopausal women [22,26,34,36,37]. In addition, adjustment for age and BMI has not always been performed. Both factors exert an important influence on adiponectin plasma levels [6,10,29,38]. Only one prior study examined the association between estradiol and the HMW isoform, which, as previously mentioned, is the active form of adiponectin in plasma [25]. In this latter investigation, a negative association between HMW adiponectin and estradiol was reported in accordance with our findings, supporting the view that the circulating concentrations of the HMW isoform are more strongly influenced by estradiol than the concentrations of total adiponectin [25].

We could not confirm the finding of a negative association between HMW adiponectin and progesterone in the same study, possibly because of differences between the study groups, which included pregnant women with supraphysiologic progesterone levels. It could be proposed that progesterone at far beyond physiologic levels may exert an effect on HMW adiponectin, whereas at physiologic levels, its effects on adipose tissue are insignificant. In accordance with this proposal, in vitro investigations were unable to demonstrate a consistent effect of progesterone on fat cell differentiation or metabolism; and progesterone receptors messenger RNAs (mRNAs) were barely detectable [39].

Regarding the effect of androgens, the negative association of androgens with the HMW to adiponectin ratio was strongest for testosterone. Free testosterone, androstenedione, and DHEA-S are less associated in both unadjusted and adjusted analysis.

Adipose tissue is a target organ for sex steroid action. The suppressive effect of androgens on adiponectin in vivo is undisputed: In hypogonadal men, testosterone treatment suppresses adiponectin; and antiandrogenic therapy of women with polycystic ovary syndrome causes an increase in circulating adiponectin [36,40-43]. The mechanisms underlying the regulatory effect of testosterone on adiponectin production are still poorly understood. Androgen receptors are present in preadipocytes and adipocytes, particularly in visceral adipocyte tissue; and it has been suggested that testosterone might modulate adiponectin expression via these receptors [44]. On the other hand, newer in vitro data reveal a strong suppression of adiponectin mRNA expression after incubation with male serum, but not after incubation with testosterone alone [45]. Furthermore, testosterone does not interfere with the mRNA abundance of the adiponectin gene in adipocytes, suggesting that the regulation occurs at a posttranscriptional level [31,45-47].

Why does testosterone treatment cause a decrease in circulating adiponectin, whereas, on the other hand, it is not associated with adiponectin plasma concentrations in the present and several other studies [26,36,43,48]? Xu et al [47] demonstrated in rodents and hypogonadal men that testosterone reduces selectively circulating concentrations of HMW adiponectin, but not LMW and MMW adiponectin. These data provide evidence for a testosterone-mediated reduction only of HMW adiponectin secretion from adipocytes and explain the failure to find an association between adiponectin and testosterone in this and several other studies. The influence of testosterone on HMW adiponectin is, however, reflected in our results, even if the shown association between testosterone and the HMW to total adiponectin ratio, together with the failing association between this androgen and the HMW isoform, indicates that the underlying mechanisms are complex. Xu et al [47] speculate that the 3 oligomeric complexes of adiponectin might be released from adipocytes via distinct secretory pathways, which renders it possible for testosterone to selectively impede the secretion of HMW adiponectin from adipocytes.

The widespread presence of receptors for HMW adiponectin in the cardiovascular system, muscle, and nervous system serves to underline the important metabolic role of this cytokine [1]. Clinical studies have revealed the close association between a low HMW to total adiponectin ratio and the development of diabetes, MS, hypertension, and cardiovascular disease [12,18,22,35]. Given the important role of HMW adiponectin in increasing insulin sensitivity and in preventing atherosclerosis, the sexual differences in HMW adiponectin might partly explain the fact that men have a higher incidence of atherosclerosis and are more susceptible to insulin resistance than women.

Because the relative influence of estrogens and androgens on adiponectin and its HMW isoform is still under debate, our study focused on the influence of sex hormones on these cytokines in healthy premenopausal women. According to

our results, elevation of testosterone might result in a decrease in HMW to adiponectin ratio, which as mentioned above is believed to have a negative metabolic impact. Theoretically, hormonal treatment could, by modifying the HMW to adiponectin ratio, modulate cardiovascular risk factors in young women. Hormonal contraception, for example, may influence the HMW to adiponectin ratio directly or via its effect on circulating testosterone and estradiol. Given the cardiovascular risk associated with long-term use of hormonal contraceptives, modifications of HMW adiponectin might contribute to the elevated cardiovascular risk seen in those women. However, this has not been shown and will be the focus of future studies.

The effect of DHEA-S on adipocytokines has been investigated in vitro, in animal studies, and in a small study with HIV-positive patients. In vitro, DHEA-S has been shown to increase adiponectin expression [49]. Dehydroepiandrostenedione sulfate treatment of rats, but not of HIV-positive humans, raises adiponectin plasma levels [50,51]. After adjustment for age and BMI, we detected no correlation between DHEA-S and total adiponectin, the HMW isoform, or the HMW to total adiponectin ratio. Therefore, we suppose that, in premenopausal women, the role of physiologic levels of DHEA-S in the regulation of adiponectin and the HMW isomer is less important than that of testosterone.

Investigation of the association between HMW adiponectin and the HMW to total adiponectin ratio with androgen plasma levels as well as estradiol and the estrogen to androgen ratio in healthy young women is the novelty of the present study. Blood samples were taken in the morning because fasting levels of adiponectin are relatively stable during the morning hours. Although 2 authors did not demonstrate fluctuations of adiponectin during the regular cycle, to date, it remains unknown whether the—in women, more important HMW isoform varies. Therefore, we took all blood samples during the same phase of the cycle. Another advantage of our study is that women were premenopausal, healthy, and of normal weight, inasmuch as BMI as well as several diseases and menopause may change the level of adiponectin and the HMW isomer. In addition, all associations were tested before and after adjustment for age and BMI. Our study has some limitations. Although the results are quite clear, the data have to be regarded as preliminary because of the small sample size. Furthermore, our findings may apply only for premenopausal women. The data are not qualified for conclusions on the underlying regulatory mechanisms. Testosterone and FT are measured by radioimmunoassays, which are less accurate in comparison with gas chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry. Absolute testosterone concentrations measured by radioimmunoassay have been shown to be falsely high in comparison with those measure by mass spectrometric methods. Because we focused not on absolute steroid hormone values but on the correlation between testosterone and adiponectin isomers, this lack of precision should only have a minor influence on our results. Even if measurements with mass spectrometry are very precise and are expected to be the criterion standard in the future, there are at the moment interlaboratory differences in steroid measurement, too, which are not solved yet [52].

In conclusion, this study demonstrates that, in premenopausal women, estradiol is negatively associated with HMW adiponectin, whereas the androgens testosterone, FT, and androstenedione are negatively associated with the HMW to total adiponectin ratio. Thus, one mechanism whereby sex steroids may influence the cardiovascular risk of women could be the alteration of the relation between HMW and total adiponectin in the plasma through testosterone or estradiol.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2009.12.010.

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