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Altered relationship between body fat and plasma adiponectin in end-stage renal disease

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Abstract

Patients with end-stage renal disease (ESRD) show an inverse association between body mass index and risk of death from cardiovascular disease. Paradoxical epidemiology may suggest some beneficial effects of body fat in ESRD. Because an antiatherogenic adipocytokine adiponectin is increased in uremic plasma, we tested a hypothesis that, in ESRD, plasma adipocytokine profile may be less atherogenic or that the relationship between body fat and adipocytokines may be altered. The subjects were 103 patients with ESRD undergoing hemodialysis and 166 healthy subjects comparable in age and sex. We measured body fat mass by dual-energy x-ray absorptiometry and plasma levels of adiponectin and leptin by enzyme-linked immunosorbent assay. The ESRD group showed a significant increase in plasma adiponectin, leptin, and adiponectin/leptin ratio than the healthy subjects. Although sex and fat mass were significant factors correlating with plasma adiponectin level in the healthy group, none of these were significantly associated with plasma adiponectin in the patients with ESRD. In contrast, leptin showed significant relationships with sex and fat mass regardless of the presence of ESRD. Plasma adiponectin correlated negatively with plasma triglycerides and positively with high-density lipoprotein cholesterol in both healthy and ESRD groups, suggesting that uremic adiponectin retains its actions in favor of its antiatherogenicity. Thus, plasma adipocytokine profile was altered in ESRD, and the effects of body fat and sex on adiponectin were less significant in the patients with ESRD.

1. Introduction

Atherosclerosis is advanced [1-4] and cardiovascular mortality rate is substantially elevated [5] in patients with end-stage renal disease (ESRD). In contrast to the general population, a lower body mass index in patients with ESRD is one of the major predictors of increased all-cause and cardiovascular mortality rates [6,7]. The reverse epidemiology [8] may be explained by several possibilities such as the coexistence of malnutrition, inflammation, and atherosclerosis [9]. Another explanation would be that adipose tissue might play some protective roles against death in some conditions such as ESRD, although no previous study examined such a possibility.

Adipose tissue produces not only atherogenic factors but also antiatherogenic proteins. For example, adipocytes secrete tumor necrosis factor α [10], plasminogen activator inhibitor 1 [11], and leptin [12], resulting in insulin resistance, blood coagulation, atherosclerosis, and other health problems. Adiponectin, or apM1, has been newly identified as another adipocyte-derived secretary protein that is the most abundant protein that human fat cells express [13]. In contrast to other adipocytokines, adiponectin has antiatherogenic properties such as inhibition of monocytic cell adhesion to endothelial cells [14], suppression of vascular smooth muscle cell proliferation [15], and inhibition of foam cell formation from macrophages [16]. Plasma concentration of adiponectin is decreased in patients with coronary artery disease [17] and type 2 diabetes mellitus [17-19]. Adiponectin concentration is higher in women than in men [17], and it is inversely correlated with

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body mass index in subjects without uremia [19-21]. Zoccali et al [22] reported that adiponectin level was a significant predictor of reduced risk for cardiovascular events in their hemodialysis cohort. Interestingly, unlike other high-risk groups, their patients undergoing hemodialysis had 2 to 3 times higher plasma adiponectin concentration than healthy control subjects. We [23] recently reported that the molecular forms of adiponectin in uremic plasma were not different from those in nonuremic plasma and no adiponectin fragments were detected in uremic plasma, suggesting that patients with ESRD have an increased plasma level of intact adiponectin.

In the present study, we measured adiponectin and another adipocytokine leptin in patients undergoing hemodialysis to test the hypothesis that plasma adipocytokine profile may be less atherogenic in patients undergoing hemodialysis than in healthy subjects. Also, we examined the possibility that a relationship between body fat and adipocytokines may be altered in ESRD.

2. Methods

2.1. Subjects

This study consisted of 103 nondiabetic patients with ESRD treated with hemodialysis and 166 healthy subjects. These 2 groups were comparable in age and sex. No one was treated with a thiazolidinedione, which is known to affect adiponectin concentration. Characteristics of the subjects are given in Table 1. They gave informed consent and this study was approved by the institutional ethical committee (Inoue Hospital Approval No. 111).

Table 1
Subjects

	Healthy subjects	Patients with ESRD	*P*
Number	166	103	–
Sex (M/F)	51:115	36:67	.471
Age (y)	52.6 ± 0.7	53.8 ± 0.9	.329
Height (m)	1.58 ± 0.01	1.57 ± 0.01	.351
Weight (kg)	57.0 ± 0.6	52.6 ± 0.8	<.0001
Fat mass (kg)	14.1 ± 0.3	13.1 ± 0.5	.094
Lean mass (kg)	42.9 ± 0.6	39.5 ± 0.7	.0002
Body mass index (kg/m^2)	22.8 ± 0.2	21.3 ± 0.2	<.0001
Systolic BP (mm Hg)	122 ± 1	151 ± 3	<.0001
Diastolic BP (mm Hg)	75 ± 1	86 ± 1	<.0001
Total cholesterol (mg/dL)	202 ± 2	167 ± 4	<.0001
Triglycerides (mg/dL)	110 ± 4	119 ± 6	.197
HDL cholesterol (mg/dL)	61 ± 1	40 ± 1	<.0001
Glucose (mg/dL)	98 ± 1	77 ± 1	<.0001
Insulin (μU/mL)	6.5 ± 0.4	6.9 ± 0.4	.563
Creatinine (mg/dL)	–	11.9 ± 0.2	–
Years on HD	–	7.6 ± 0.5	–

P Values by analysis of variance with the exception of that for gender (χ^2 test). Mean ± SE.
BP indicates blood pressure; HDL, high-density lipoprotein; HOMA-IR, insulin resistance index by homeostasis model assessment; HD, hemodialysis.

The patients undergoing hemodialysis received 12 to 15 hours of hemodialysis per week using bicarbonate dialysate. The diagnosis of renal disease was chronic glomerulonephritis (n = 74), toxemia of pregnancy (n = 7), polycystic kidney (n = 4), hypertensive nephrosclerosis (n = 4), lupus nephritis (n = 3), gout (n = 2), and others (n = 9). Diabetic patients were excluded because of the known effect of diabetes mellitus on plasma adiponectin levels [17].

The healthy subjects were participants of a local health check program in Osaka City who had no liver dysfunction, no proteinuria, and no fasting hyperglycemia of 126 mg/dL or higher.

2.2. Measurement of body fat mass

Body fat mass was directly measured by dual-energy x-ray absorptiometry using a QDR-2000 (Hologic, Waltham, Mass). Reproducibility (CV) of the measurement was less than 2% [24].

2.3. Assays of adiponectin, leptin, and others

Blood was collected in the morning after an overnight fast into tubes containing EDTA-2Na. Plasma was separated by centrifugation at 4°C and kept frozen at −40°C until assays were performed. Plasma adiponectin concentration was measured by enzyme-linked immunosorbent assay as described by Arita et al [20]. Plasma leptin concentration was measured by radioimmunoassay using a commercial kit (Linco Research Inc, St Charles, Mo) as previously described [25]. Other measurements were done by routine biochemical methods.

2.4. Statistical analysis

Continuous variables were summarized as mean ± SE, and the difference between means was evaluated by analysis of variance. Difference in prevalence was evaluated by χ^2 test. Correlation between variables was evaluated by linear regression. *P* Values less than .05 were taken to be significant. All these analyses were performed with commercial software for Windows computers (StatView 5, SAS Institute Inc, Cary, NC).

3. Results

3.1. Plasma adiponectin, leptin and adiponectin/leptin ratio

The patients with ESRD showed a significantly increased mean plasma adiponectin level than the healthy subjects (Fig. 1). The ESRD group also showed a significant increase in plasma leptin, another adipocytokine. The ratio of adiponectin to leptin was significantly elevated in the ESRD group as compared with that of the healthy group.

3.2. Effects of body fat and sex on adipocytokines

The healthy group was divided into 8 categories according to sex and body fat mass at the interval of 5 kg to examine the effects of sex and fat mass on adipocytokine levels (Fig. 2).

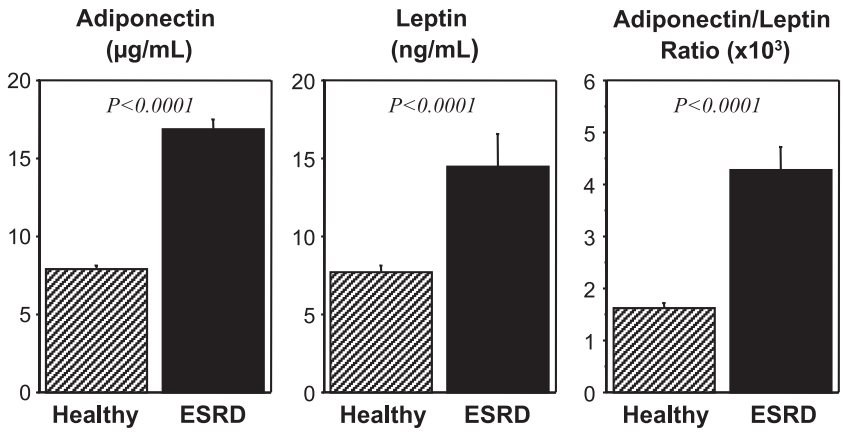

Fig. 1. Comparison of plasma adipocytokine levels between the healthy (n = 166) and ESRD (n = 103) groups. Mean ± SE. *P* values by analysis of variance.

Leptin level was higher in women than in men and in those with larger amounts of fat mass. Plasma adiponectin was also higher in women than in men but was lower in those with larger amounts of body fat. These effects of sex and fat mass were highly significant in the healthy subjects.

The ESRD group was similarly divided into 8 categories according to sex and body fat mass (Fig. 2). As was in the healthy subjects, leptin was higher in women than in men and in those with larger amounts of body fat. In contrast, plasma adiponectin was not significantly different between men and women in the ESRD group. Also, no significant association was found between body fat mass and adiponectin in the patients with ESRD.

3.3. Correlations between plasma adiponectin and other metabolic parameters

In the healthy subjects, plasma adiponectin correlated negatively with triglycerides and positively with high-

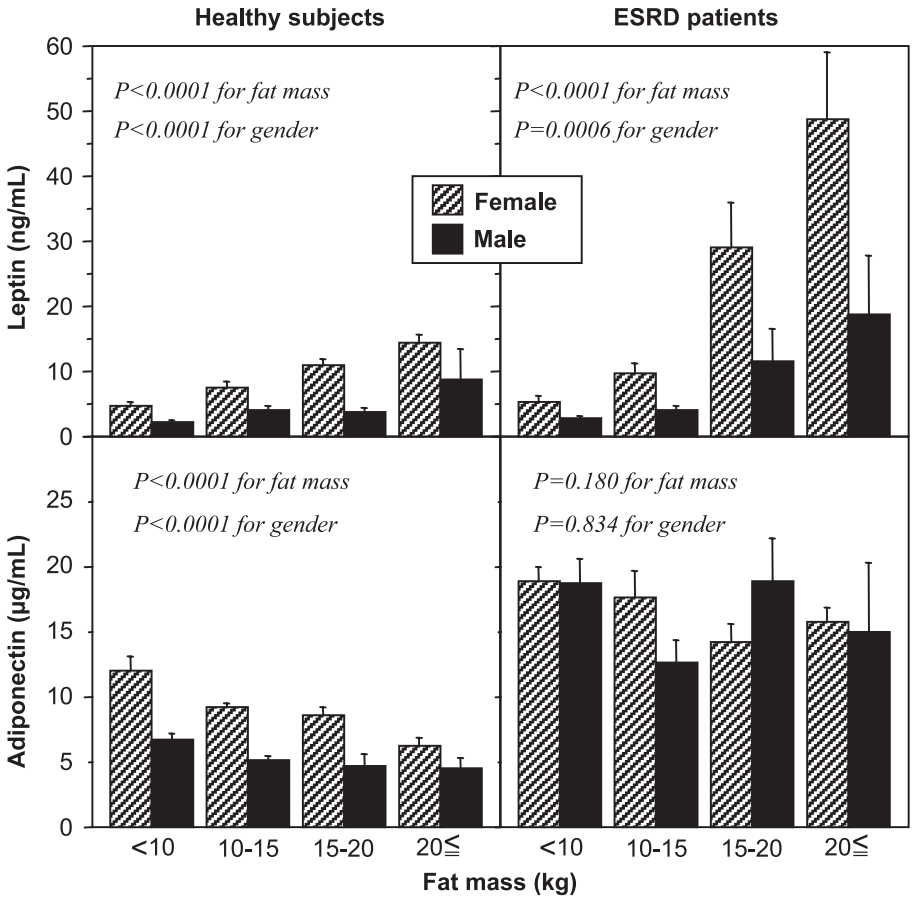

Fig. 2. Relationship between body fat mass and plasma adipocytokine levels. The healthy group was stratified into 8 categories by sex and fat mass, and the effects of sex and fat mass were evaluated by 2-way analysis of variance (left panels). The same analysis was performed for the ESRD group (right panels).

Table 2
Correlation between plasma adiponectin and other parameters

	Healthy			ESRD		
	Women	Men	Total	Women	Men	Total
Body mass index	−0.391*	−0.413**	−0.336*	−0.168	−0.245	−0.186
Fat mass	−0.432*	−0.337***	−0.179***	−0.207	−0.158	−0.179
Lean mass	−0.183***	−0.463*	−0.502*	0.000	−0.146	−0.043
Total cholesterol	0.084	−0.016	0.169***	−0.001	−0.037	−0.015
Triglycerides	−0.202***	−0.313***	−0.290*	−0.253***	−0.444**	−0.342*
HDL cholesterol	0.416*	0.449*	0.485*	0.284***	0.432**	0.332*
Fasting glucose	−0.034	−0.291***	−0.138	−0.132	−0.118	−0.126
Insulin	−0.103	−0.260	−0.152	−0.076	0.198	0.045
HOMA-IR	−0.101	−0.270	−0.176***	−0.071	0.149	0.042
Leptin	−0.197***	−0.221	0.060	−0.163	−0.145	−0.130
Age	0.050	0.145	0.114	0.149	−0.260	−0.015
Years on HD	–	–	–	0.023	−0.226	−0.088

The table gives simple regression coefficients (r values) and level of significance.
Abbreviations are explained in the second footnote to Table 1.
* $P < .001$.
** $P < .01$.
*** $P < .05$.

density lipoprotein cholesterol (Table 2). These correlations remained significant when analyzed in men and women separately. The same was true for the patients with ESRD. Plasma adiponectin did not show consistent correlations with total cholesterol, blood glucose, insulin, leptin, age, or years on hemodialysis treatment.

4. Discussion

In the present study, patients with ESRD showed a significant increase in both adiponectin and leptin, and the increase in adiponectin was more pronounced as evidenced by a significant elevation of the adiponectin/leptin ratio in the ESRD group. In contrast to the healthy subjects, however, adiponectin in the patients with ESRD showed no significant correlation with body fat or sex. These results show the relative increase in antiatherogenic adipocytokine and an altered relationship between fat mass and adipocytokine in ESRD.

There is a paradoxical and inverse association between higher adiposity and lower risk of mortality in patients with ESRD [6,7], suggesting that the adverse effect of increased adipose tissue is reduced or even reversed in ESRD. With this regard, the present finding may be of importance in that the effect of body fat on adiponectin concentration was not significant in the patients with ESRD. This finding was in sharp contrast to the significant association between fat mass and leptin in the ESRD group, resulting in the significantly elevated adiponectin/leptin ratio in the patients with ESRD. These results suggest that the overall effect of adipocytokines may be less atherogenic in the patients with ESRD than in the healthy subjects.

We confirmed the increased plasma adiponectin level in patients with ESRD that was first reported by Zoccali et al [22] and recently by Huang et al [26]. The present study confirmed their report that significant correlations were present between adiponectin and plasma lipids in favor of its antiatherogenic functions in both healthy and ESRD groups. We recently reported that no adiponectin fragments were detected in uremic plasma by gel filtration chromatography followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis/Western blotting [23], suggesting that patients undergoing hemodialysis had apparently intact forms of adiponectin. Thus, the increased adiponectin in ESRD appeared to have biologic effects, although we do not know the mechanism for the increased adiponectin in ESRD.

The present study failed to find significant difference in adiponectin between sexes in the patients with ESRD. A recent study by Nishizawa et al [27] revealed that the sex-related difference in adiponectin was due not to estrogen but to androgen and that testosterone decreased the secretion of adiponectin. Therefore, reduced testosterone levels in male patients with ESRD [28] would explain the absence of sex-related difference in adiponectin.

There are some differences between our results and the report by Zoccali et al [22]. They found the sex-related difference in adiponectin and the inverse association between adiponectin and body mass index in their patients undergoing hemodialysis, whereas we failed to confirm these associations using the same enzyme-linked immunosorbent assay system for adiponectin measurement. The reasons for the differences are unknown, but the study by Zoccali et al used only body mass index whereas we used fat mass directly measured by x-ray absorptiometry. Ethnicity was different between the 2 studies. The mean body mass index was higher in the Italian patients than in our Japanese patients. We excluded diabetic patients whereas Zoccali et al included them.

In conclusion, our study revealed the changes in plasma adipocytokine profile and the fat mass-adipocytokine relationship in ESRD. Further studies are needed to elucidate the roles of this interesting protein in nutritional and metabolic disorders and cardiovascular disease among patients with ESRD.

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