Adiponectin Is Related to CD146, a Novel Marker of Endothelial Cell Activation/Injury in Chronic Renal Failure and Peritoneally Dialyzed Patients

JOLANTA MALYSZKO, JACEK S. MALYSZKO, SZYMON BRZOSKO, SLAWOMIR WOLCZYNSKI, AND MICHAL MYSLIWIEC

Department of Nephrology and Transplantology, Department of Endocrinological Gynecology, Medical University, 15-540 Białystok, Zarauvia 14, Poland

Adiponectin has antiatherogenic properties and attenuates endothelial inflammatory responses. CD146 is a novel cell adhesion molecule localized at the endothelial junction. In renal failure, endothelial dysfunction and atherosclerosis are almost universal. We studied possible correlations between adiponectin, CD146, and other markers of endothelial cell injury in patients with chronic renal failure (CRF) on conservative treatment and patients with and without diabetic nephropathy maintained on chronic ambulatory peritoneal dialysis (CAPD).

We assessed adiponectin, tissue factor pathway inhibitor (TFPI), plasminogen activator inhibitor (PAI-1), thrombin-activatable fibrinolysis inhibitor, and endothelial function/injury markers: von Willebrand factor, thrombomodulin, vascular cell adhesion molecule (VCAM), intercellular adhesion molecule, and CD146.

Adiponectin was elevated in patients with CRF and on CAPD. It correlated significantly, with PAI-1, thrombin-activatable fibrinolysis inhibitor, intercellular adhesion molecule, VCAM, and CD146 in nondiabetics on CAPD. In diabetics, CAPD adiponectin correlated positively with C146 and VCAM and negatively with PAI and TFPI. In multivariate regression analysis, only CD146 remained a positive predictor of adiponectin in all CAPD patients. In CRF, adiponectin correlated with CD146. In healthy volunteers, adiponectin correlated with TFPI and CD146.

Elevated adiponectin related to CD146 may be the expression of a counterregulatory response aimed at mitigating the consequences in endothelial damage and increased cardiovascular risk in renal failure. (J Clin Endocrinol Metab 89: 4620–4627, 2004)
previous studies (24) indicated that CAPD patients presented a hypercoagulable state. According to Zoccali et al. (12), elevated adiponectin in hemodialyzed patients and nephrotic syndrome (13), two entities prone to cardiovascular events, may act as a protective factor against atherosclerosis in these patients. In hypertensive patients, adiponectin was found to be higher than in normotensive patients (25). Due to the fact that endothelial cell damage or injury is invariably associated with such clinical conditions as thrombosis, hypertension, renal failure, and atherosclerosis, and adiponectin is considered as a novel modulator for endothelial adhesion molecules, the aim of the study was to assess adiponectin in correlation with markers of endothelial cell injury in patients with CRF on conservative treatment or maintained on CAPD.

Patients and Methods

Open-label, unblinded evaluation of the pathological differences between four groups of subjects was used: CRF patients, diabetic and nondiabetic CAPD patients, and healthy volunteers. The study was performed on 39 nondiabetic patients with CRF on conservative treatment (age range, 24–69 yr; 22 females, 17 males) admitted to the hospital to undergo kidney biopsy, 43 nondiabetic patients maintained on CAPD (age range, 23–70 yr; 24 females, 19 males), and 19 diabetic CAPD patients (age range, 48–77 yr; 6 females, 13 males) who met the following criteria: a stable clinical state, no thrombosis or inflammation (C-reactive protein within normal range), without uncontrolled hypertension, no oral contraception in women of child-bearing age, stable, and no more than twice the normal alanine aminotransferase and aspartaginine aminotransferase activities (upper range 45 U/liter). None of the patients investigated had received blood transfusions for at least 1.5 months, and no drugs known to affect hemoestasis were administered for at least 2 wk prior to the study. All the CRF subjects were biopsied, and histopathological diagnosis was established as follows: IgA nephropathy in 14 cases, membrano-proliferative glomerulonephritis in eight cases, membranous nephropathy in six cases, focal segmental glomerulosclerosis in four cases, and submicroscopic glomerulonephritis in one case. Biopsy was not diagnostic in six cases. During the study, none of the patients received prednisone, anticoagulants, or cytotoxic drugs. In nondiabetic CAPD patients, renal failure was due to glomerulonephritis (n = 28; biopsy-proven glomerulonephritis, n = 21), chronic interstitial nephritis (n = 10), polycystic kidney disease (n = 4), and unknown cause (n = 1). CAPD patients with diabetic nephropathy (n = 19) due to type 2 diabetes mellitus were also included in the study (glycosylated hemoglobin, 8.5–12%). All the diabetic CAPD patients were treated with sc insulin. All the patients were informed about the aim of the study and gave their consent. The study was approved by the local ethics committee (Medical University, Białystok, Poland).

Blood was drawn in the morning between 0800 and 0900 h to avoid circadian variations (26) and anticoagulated with 3.8% sodium citrate (volume corrected for hematocrit). The dialyzed patients were on CAPD for 1–5 yr (mean time on CAPD for nondiabetic patients was 24 months vs. 18 months for diabetic CAPD patients, P > 0.05). All the CAPD patients were performing 4-2 exchanges a day. According to the peritoneal equilibration test, none of the patients had highly permeable peritoneal membrane. They were using the Baxter Twin Bag system or the Fresenius Stay Safe system. Dwell times were generally 4–6 h during the day and 8 h overnight. The glucose concentration ranged from 1.36–3.86%. None of the patients was administered with icodextrin. The osmotic pressure of CAPD fluid was adjusted in accordance with the extent of ultrafiltration in each patient. Dialysis adequacy was assessed by measuring urea kinetic modeling (mean urea kinetic modeling, 2.38 ± 0.44). The control group consisted of 33 healthy volunteers (age range, 26–62 yr; 19 females, 14 males) recruited mainly from the medical staff and their families. Venous blood samples were collected into 3.8% sodium citrate in 9:1 volume ratio. The blood was centrifuged at 2500 × g for 15 min at room temperature to yield platelet-poor plasma. Samples were stored frozen at −40°C before analysis.

All the tests performed can be categorized as follows: for assessment of coagulation, tissue factor pathway inhibitor (TFPI) (also considered as a marker of endothelial dysfunction); for assessment of fibrinolysis, PAI-1 and thrombin-activatable fibrinolysis inhibitor (TAI); and for assessment of endothelial function/injury, von Willebrand factor (vWF), thrombomodulin, VCAM, ICAM, and CD146.

Plasma adiponectin was assayed using a commercially available RIA (Human Adiponectin RIA kit; Linco Research, St. Charles, MO). Markers of endothelial cell injury (vWF and thrombomodulin) and adhesion molecules (ICAM and VCAM) were studied by ELISA using commercially available kits from American Diagnostica (Greenwich, CT) and R&D Systems (Quantikine, Abingdon, UK), respectively. CD146 was assayed by ELISA using kits from Biocytex (Marseille, France; CyQuant ELISA). PAI was assayed using commercially available kits from Biopool (Umea, Sweden). TFPI was studied using kits from American Diagnostica. TAFI concentration was assayed using kits from Affinity Biologicals (Hamilton, Ontario, Canada). Hemoglobin, erythrocyte count, platelet count, fibrinogen, total protein, cholesterol, triglycerides, and albumin concentration were measured by standard laboratory methods.

Data given were analyzed using Statistica 5.1 computer software. Normality of variable distribution was tested using the Shapiro-Wilk W test. If possible, data were logarithmically transformed to achieve normal distribution (thrombomodulin, age). Data were reported as means ± sd. ANOVA (with post hoc Tukey test for unequal groups) or Kruskall-Wallis ANOVA (the difference between the mean of two variables was calculated by Mann-Whitney U test) were used to compare differences between groups with P < 0.05 considered statistically significant, when appropriate. Linear regression analysis employed Pearson or Spearman coefficients as appropriate. Multiple regression analysis was used to determine independent factors affecting dependent variables. Factors showing linear correlation with adiponectin were included in multiple regression analysis.

Results

Basal clinical characteristics of the studied groups are presented in Table 1. Healthy volunteers and both groups of patients with CRF (on dialyses and on conservative treatment) did not differ significantly regarding age and body mass index. In diabetic CAPD patients, platelet count was significantly higher when compared with nondiabetic CAPD patients, CRF patients, and healthy volunteers. Fibrinogen was significantly elevated in the three groups of patients with renal failure relative to the healthy volunteers. Fibrinogen was significantly higher in diabetic and nondiabetic CAPD patients relative to CRF. Triglycerides and cholesterol were elevated in diabetic and nondiabetic CAPD patients when compared with the control group and CRF patients, whereas total protein and albumin were significantly lower in nondiabetic and diabetic CAPD subjects when compared with CRF and the control group.

Markers of endothelial cell injury, thrombomodulin, vWF, ICAM, VCAM, and CD146, were significantly elevated in nondiabetic and diabetic CAPD patients and CRF patients when compared with healthy volunteers with the highest values observed in CAPD patients. Concentrations of TFPI were significantly higher in patients with renal failure when compared with the healthy volunteers. Concentrations of TAFI were higher in diabetic and nondiabetic CAPD patients than in CRF patients. TAFI concentration in healthy volunteers was significantly lower when compared with three groups of patients with renal failure. Adiponectin in CAPD patients was significantly higher when compared with patients with CRF on conservative treatment. Adiponectin in diabetic CAPD patients tended to be lower than in nondiabetic CAPD subjects; however, the difference did not reach
TABLE 1. Biochemical characteristics of patients with CRF, peritoneally dialyzed subjects with diabetic nephropathy (CAPD + DM) and without diabetic nephropathy (CAPD), and the control group

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 33)</th>
<th>CRF (n = 39)</th>
<th>CAPD + DM (n = 19)</th>
<th>CAPD (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.0 ± 10.9</td>
<td>49.4 ± 12.6</td>
<td>56.8 ± 9.2</td>
<td>52.3 ± 13.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 3.4</td>
<td>23.7 ± 3.2</td>
<td>25.1 ± 2.4</td>
<td>24.6 ± 2.8</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14.6 ± 2.19</td>
<td>12.35 ± 2.74</td>
<td>11.80 ± 1.34</td>
<td>10.99 ± 1.57</td>
</tr>
<tr>
<td>Platelet count (× 10⁹/liter)</td>
<td>234 ± 62</td>
<td>195 ± 64</td>
<td>287 ± 82</td>
<td>232 ± 87</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.87 ± 0.29</td>
<td>3.98 ± 2.04</td>
<td>6.96 ± 1.93</td>
<td>7.78 ± 2.31</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>(μmol/liter)</td>
<td>(351.83 ± 180.34)</td>
<td>(615.26 ± 170.61)</td>
<td>(687.75 ± 204.20)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>(210 ± 84)</td>
<td>(313 ± 62)</td>
<td>416 ± 109</td>
<td>394 ± 116</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>(174.62 ± 34.23)</td>
<td>(198.46 ± 38.85)</td>
<td>226.14 ± 50.12</td>
<td>226.54 ± 53.08</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>(81.42 ± 34.51)</td>
<td>(136.28 ± 38.94)</td>
<td>146.57 ± 59.60</td>
<td>184.07 ± 73.45</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>(0.92 ± 0.39)</td>
<td>(1.54 ± 0.44)</td>
<td>(1.66 ± 0.67)</td>
<td>(2.08 ± 0.83)</td>
</tr>
<tr>
<td>(g/liter)</td>
<td>(6.91 ± 3.32)</td>
<td>(65.12 ± 10.52)</td>
<td>(60.93 ± 8.70)</td>
<td>(62.93 ± 8.04)</td>
</tr>
<tr>
<td>platelet factor 3</td>
<td>(4.48 ± 1.05)</td>
<td>(3.89 ± 0.99)</td>
<td>3.17 ± 0.61</td>
<td>3.34 ± 0.56</td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>(44.84 ± 10.52)</td>
<td>(38.91 ± 9.85)</td>
<td>(31.71 ± 6.12)</td>
<td>(33.4 ± 5.59)</td>
</tr>
</tbody>
</table>

Data given are means ± SD.

* P < 0.05; * P < 0.01; * P < 0.001 vs. control.

** P < 0.05; ** P < 0.01; ** P < 0.001 CRF vs. CAPD, CRF vs. CPAD + DM.

# P < 0.05 CAPD + DM vs. CAPD.

b × 88.4.
c × 0.026.
d × 0.0113.

TABLE 2. Hemostasis in patients with CRF, peritoneally dialyzed subjects with diabetic nephropathy (CAPD + DM) and without diabetic nephropathy (CAPD), and the control group

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 33)</th>
<th>CRF (n = 39)</th>
<th>CAPD + DM (n = 19)</th>
<th>CAPD (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD146 (μg/ml)</td>
<td>310.1 ± 104.9</td>
<td>378.9 ± 138.2</td>
<td>650.3 ± 166.49</td>
<td>575.8 ± 142.8</td>
</tr>
<tr>
<td>ICAM (ng/ml)</td>
<td>95.41 ± 46.78</td>
<td>181.7 ± 150.3</td>
<td>290.8 ± 81.1</td>
<td>253.8 ± 111.2</td>
</tr>
<tr>
<td>VCAM (ng/ml)</td>
<td>450.1 ± 179.8</td>
<td>1237.3 ± 259.2</td>
<td>1797.6 ± 645.6</td>
<td>1781.0 ± 538.3</td>
</tr>
<tr>
<td>Thrombomodulin (ng/ml)</td>
<td>3.10 ± 1.28</td>
<td>9.53 ± 3.19</td>
<td>13.06 ± 4.16</td>
<td>12.98 ± 4.02</td>
</tr>
<tr>
<td>vWF (%)</td>
<td>87.53 ± 8.12</td>
<td>137.74 ± 28.61</td>
<td>138.74 ± 16.45</td>
<td>147.32 ± 32.43</td>
</tr>
<tr>
<td>TFPI concentration (ng/ml)</td>
<td>35.787 ± 6.89</td>
<td>67.43 ± 25.43</td>
<td>107.15 ± 46.56</td>
<td>110.65 ± 45.52</td>
</tr>
<tr>
<td>TAFI concentration (% of standard plasma)</td>
<td>114.13 ± 33.72</td>
<td>176.54 ± 58.60</td>
<td>267.98 ± 76.65</td>
<td>234.41 ± 113.29</td>
</tr>
<tr>
<td>PAI concentration (ng/ml)</td>
<td>8.12 ± 2.21</td>
<td>13.12 ± 5.76</td>
<td>14.08 ± 4.73</td>
<td>13.98 ± 3.21</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>9.68 ± 5.68</td>
<td>16.58 ± 1.94</td>
<td>26.00 ± 14.33</td>
<td>36.08 ± 23.19</td>
</tr>
</tbody>
</table>

Data given are means ± SD.

* P < 0.05; * P < 0.01; * P < 0.001 vs. control.

** P < 0.05; ** P < 0.01 CRF vs. CAPD, CRF vs. CPAD + DM.

/ P < 0.05; / P < 0.01 CAPD + DM vs. CAPD.

statistical significance (P = 0.09). In diabetic CAPD patients, levels of TAFI, ICAM, and CD146 were significantly higher when compared with nondiabetic CAPD patients.

Patients with CRF on the conservative treatment had no preexisting CVD (ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease). Seventeen CAPD patients (both diabetic and nondiabetic) with CRF (ischemic heart disease, n = 14; and myocardial infarction, n = 3) were older than 45 patients on CAPD without CVD (56.07 ± 10.67 vs. 47.59 ± 12.82 yr, P < 0.001), had lower serum high-density lipoprotein (39.33 ± 4.30 vs. 52.67 ± 9.61 mg/dl, P < 0.01), higher plasma PAI levels (15.05 ± 4.25 vs. 11.68 ± 2.59 ng/ml, P < 0.01), and lower serum adiponectin (28.91 ± 9.31 vs. 46.27 ± 13.79 μg/ml, P < 0.001). The rest of the studied parameters did not differ significantly between these two groups. Adiponectin did not depend upon histopathological diagnosis in CRF patients or underlying disease in CAPD patients (glomerulonephritis vs. chronic interstitial nephritis), except diabetes in these subjects.

Adiponectin correlated significantly with CD146 (r = 0.46; P < 0.01; Fig. 1), ICAM (r = 0.40; P < 0.05; Fig. 2), VCAM (r = 0.29; P < 0.05; Fig. 3). PAI concentration (r = −0.50; P < 0.05) and TAFI concentration (r = −0.41; P < 0.05) in nondiabetic CAPD patients. In CAPD patients with diabetic nephropathy, adiponectin was related negatively to PAI concentration (r = −0.56; P < 0.05) and positively to VCAM (r = 0.53; P < 0.05) and CD146 (r = 0.55; P < 0.05; Fig. 4). In addition, CD146 correlated with vWF (r = 0.51; P < 0.05) in diabetic CAPD patients. In patients with CRF on conservative treatment, adiponectin correlated with CD146 (r = 0.32; P < 0.05; Fig. 5), whereas in healthy volunteers, adiponectin correlated with CD146 (r = 0.44; P < 0.05; Fig. 6) and TFPI concentration (r = −0.51; P < 0.05).

Multiple regression analysis in CAPD patients without diabetic nephropathy showed that adiponectin was independently related only to CD146 (β-value, 0.44; P < 0.01). The equation explained 52% of the variation of adiponectin in this group. β-values were as follows: for PAI-1, −0.41, P = 0.05;
for TAFI, −0.25, P = 0.2; for ICAM, −0.2, P = 0.92; and for VCAM, 0.19, P = 0.35. Multiple adjusted $r^2$ for variables in the equation was 0.52 ($F = 6.2179; P < 0.00479; \text{se of estimate} = 0.38627$).

In multiple regression analysis (all CAPD patients with and without diabetic nephropathy), adiponectin was also independently related only to CD146 ($\beta$-value, 0.41; $P = 0.001$). The equation explained 33% of the variation of adiponectin in this group. $\beta$-values were as follows: for PAI, −0.34, $P = 0.05$; for VCAM, 0.18, $P = 0.16$; and for TFPI, 0.21, $P = 0.09$. Multiple adjusted $r^2$ for variables in the equation was 0.29 ($F = 8.0069; P < 0.00020; \text{se of estimate} = 0.38242$).

**Discussion**

We have reported for the first time that adiponectin is related to CD146, a novel endothelial cell injury marker, in patients with renal failure maintained on conservative treatment or peritoneal dialyses and healthy volunteers. Moreover, plasma CD146 is a positive predictor of adiponectin in CAPD patients (nondiabetic and diabetic). We have also shown correlations between adiponectin and other markers of endothelial cell injury as well as with PAI in CAPD patients.

Adipose tissue secretes various bioactive substances, including leptin, TNFa, adiponectin, and PAI-1 (an important
source), and may thus contribute to the CVD. PAI is closely involved in the development of atherosclerosis. In CAPD patients, prone to atherosclerosis and cardiovascular complications, adiponectin was inversely related to PAI in both diabetic and nondiabetic peritoneally dialyzed subjects. In the recent study, Maruyoshi et al. (27) reported a similar correlation in patients with stable angina. Moreover, in multiple regression analysis, PAI, in addition to sex and angina pectoris, was an independent determinant of hyperadiponectinemia. In our study, PAI was higher and adiponectin was lower in CAPD patients with CVD than in patients without CVD. However, in patients with CVD, correlation between adiponectin and PAI did not reach statistical significance ($r = -0.51, P = 0.084$). Correlation between PAI-1 and adiponectin in CAPD patients (both diabetic and nondiabetic) may support the hypothesis that adiponectin acts as a protective factor for the cardiovascular system. Adiponectin binds to the major collagen components of the vascular intima and accumulates in the vascular wall when the endothelium is damaged (11). Adiponectin suppresses the attachment of monocytes to endothelial cells (8), the fundamental step of experimental vascular damage as well as an
early event in the atherosclerotic process. Adhesion molecules, i.e. E-selectin, ICAM-1, and VCAM-1, have been detected in human atherosclerotic lesions (28). In our recent study (29), we reported CRF patients (n/H11005 23), particularly maintained on CAPD (n/H11005 24), exhibited an evidence of endothelial cell injury. In this study, we further evaluated correlation between adiponectin and markers of endothelial damage in larger population and found that adiponectin was related to CD146 and adhesion molecules in CAPD patients. In patients without renal failure, hypoadiponecetinemia is closely related to endothelial dysfunction (30, 31). In hypertensive patients (essential hypertension), adiponectin was positively related to endothelium-dependent vasodilation (31) or to peak forearm blood flow and total reactive hyperemic flow in men (30). Moreover, in the recent study, Tan et al. (32) showed an association between low adiponectin and impaired endothelium-dependent vasodilation. This association was independent of diabetes mellitus (type 2). In contrast, endothelium-independent vasodilation was related to adiponectin in healthy volunteers but was not significantly associated with adiponectin in impaired fasting glucose, glucose intolerance, or type 2 diabetes mellitus (33). It has been suggested that adiponectin appeared to be significantly related to vascular dysfunction in apparently healthy humans.

FIG. 5. Correlation between plasma adiponectin and plasma CD146 in patients with CRF on conservative treatment (linear regression analysis, \( r = 0.32, P < 0.05 \)).

FIG. 6. Correlation between plasma adiponectin and plasma CD146 in healthy volunteers (linear regression analysis, \( r = 0.40, P < 0.05 \)).
On the other hand, in these studies, no correlations between adiponectin and renal function as well as adiponectin and other markers of endothelial cell injury were evaluated. In nephrotic syndrome, adiponectin was inversely related to glomerular filtration rate (13), whereas in our study on patients with renal failure without nephrotic syndrome, adiponectin was not related to CRF or proteinuria. In the study of Stenvinkel et al. (34), no significant correlations among adiponectin, age, and renal function (assessed as glomerular filtration rate) were observed in hemodialyzed patients. Insulin-dependent diabetes mellitus patients (n = 17) have significantly higher adiponectin than nondiabetic patients (n = 71) and noninsulin-dependent diabetes mellitus (n = 19) patients. Adiponectin between nondiabetic patients and noninsulin-dependent diabetes mellitus subjects did not differ significantly, as we observed in our study. In the study of Zoccali et al. (12), only hemodialyzed diabetic women had lower adiponectin than nondiabetic women. In contrast to the former study (12), no difference in adiponectin was noted comparing 70 hemodialyzed patients without a history of CVD and 37 patients with a history of CVD (34). Our CAPD patients with a history of CVD had significantly lower adiponectin than patients without a history of CVD. As stated by Stenvinkel et al. (34), the classification in CVD in their study was made only on the basis of clinically manifest events; therefore, the true prevalence of atherosclerotic vascular disease might have been underestimated (35). CAPD patients are particularly prone to atherosclerosis due to additional glucose load into the peritoneum, hyperinsulinemia, and hypoalbuminemia (22). Our findings of significantly lower adiponectin in CAPD patients with a history of CVD when compared with those without history of CVD corroborate with the report of Zoccali et al. (12) and others (36, 37).

The reason(s) why patients with CRF or maintained on dialysis have elevated adiponectin levels are not evident. The role of the kidney in the metabolism of adiponectin has been barely investigated. Chudek et al. (38) revealed that successful kidney transplantation is accompanied by a significant reduction of adiponectin concentration. Their findings suggest that kidneys play a role in adiponectin degradation and/or elimination. Kashimura et al. (39) found that patients with advanced diabetic nephropathy (mean serum creatinine 2.00 mg/dl) had elevated adiponectin despite increased urinary adiponectin excretion relative to diabetic patients with normo- and microalbuminuria and normal renal function. They suggested that adiponectin synthesis in adipose tissue and its secretion into the blood might be enhanced to mitigate microvascular damage. Adiponectin receptors are expressed in human vascular cells, indicating a direct effect of adiponectin on endothelium (40). However, in hemodialyzed patients, Zoccali et al. (12) suggested that biologic phenomenon underlying the cardioprotective role of adiponectin had to be down-regulated, probably at the receptor level, thus resetting at a higher plasma concentration the association between adiponectin and cardiovascular complications.

CD146, a member of the immunoglobulin superfamily, was characterized as a novel cell adhesion molecule involved in the control of the cell-cell cohesion (16). It is constitutively and highly expressed by the endothelium, located at the endothelial junction but outside the adherens (16). For the first time, Bardin et al. (18) found that in CRF, CD146 levels were significantly higher when compared with healthy volunteers and suggested that CD146 was a novel endothelial marker. They also found an increased expression of CD146 on kidney biopsies from five patients with renal failure. However, they did not study correlations between CD146 and other markers of endothelial cell injury. We observed that CD146 were significantly higher in CRF, particularly in CAPD patients. Moreover, CD146 was significantly elevated in diabetic CAPD patients relative to nondiabetic CAPD patients. In our study, we found statistically significant correlations between CD146 and adiponectin in CRF, CAPD, and in the healthy volunteers. In hemodialyzed patients, Zoccali et al. (12) described a slight inverse correlation between adiponectin and vWF in women (r = -0.19, P = 0.04) but not in men (r = -0.17, P = 0.098). In diabetic CAPD patients, CD146 correlated positively with vWF. It may support the hypothesis that CD146 could serve as a novel marker of endothelial cell injury.

Bardin et al. (18) suggested that elevation of CD146 in patients with CRF could be due to an increased release or to a reduced elimination. However, they did not study CD146 correlation with renal function. Mean serum creatinine in our study was very similar to that in the study of Bardin et al. (18). In our study, CD146 was not related to renal function in healthy volunteers or patients with CRF on conservative treatment or on CAPD. On the other hand, CD146 molecules are also found in activated T cells (41). In CRF, a decreased T cell number, reduced T cell life span and increased susceptibility to early activated T cell apoptosis are observed (42). Because CRF and renal replacement therapy are associated with T lymphopenia and progressive immunodeficiency (43), we could speculate that conditions affecting junctional functions may modify CD146 levels. In CRF and dialysis therapy, uremic toxins may alter the regulation of vessel permeability. Thus, elevated CD146 may reflect altered endothelial permeability. Moreover, increased urinary CD146 excretion was observed in CRF (18). On the basis of our findings and the study of Bardin et al. (18), we may suggest that elevated CD146 in CRF and dialysis patients is due to enhanced release of this molecule from its junctional localization.

In conclusion, we have reported for the first time a significant correlation between adiponectin and CD146, a novel marker of endothelial dysfunction, in patients with renal failure on conservative treatment and peritoneal dialyses. Adiponectin may take part in an equilibrium between the release of adhesion molecules and other substances from endothelium in patients with renal failure. Elevated adiponectin may be the expression of a counterregulatory response aimed at mitigating the endothelial damage and cardiovascular risk in renal failure.

Acknowledgments

Received February 27, 2004. Accepted June 1, 2004.

Address all correspondence and requests for reprints to: Jolanta MalyPowko, Department of Nephrology and Transplantology, Medical University, 15-540 Bialystok, Zurawia 14, Poland. E-mail: jolmal@poczta.onet.pl.

S.B. receives a scholarship from the Foundation for Polish Science.

References

2. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabonowitz D,

J Clin Endocrinol Metab. September 2004, 89(9):4620–4627

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Downloaded from https://academic.oup.com/jcem/article-abstract/89/9/4620/2844758 by guest on 19 March 2019