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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1201 – 1208
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

The effect of renal transplantation on adiponectin and its isoforms and receptors

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Received 17 November 2006; accepted 4 April 2007

Abstract

Insulin resistance (IR) and other proatherogenic risk factors associated with end-stage kidney disease (ESKD) are improved by renal transplantation. Adiponectin is a protein with insulin-sensitizing, anti-inflammatory, and antiatherogenic properties. It exists in several isoforms, but the high molecular weight (HMW) isoform correlates best with insulin sensitivity. Paradoxically, the levels of this protein and its HMW isoform are increased in ESKD. We measured the homeostasis model assessment for insulin resistance (HOMA-IR), plasma adiponectin and its isoforms, and messenger RNA for adiponectin receptors (AdipoR1 and AdipoR2) on peripheral blood mononuclear cells in 54 stable transplant recipients, 50 patients established on hemodialysis, and 52 controls; groups were matched for body mass index and sex. HOMA-IR values were significantly higher in patients with ESKD compared with controls ($P < .0005$) and transplant patients ($P < .05$) but there was no difference between the latter 2 groups. Adiponectin levels were also higher in patients with ESKD compared with controls ($P < .0005$), and although levels were lower in the transplant group, they remained higher than in controls ($P < .0001$). However, although the absolute amount of HMW isoform in transplant patients remained higher than in controls ($P < .0001$), the proportion was similar, and less than in patients with ESKD ($P < .005$). The absolute amount of the HMW isoform correlated with superior metabolic indices in all 3 cohorts. AdipoR1 and AdipoR2 messenger RNA levels after transplantation were significantly lower than those of ESKD subjects ($P < .0001$, $P < .01$), but transplant patients had less AdipoR1 than controls, although their AdipoR2 levels were higher. AdipoR1 correlated with AdipoR2 in all 3 cohorts. We conclude that HOMA-IR was lower in the transplant group compared with the group on hemodialysis and this coincided with lower total adiponectin levels and absolute amount of the HMW isoform and AdipoR on peripheral blood mononuclear cells. Lower AdipoR after transplantation may be secondary to immunosuppression and/or an improvement in glomerular filtration rate and the uremic milieu.

1. Introduction

End-stage kidney disease (ESKD) carries a high risk for morbidity and mortality from premature vascular disease [1]. Patients with ESKD, irrespective of primary diagnosis [2], display a wide range of risk factors including components of the metabolic syndrome. After successful renal transplantation, the mortality rate from vascular disease falls significantly [3], despite a continuing high incidence of vascular risk factors, including those associated with the metabolic syndrome [4]. Although it is recognized that posttransplant diabetes mellitus (PTDM) affects graft and patient survival [5], insulin resistance (IR) per se appears to be an independent risk factor for graft longevity [6]. Hence, the factors contributing to this improved survival posttransplantation remain uncertain.

The multifunctional glycoprotein adiponectin is thought to enhance insulin sensitivity and protect against atherosclerosis. It also has anti-inflammatory properties [7]. Adiponectin shows homology with the C1q subunit of the first component of complement and circulates in low (LMW), middle (MMW), and high molecular weight (HMW) isoforms. Clinical data suggest that the HMW isomer is the most important correlate of insulin sensitivity

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doi:10.1016/j.metabol.2007.04.016

Table 1
Anthropometric and fasting metabolic characteristics of controls, patients with ESKD, and patients with a transplant

Characteristic	Controls (n = 54)	Transplants (n = 52)	ESKD (n = 50)
Males (n)	24	24	29
Age (y)	47.2 ± 4.0	48.2 ± 14.3	58.3 ± 15.6 [a,b]
BMI (kg/m^2)	26.0 ± 4.0	25.8 ± 4.8	26.1 ± 4.7
HOMA-IR	2.3 ± 1.5	2.6 ± 1.5	5.2 ± 6.1 [b,c]
Total cholesterol (mmol/L)	5.3 ± 1.2	5.3 ± 1.1	4.2 ± 1.1 [a,b]
Triglycerides (mmol/L)	1.4 ± 0.9	1.7 ± 0.8 [d]	1.9 ± 1.2 [e]
LDL cholesterol (mmol/L)	3.3 ± 1.1	2.9 ± 1.0	2.2 ± 0.9 [b,f]
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.6 ± 0.6	1.2 ± 0.4 [a,g]
Uric acid (mmol/L)	0.3 ± 0.1	0.4 ± 0.1 [e]	0.4 ± 0.1 [e]
hs-CRP (mg/L)	1.0 (1.0-40.0)	2.0 (1.0-54.0) [e]	7.0 (1.0-48.0) [a,b]
GFR (mL/min)	116.3 ± 32.9	68.0 ± 21.5 [b]	
ACEI/AIIRB (n)	2	24 [b]	15 [b]
Statin (n)	4	24 [b]	17 [g]

Values are expressed as mean ± SD. hs-CRP data are expressed as median (range).
[a] $P < .0005$ vs transplants.
[b] $P < .0005$ vs controls.
[c] $P < .05$ vs transplants.
[d] $P < .01$ vs controls.
[e] $P < .05$ vs controls.
[f] $P < .01$ vs transplants.
[g] $P < .005$ vs controls.

[8], whereas, in vitro, adiponectin has been shown to activate different pathways according to its oligomeric state [9]. Yamauchi et al [10] have described 2 receptors for adiponectin, adiponectin receptor 1 (AdipoR1) and AdipoR2. AdipoR1 binds to the globular component of adiponectin, whereas AdipoR2 interacts with the full-length molecule [10]. These receptors increase adenosine monophosphate kinase and peroxisome proliferator-activated receptor-γ activity, fatty acid oxidation, and glucose uptake. Levels of adiponectin are decreased in obesity, coronary artery disease, and type 2 diabetes mellitus [7]. However, patients with ESKD show an increase in adiponectin concentration despite a high frequency of IR [11,12]. The rise in concentration reflects an increase in each of the defined isoforms, including the HMW (ie, insulin-sensitizing) fraction. Furthermore, we have shown increased expression of AdipoR1 and AdipoR2 messenger RNA (mRNA) on peripheral blood mononuclear cells (PBMCs) in these patients [13], that is, in the presence of elevated serum adiponectin levels. We proposed that these changes represented a physiologic response to the inflammatory milieu of renal failure. Hence, it was of interest to define any change in adiponectin/receptor interaction following substantial reduction or abolition of renal failure by successful renal transplantation. We examined levels of adiponectin and its multimeric distribution and mRNA for receptors on PBMCs after transplantation and whether different immunosuppressive agents influenced these findings.

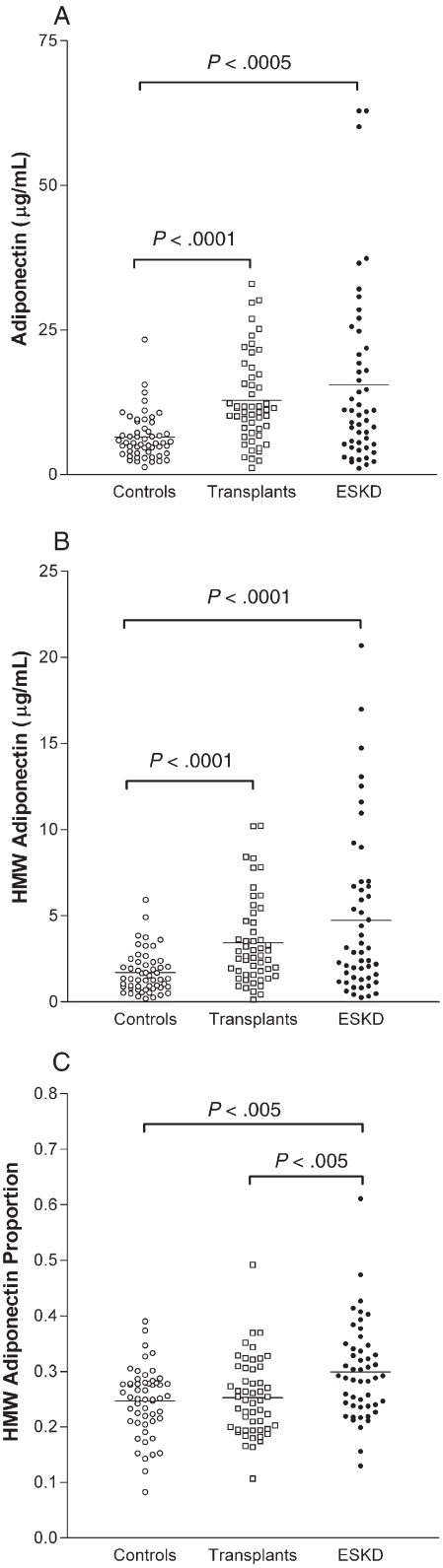

Fig. 1. Plasma adiponectin and its HMW isoform in controls, patients with a kidney transplant, and those with ESKD. (A) Plasma adiponectin. (B) HMW proportion. (C) Absolute amount of HMW adiponectin. Horizontal bars indicate the mean.

2. Methods

2.1. Study population

Fifty-two patients with kidney transplants (24 men, 28 women; age, 19-71 years) were recruited from a specialized clinic from June to December 2005, within the Prince of Wales Hospital Renal Unit, Sydney, Australia. They had received a successful transplant at least 6 months before and had had stable renal function for more than 3 months. There had been no episodes of acute rejection for at least 6 months and no change in immunosuppressive therapy for 3 months before recruitment. The causes of kidney failure in the transplant group were various primary glomerulonephritides (GN) (n = 27), adult polycystic kidney disease (ADPKD) (n = 8), reflux nephropathy (n = 5), lupus nephritis (n = 4), medullary cystic disease (n = 2), unknown etiology (n = 2), and 1 each of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS), Wegener granulomatosis, pelviureteric junction obstruction, and chronic interstitial nephritis. The time since transplantation ranged from 0.5 to 25 years, with a mean of 6 years. Thirty-nine patients received cadaveric kidney transplants and 13 had live donors. Four patients developed PTDM. Fifty patients on maintenance hemodialysis (29 men, 21 women; age, 18-79 years) were recruited from the Prince of Wales and St George Hospitals' Renal Units, Sydney, Australia. The causes of ESKD in the hemodialysis group were various primary GN (n = 16), ischemic hypertensive nephrosclerosis (n = 12), reflux nephropathy (n = 5), ADPKD (n = 2), chronic interstitial nephritis (n = 2), Wegener granulomatosis (n = 2), analgesic nephropathy (n = 2), and 1 each of the following: medullary cystic kidney disease, lupus nephritis, TTP-HUS, and unknown (n = 6). Patients were free of clinically overt infection, and those with Wegener granulomatosis, lupus nephritis, and TTP-HUS on hemodialysis had inactive disease at the time of recruitment. The patients undergoing hemodialysis received 12 to 15 hours of treatment per week, using a bicarbonate dialysate. The duration of hemodialysis ranged from 1 to 10 years, with an average of 3.5 years. Patients with diabetes were excluded because of the known effect of diabetes mellitus on plasma adiponectin levels [14]. Fifty-four controls (24 men, 30 women; age, 24-71 years) consisted of healthy volunteers without clinical or laboratory evidence of renal disease or diabetes. Information regarding antirejection regimens, treatment with lipid-lowering agents (ie, statins), angiotensin-converting enzyme inhibitors (ACEIs), and/or angiotensin II receptor antagonists (AIIRA) was collected. ACEI and AIIRA were stratified as a single group, as current evidence suggests that there is no difference in their effect on total adiponectin levels [15]. Subsets of the hemodialysis and control groups have been used for a previous study [13]. This study was approved by the Prince of Wales and St George Hospitals' Human Research Ethics Committees, and all subjects gave written informed consent.

2.2. Assay of plasma adiponectin and biochemical analysis

After an overnight fast, venous blood was taken for analysis of plasma lipids (cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol), full blood count, creatinine, glucose, insulin, plasma adiponectin, and high-sensitivity C-reactive protein (hs-CRP). Samples were chilled immediately and centrifuged at 3000 rpm, and the serum was kept at −20°C until analysis. Adiponectin was measured using a sensitive enzyme-linked immunosorbent assay (R&D, Minneapolis, MN). Other tests were performed in a routine laboratory. Glomerular filtration rate (GFR) was calculated by the Cockcroft-Gault equation. Insulin resistance was estimated by using the homeostasis model assessment for insulin resistance (HOMA-IR) (ie, plasma glucose level [mmol/L] × plasma insulin level [μU/mL]/22.5), which has been validated for use in both kidney failure [16] and kidney transplantation [17].

2.3. Anthropometry

Anthropometric data were obtained for each subject at enrolment into the study. They included weight in kilograms (dry weight for those on hemodialysis) and height in centimeters. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

2.4. Adiponectin receptors from buffy coat

To explore the relationship between adiponectin and its 2 receptors, the expression of mRNA for AdipoR1 and AdipoR2 in PBMCs in relation to 18S mRNA was determined by real-time reverse transcription-polymerase chain reaction as previously described [13].

2.5. Superose column chromatography for the measurement of adiponectin isoforms

Adiponectin in plasma was resolved into LMW, MMW, and HMW isoforms by chromatography on a fast protein liquid chromatography apparatus as previously described by Peake et al [18].

2.6. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS 13.0, SPSS, Chicago, IL). Data are shown as the mean ± SD. Statistical significance was assessed using unpaired *t* tests or the Mann-Whitney *U* test. In view of the nonparametric distribution of plasma adiponectin, HOMA-IR, CRP, triglyceride, total cholesterol, low-density lipoprotein (LDL), HDL, AdipoR1, AdipoR2, HMW, MMW, and LMW adiponectin, age, and BMI, logarithmically transformed values were used for statistical analysis. A 2-way between-groups analysis of variance was performed to examine the effect of age on adiponectin and its HMW isoform. A 1-way between-groups analysis of covariance was conducted to compare the difference in correlations between AdipoR1 and AdipoR2

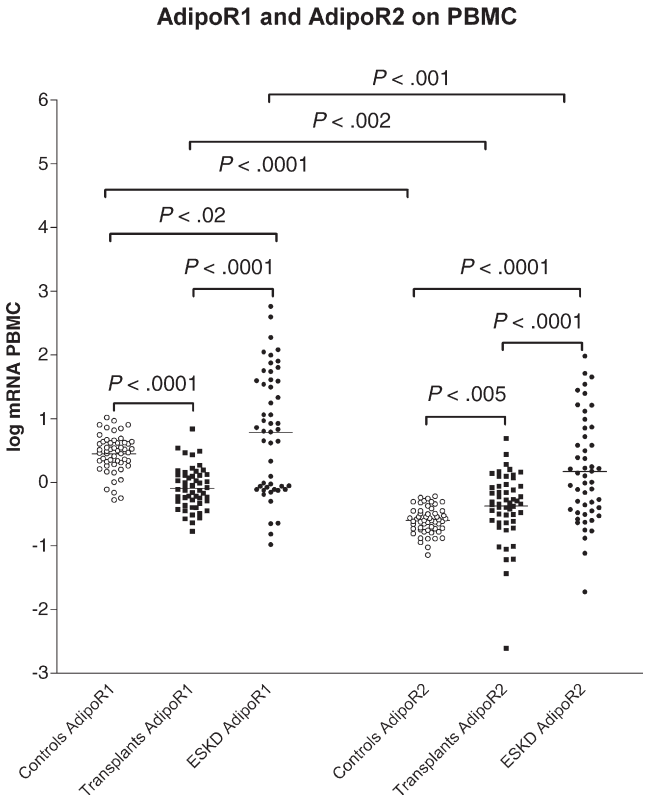

Fig. 2. AdipoR1 and AdipoR2 mRNA in PBMC in controls and in patients with a kidney transplant and patients with ESKD. Horizontal bars indicate the mean.

of the 3 cohorts. Pearson correlation analysis was used to evaluate the bivariate relationship between individual variables with plasma adiponectin. $P < .05$ was considered statistically significant. Multiple regression analysis was performed in all 3 cohorts, initially as 1 group, then as 3 separate groups, with HMW adiponectin (total) as a dependent variable and BMI, HOMA-IR, HDL, triglycerides, and age as independent variables.

3. Results

Anthropometric and biochemical data for patients and controls are shown in Table 1. The 3 groups were matched for sex and BMI. The ESKD group was more insulin resistant when compared with the transplant and control groups, whereas the latter 2 groups had similar values for HOMA-IR. Patients on hemodialysis had lower total cholesterol levels compared with controls and transplant patients. The ESKD and transplant groups were hypertriglyceridemic compared with controls. CRP levels in the 3 groups showed the following order: ESKD > transplants > controls. The control group had lower uric acid levels than either the transplant or ESKD groups; they also had a higher GFR than the transplant group. We also analyzed the transplant and ESKD groups in terms of those who had had "inflammatory" or "noninflammatory" kidney disease. Inflammatory diseases included primary forms of GN, lupus nephritis, Wegener granulomatosis, and TTP-HUS (n =34); noninflammatory diseases included ADPKD, reflux nephropathy, and medullary cystic kidney disease (n = 18). C-reactive protein levels were 4.5 ± 9.7 and 7.2 ± 8.2 mg/L, respectively; these were not significantly different. The ESKD group was similarly divided into those with inflammatory (n = 27) and noninflammatory (n = 27) types of kidney diseases. Metabolic parameters including adiponectin and its receptors were compared. There was no difference in BMI, HOMA, total cholesterol, adiponectin,

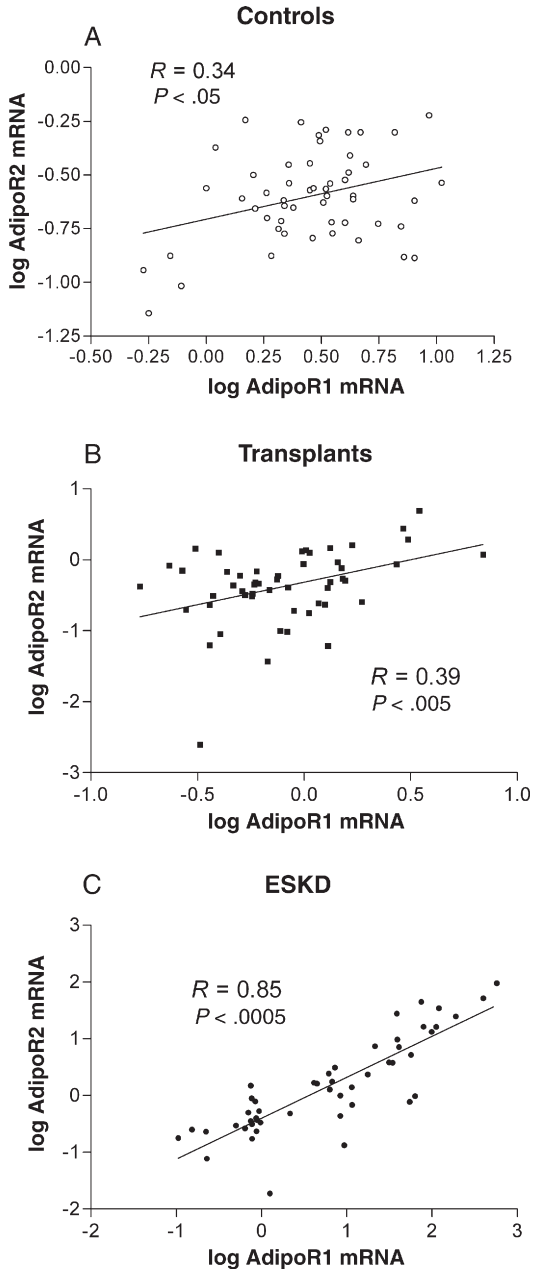

Fig. 3. The correlation between mRNA levels for AdipoR1 and AdipoR2 in PBMCs in controls, patients with a kidney transplant, and patients with ESKD.

Table 2
Anthropometric, fasting metabolic characteristics, adiponectin, HMW adiponectin, and AdipoR for transplants

Characteristic	Cyclosporin (n = 18)	Tacrolimus (n = 17)	Sirolimus (n = 13)	Other (n = 4)
Males (n)	6	11	6	1
MMF/Aza (n)	13/2	11/5	11/1	3/1
Age (y)	42.4 ± 15.4	54.9 ± 12.6[a,b,c]	44.1 ± 12.4	57.8 ± 6.2
BMI (kg/m^2)	25.8 ± 5.7	26.4 ± 2.9	24.3 ± 5.3	27.6 ± 6.5
HOMA-IR	3.0 ± 1.5	2.4 ± 1.2	2.2 ± 1.8	3.7 ± 0.9
Total cholesterol (mmol/L)	5.0 ± 1.1	5.0 ± 1.0	5.7 ± 1.0	5.7 ± 0.8
Triglycerides (mmol/L)	1.7 ± 0.9	1.6 ± 0.6	1.8 ± 1.1	1.3 ± 0.2
LDL cholesterol (mmol/L)	2.7 ± 1.0	2.8 ± 1.0	3.0 ± 1.2	3.5 ± 0.8
HDL cholesterol (mmol/L)	1.5 ± 0.5	1.5 ± 0.5	1.7 ± 0.8	1.6 ± 0.3
Uric acid (mmol/L)	0.4 ± 0.1	0.4 ± 0.1	0.36 ± 0.1	0.4 ± 0.1
hs-CRP (mg/L)	1.0 (1.0-20.0)	1.0 (1.0-54.0)	2.0 (1.0-27.0)	3.5 (1.0-10.0)
GFR (mL/min)	72.5 ± 23.4	68.8 ± 21.1	62.3 ± 20.5	66.1 ± 23.3
Adiponectin (μg/mL)	12.0 ± 7.4	11.7 ± 4.8	13.4 ± 10.0	20.0 ± 10.0
HMW adiponectin (μg/mL)	3.1 ± 2.5	3.2 ± 1.4	3.3 ± 3.1	6.3 ± 3.4
HMW adiponectin proportion	0.23 ± 0.07	0.28 ± 0.08[a,b]	0.23 ± 0.05	0.31 ± 0.03[d]
AdipoR1 (arbitrary units)	0.7 ± 0.4	1.4 ± 1.6	0.9 ± 0.7	2.0 ± 1.0[e]
AdipoR2 (arbitrary units)	0.5 ± 0.4	0.8 ± 0.7[a]	0.7 ± 0.5	1.5 ± 2.3[b]

Values are expressed as mean ± SD. hs-CRP data are expressed as median (range). Other indicates prednisolone + antimetabolite.
[a] P < .05 vs cyclosporin.
[b] $P < .05$ vs sirolimus.
[c] $P < .05$ vs other.
[d] $P < .005$ vs sirolimus.
[e] $P < .005$ vs cyclosporin.

and its isoforms or receptors between these 2 groups. Those with an inflammatory type of kidney disease had lower LDL cholesterol level, with a mean ± SD of 1.9 ± 0.8 vs 2.6 ± 0.9 mmol/L.

The ESKD and transplant groups had higher adiponectin levels than controls; levels in transplants and ESKD were comparable (Fig. 1A). Similarly, the ESKD and transplant groups had higher absolute amounts of the HMW isoform compared with controls (Fig. 1B). The ESKD group had an increased proportion of the HMW isoform (Fig. 1C), but the transplant group had a similar proportion to the control group. Subjects with ESKD were significantly older than controls and transplant patients, but a 2-way analysis of covariance using age as a continuous and categorical variable showed there was no influence of age on adiponectin, absolute HMW adiponectin levels, and HMW proportion. The HMW isoform (absolute amount) correlated with superior metabolic indices in all 3 groups (transplant group: HOMA-IR, $R = -0.39$, $P < .05$; triglycerides, $R = -0.30$, $P < .05$; HDL, $R = 0.44$, $P = .002$; ESKD group: BMI, $R = -0.44$, $P = .001$; HOMA-IR, $R = -0.52$, $P = .001$; HDL, $R = 0.37$, $P < .05$; control group: HDL, $R = 0.35$, $P = .001$; uric acid, $R = -0.46$, $P < .0005$). The proportion of the HMW isoform correlated inversely with BMI and HOMA-IR in the ESKD group only ($R = -0.36$, $P = .01$ and R −0.45, $P < .005$, respectively). Multiple regression analysis performed for the entire group and for each of the 3 cohorts separately showed that with total HMW adiponectin as the dependent variable and BMI, HOMA-IR, HDL, and triglycerides as independent variables, plasma HMW adiponectin concentration significantly depends only on HDL. The analyses focused on HMW adiponectin, as this isoform has been shown to be the best correlate of insulin sensitivity [8]. There was no difference in levels of adiponectin or its HMW isoform between those who received a cadaveric or live donor kidney transplant.

The transplant group had less AdipoR1 mRNA on PBMC than the control and ESKD groups ($P < .0001$ for both; Fig. 2). In contrast, the transplant group had more AdipoR2 mRNA on PBMCs than controls ($P = .005$), but levels were lower than in the ESKD group ($P = .0001$). There was a greater amount of AdipoR1 mRNA compared with AdipoR2 mRNA ($P < .002$ for each) in all 3 cohorts. AdipoR1 and AdipoR2 on PBMC did not correlate with BMI, HOMA-IR, levels of total adiponectin, or of its HMW isoform in any cohort. AdipoR1 correlated with AdipoR2 on PBMCs in all 3 groups (see Fig. 3). However, significant differences between the groups in the slope of the regression lines between RI and R2 were present ($P < .0005$ for all comparisons) reflecting the lesser amounts of AdipoR1 in transplant patients when compared with the control group. In the ESKD group, AdipoR1 and AdipoR2 correlated with CRP ($R = -0.35$ and -0.38, respectively, $P < .05$ for both pairs). In controls, AdipoR1 correlated with triglyceride and LDL concentration ($R = -0.87$, $P < .0005$ and $R = 0.56$, $P < .0005$), and AdipoR2 with HDL and uric acid ($R = -0.33$, $P < .05$ and $R = 0.47$, $P < .0005$). There was no difference in levels of AdipoR mRNA on PBMCs between those who had a cadaveric or live donor kidney transplant.

We separated the transplant group according to immunosuppressive regimen to examine the effect of these medications on adiponectin, its HMW isoform, and AdipoR. Anthropometric and biochemical data for patients and controls are shown in Table 2. Eighteen subjects were treated with cyclosporine, 17 with tacrolimus, 13 with sirolimus, and 4 with prednisolone and an antimetabolite alone. We found no difference in adiponectin and its multimeric distribution and receptors when comparing those patients on sirolimus and those on a calcineurin antagonist (ie, cyclosporine and tacrolimus stratified as a single group). Comparison of those on sirolimus to those on cyclosporine or tacrolimus (as separate groups) revealed

an increased proportion of the HMW isoform in those on tacrolimus, but no difference in HOMA-IR or absolute amount of the HMW isoform. There were no differences with respect to IR, AdipoR, or adiponectin between those on mycophenolate mofetil (MMF) compared with those on azathioprine (Aza) (data not shown). Analysis of those on MMF compared with those on Aza within the subgroups of cyclosporine, tacrolimus, and sirolimus similarly showed no difference with respect to adiponectin and its isoforms or receptors. There was also no relationship between the dose of prednisolone and adiponectin, its HMW isoform, or HOMA-IR, or of the age of the transplant and these factors. The average dose of prednisolone was 6.3 mg/d.

There was no difference within the 3 groups with respect to adiponectin and its receptors when comparing those on statins and those not. Similarly, there was no difference in those on and not on an ACEI and/or AIIRA.

4. Discussion

This study highlights the impact of successful renal transplantation on the plasma adiponectin/receptor axis. The differences we observed in total adiponectin in a control group compared with patients with ESKD on hemodialysis parallel those observed by Chudek et al [19]. However, in their study, HOMA-IR remained high, whereas we observed levels similar to controls, as has been reported by other workers [20]. The discrepant HOMA-IR measurements may be explained by the difference in sampling times between these studies. Our patients were, on average, 6 years posttransplantation compared with an average of 29 days in the Chudek et al study [19]. It would be anticipated that doses of immunosuppressive therapy would reduce with time following transplantation, thus modifying the influence of potentially diabetogenic medications on insulin sensitivity [21]. Although the controls and transplant recipients were younger than patients with ESKD, and a higher proportion of those in the transplant and ESKD groups were receiving ACEI/AIIRA and statins, statistical analysis showed that age did not have an additional effect on adiponectin levels or its multimeric distribution. Comparison of those with an inflammatory type of kidney disease compared with those with a noninflammatory cause in both the transplant and ESKD groups showed no difference in CRP, AdipoR, total adiponectin, or the proportion of HMW isoform. This is consistent with the view that the inflammatory features of certain kidney diseases subside or remit once the state of ESKD is reached. There was also no significant difference in AdipoR, total adiponectin, or the proportion of HMW isoform between those treated with ACEI and AIIRA and untreated patients, although these medications have been reported to increase adiponectin levels [22]. The use of statins did not alter adiponectin levels or the HMW proportion, which concurs with other studies [23].

The metabolism of adiponectin, particularly in those with kidney disease, is unclear. It has been suggested that the difference in those with a kidney transplant is secondary to an improvement in GFR, thus supporting the hypothesis that the kidneys play a role, either directly or indirectly, in the turnover of this protein [19]. Others have found a negative correlation between adiponectin levels and GFR [24]; this was not observed in our study. Adiponectin is known to be induced by stimuli such as inflammatory cytokines [25]; hence, a reduction in the inflammatory milieu associated with ESKD [26] may contribute to lower adiponectin levels in the transplant group.

It has been proposed that the HMW proportion of adiponectin correlates with insulin sensitivity in man [8,27]. Our group has found [13] that the HMW isoform is increased in ESKD, despite reduced insulin sensitivity, and suggested that this may reflect a physiologic response to an inflammatory atherogenic state [26]. Despite higher amounts of this moiety in the transplant group (ie, compared with controls), the proportion of the HMW isoform was virtually identical to that of controls, as was HOMA-IR. This difference in the multimeric profile of adiponectin after transplantation may also reflect a decrease in (proinflammatory) cytokine levels secondary to an improved GFR and the presence of immunosuppression.

The risk from vascular disease declines markedly after successful kidney transplantation despite the persistence of vascular risk factors [4]. Approximately 60% of such patients require antihypertensive therapy and/or a lipid-lowering agent [28,29]. Posttransplant diabetes mellitus will occur in approximately 50% of transplant patients [30]. Central adiposity is prevalent and is potentially aggravated by steroid medication. Thus, although the features of the metabolic syndrome persist, the annual risk of a vascular event is much reduced. We demonstrated a significantly lower HOMA-IR in the transplant group and this was accompanied by a lower total adiponectin and the HMW isoform, although higher levels of these moieties typically favor insulin sensitivity.

Most studies of AdipoR in monocyte/macrophages have shown an anti-inflammatory role for these receptors on the addition of adiponectin [31,32] but the factors controlling their expression are not clear. We have reported that AdipoR on PBMCs are increased in ESKD [13], a finding that may be secondary to the proinflammatory nature of uremia and/or hemodialysis. AdipoR1 mRNA correlated with AdipoR2 mRNA on PBMCs in all 3 cohorts. However, although AdipoR1 and AdipoR2 in transplant recipients decreased to levels below those found in ESKD, and, in the case of AdipoR1, to levels below those of controls, AdipoR2 still remained higher than levels found in the control group. This suggests that AdipoR1 and AdipoR2 respond differently to a range of stimuli, a phenomenon observed by other workers. Thus, hyperinsulinemia increased AdipoR1 but not AdipoR2 in skeletal muscle [33], and in our patients, insulin levels were

significantly reduced after transplantation. However, there was no relationship between AdipoR on PBMC and anthropometric parameters, HOMA-IR, adiponectin levels, or its multimeric distribution. In ESKD, AdipoR mRNA on PBMCs correlated with CRP and, in the control group, with several metabolic indices (LDL, triglyceride, HDL, and uric acid). These data suggest that AdipoR on PBMCs in ESKD and transplant recipients may be influenced by changes in inflammatory stimuli associated with the uremic milieu and/or immune modulation.

The effect of each immunosuppressive agent on metabolic and inflammatory pathways is complex, and we acknowledge that transplant recipients represent a heterogeneous group. Although there was no difference in HOMA-IR when comparing those on cyclosporine, tacrolimus, and sirolimus, we observed an increased proportion of the HMW isoform in those taking tacrolimus, possibly reflecting a response to the increased diabetogenic potential of this agent [34]. In renal transplantation, sirolimus offers no clinical benefit [35,36] over calcineurin inhibitor with respect to insulin sensitivity. These clinical findings concur with our data, as we found virtually identical levels of adiponectin and HOMA-IR in each of these groups. Although glucocorticoids suppress adipocyte secretion of adiponectin in vitro [37], we did not detect a relationship between prednisolone dose and adiponectin levels, possibly as a result of the low steroid dose (ie, 6.3 mg/d on average) used in our transplant group.

We conclude that total amounts of adiponectin and its HMW isoform are lower in patients following transplantation compared with those with ESKD, but remain higher than in healthy matched controls. However, the proportion of the HMW isoform was similar to that of the control group, as was HOMA-IR. Levels of AdipoR on PBMC were lower after kidney transplantation. AdipoR1 correlated with AdipoR2 in all subject groups, and in ESKD both correlated with CRP, possibly reflecting a role for inflammation in increasing AdipoR in ESKD. Lower levels of AdipoR and adiponectin in a transplant group may reflect an improvement in GFR, a less inflammatory environment, and the use of immune suppression, particularly given the lower ratio of AdipoR1 to AdipoR2 in the transplant subjects when compared with controls.

Acknowledgment

Dr Shen is supported by a National Health and Medical Research Council medical scholarship.

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