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ORIGINAL ARTICLE

Tacrolimus and angiotensin receptor blockers associated with changes in serum adiponectin level in new-onset diabetes after renal transplantation: single-center cross-sectional analysis

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Keywords
adiponectin, angiotensin receptor blockers, insulin resistance, new-onset diabetes after transplantation, renal transplantation, tacrolimus.

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Summary

We analysed whether pre- and post-transplant serum adiponectin levels in renal transplant patients were associated with new-onset diabetes after transplantation (NODAT). The mean post-transplant follow-up duration was 47.9 months. Of 98 previously non-diabetic renal transplant patients, 12 were diagnosed with NODAT and 86 without (non-NODAT). There was a significant inverse correlation between mean post-transplant serum adiponectin level and homeostasis model assessment for insulin resistance (HOMA-IR) ($r = -0.22$, $P = 0.03$), and a positive correlation between follow-up duration after transplantation and HOMA-IR ($r = 0.28$, $P = 0.005$). The mean pre- and post-transplant serum adiponectin levels in NODAT patients were significantly lower than those in non-NODAT patients (13.3 vs. 21.0 μg/ml and 13.0 vs. 16.4 μg/ml, $P = 0.01$ and 0.03 respectively). In addition, the post-transplant serum adiponectin level in patients treated with tacrolimus (TAC) was significantly lower than that in patients with cyclosporine (14.3 vs. 18.7 μg/ml, $P = 0.01$), while, that level in patients treated with angiotensin receptor blockers (ARB) was significantly higher than that in patients without treatment of ARB (17.9 vs. 14.7 μg/ml, $P = 0.01$). Our results indicate that post-transplant serum adiponectin levels are decreased after transplantation in association with insulin resistance in the development of NODAT, and that TAC and ARB influence the level of adiponectin in serum.

Introduction

New-onset diabetes after transplantation (NODAT) is increasingly being recognized as a serious complication in renal transplant recipients, and its development is associated with worse long-term graft function and survival, reduced long-term patient survival, and increased risk of death associated with cardiovascular disease [1]. Potentially modifiable risk factors are obesity and overweight conditions, hepatitis C virus and cytomegalovirus infections, and administration of tacrolimus (TAC) [2,3]. The natural history of NODAT shares many similarities with type 2 diabetes including insidious onset, as individuals may experience glucose intolerance and be asymptomatic for years before symptoms become clinically manifested [4]. However, the clinical characteristics and mechanisms underlying this metabolic disturbance have not been fully elucidated.

Adiponectin is a recently discovered adipocytokine that is exclusively expressed and secreted from adipose tissue

[5]. Plasma adiponectin levels in humans are significantly lower among subjects who are obese, display coronary artery disease caused by atherosclerosis, and have hypertension [6–8]. In NODAT patients, the degree of atherosclerosis determined by brachial-ankle pulse wave velocity was shown to increase with a decrease in adiponectin level [9]. In addition, this secretory protein may be involved in the pathogenesis of type 2 diabetes mellitus, based on its relationship with insulin and glucose metabolism [10,11]. In a recent study, a low pre-transplant level of adiponectin was found to be an independent risk factor for the development of NODAT, which was shown by the presence of inflammatory markers [12]. Therefore, increasing the level of adiponectin is an important therapeutic strategy for patients with hypertension, coronary arterial disease and NODAT.

The relationship between various therapeutic medications and adiponectin levels for the development of NODAT is not clear. Among TAC-treated patients, adiponectin was the only independent predictor of NODAT in a previous study, in which pre-transplant plasma adiponectin values in patients receiving TAC who developed NODAT were significantly lower than in those who did not develop the condition [12]. Further, glucocorticoids and β-blockers seem to have opposite effects on circulating adiponectin levels in renal transplant recipients [11]. Recently, angiotensin receptor blocker (ARB) treatment, given for hypertension, improved insulin resistance and increased plasma adiponectin levels in hypertensive patients with metabolic syndrome [13]. The purpose of this study was to (i) confirm whether pre- and post-transplant low serum adiponectin levels are an independent risk factor for the development of NODAT, (ii) analyse whether serum adiponectin levels in renal transplant patients are associated with insulin resistance and secretion in the development of NODAT and (iii) examine the relationships between serum adiponectin levels and therapeutic medications (immunosuppressive drugs and ARB).

Patients and methods

Patients

Among those undergoing follow-up examinations at our institution, a total of 98 previously non-diabetic patients who received renal transplantation between 1997 and 2007 were enrolled. The mean age and post-transplant follow-up duration were 45.1 years and 47.9 months respectively. Immunosuppressive drugs administered consisted of basiliximab for induction, and prednisone and cyclosporine (CyA) or TAC, with mycophenolate mofetil or azathioprine for maintenance. Informed consent was obtained and the study protocol was approved by the local ethics committee.

Definitions

New-onset diabetes after transplantation, impaired glucose tolerance (IGT), and normal glucose tolerance (NGT) were defined according to Japan Diabetes Society guidelines based on results of an oral glucose tolerance test (OGTT). The non-NODAT group included patients with IGT and NGT. Post-transplant homeostasis model assessment for insulin resistance (HOMA-IR) [fasting glucose (mg/dl) × fasting insulin (mU/ml) divided by 405] [14] and insulinogenic index (I-index) [ratio of increment of plasma insulin (mU/ml) to that of plasma glucose at 30 (mg/dl)] [15] values were obtained using OGTT-derived indexes. The I-index shows initial insulin secretion ability and its calculation method is simple, while it has been widely utilized in recent studies [16]. Criteria for the diagnosis of hypertension were systolic blood pressure greater than 140 mmHg or treatment with antihypertensive drugs, while those for hyperlipidemia were low density lipoprotein cholesterol greater than 140 mg/dl or treatment with antihyperlipidemic drugs.

Laboratory analysis

Post-transplant blood samples were collected between August and December 2007 in a fasting state, and analytic pre-transplant control samples (1–3 months pre-transplant) were also obtained. All samples were immediately centrifuged and stored at −80 °C until analysis. Serum adiponectin, C-peptide, and high-sensitivity C-reactive protein (hsCRP) levels were measured by BML laboratory.

Statistical analysis

Data are expressed as the mean ± standard deviation. A *t*-test was used to determine the differences between NODAT and non-NODAT patients, and a Mann–Whitney *U*-test was applied for quantitative variables. Pearson's or Spearman's correlations and linear regression analyses were used to assess associations between variables by partly adopting age- and gender-adjusted levels. $P < 0.05$ was considered to indicate statistical significance. The analyses were conducted using the JMP 6 Japanese Edition (SAS Institute Inc., Cary, NC, USA) and StatView-J 5.0 (Hulinks Inc., Tokyo, Japan) statistical packages.

Results

Comparisons of characteristics between NODAT and non-NODAT patients

Twelve (12.2%) patients were diagnosed with NODAT and 86 (87.8%) without (non-NODAT). The patient

Table 1. Comparisons of characteristics between NODAT and non-NODAT patients.

	NODAT (n = 12)	Non-NODAT (n = 86)	P-value
Age (years)	48.5 ± 11	44.5 ± 11.4	0.17
Gender (male/female)	9/3	53/33	0.37
Pre-transplant BMI (kg/m2)	22.2 ± 2.1	20.2 ± 2.9	0.02
Post-transplant follow-up duration (months)	57.7 ± 41.4	46.5 ± 28.8	0.61
Living donor (%)	66.7	65.1	0.96
HCV positive (%)	18.2	8.3	0.29
Hypertension (%)	54.5	54.9	0.98
Hyperlipidemia (%)	13	7.9	0.76
Calcineurin inhibitor (number of TAC/CyA)	9/3	43/43	0.1
Total steroid dose (mg)	8693 ± 5482	6742 ± 3963	0.22
TAC trough (ng/ml)	6.5 ± 3.8	4.7 ± 1.7	0.18
ARB (%)	58.3	51.2	0.64
Post-transplant fasting glucose (mg/dl)	114 ± 13.3	92 ± 8.4	<0.001
Post-transplant c-peptide (ng/ml)	3.9 ± 2.3	2.3 ± 0.8	0.01
Post-transplant HOMA-IR	3.24 ± 2.26	1.35 ± 0.83	0.004
Post-transplant I-index	0.41 ± 0.27	1.88 ± 2.28	<0.001
Post-transplant hsCRP	0.57 ± 1.2	0.4 ± 2	0.1
Pre-transplant adiponectin (μg/ml)	13.3 ± 6.2	21.0 ± 9.6	0.01
Post-transplant adiponectin (μg/ml)	13.0 ± 8.8	16.4 ± 8.1	0.03

BMI, body mass index; HCV, hepatitis C virus; TAC, tacrolimus; CyA, cyclosporine; ARB, angiotensin receptor blockers; hsCRP, high-sensitivity C-reactive protein.
Values for the variables are shown as the mean ± standard deviation.

characteristics of the study population compared between the NODAT and non-NODAT groups are shown in Table 1. NODAT patients had a higher pre-transplant body mass index (BMI) (P = 0.02), while mean post-transplant serum fasting glucose and C-peptide levels were significantly higher than those in non-NODAT patients (114 vs. 92 mg/dl and 3.9 vs. 2.3 ng/ml, P < 0.001 and 0.01 respectively). Further, the mean post-transplant HOMA-IR value in NODAT patients (3.24) was significantly higher than that in non-NODAT patients (1.35) (P = 0.004), in contrast to the mean I-index value, which was significantly lower (0.41 vs. 1.88, P < 0.001). There was no significant difference between NODAT and non-NODAT patients for the level of post-transplant hsCRP (0.57 and 0.4 mg/dl respectively) (P = 0.1). In accordance with serum adiponectin levels, the mean pre- and post-transplant serum adiponectin levels in NODAT patients were significantly lower than those in non-NODAT patients (13.3 vs. 21.0 μg/ml and 13.0 vs. 16.4 μg/ml, P = 0.01 and 0.03 respectively). In all patients, the mean post-transplant serum adiponectin level (16.8 μg/ml) was significantly lower than the pre-transplant level (20.3 μg/ml) (P = 0.009). A lower pre-transplant serum adiponectin level than the median (<19.9 μg/ml) was found to be a significant risk factor for development of NODAT, with an odds ratio of 11.0 [95% confidence interval (CI): 4.6–47.8, P = 0.03], whereas the lower post-transplant level (<15.2 μg/ml) was a relative risk factor, with an odds ratio of 3.8 (95% CI: 2.0–8.3, P = 0.057). On the other hand, there was no significant correlation between serum adiponectin and hsCRP levels for patients in both groups.

Correlations between adiponectin level, and HOMA-IR and I-index values

There was a significant inverse correlation between the mean post-transplant serum adiponectin level and HOMA-IR value (r = −0.22, P = 0.03) (Fig. 1a), and a positive correlation between follow-up duration after transplantation and HOMA-IR (r = 0.28, P = 0.005) (Fig. 1b) for all the patients. In contrast, there was no correlation between mean post-transplant serum adiponectin level and I-index value (r = 0.09, P = 0.42), or between follow-up duration after transplantation and I-index (r = 0.05, P = 0.61).

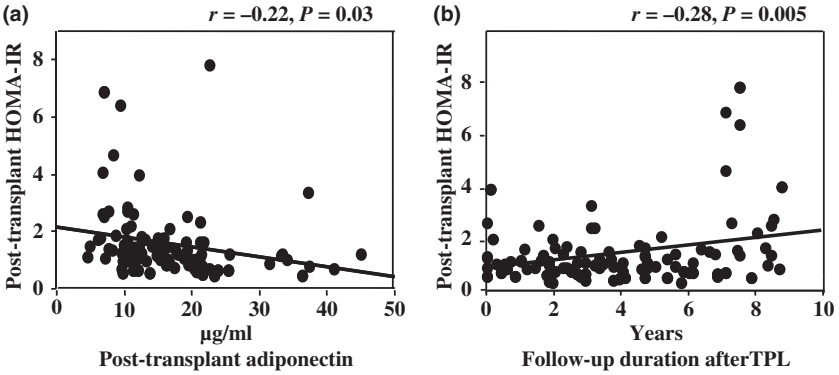

Figure 1 Correlations between HOMA-IR value and serum adiponectin levels (a) and HOMA-IR and follow-up duration after transplantation (b). TPL: transplantation.

Variable characteristics associated with adiponectin

Variable characteristics associated with post-transplant serum adiponectin levels are shown in Tables 2 and 3. There were no significant correlations between the post-transplant serum adiponectin level and various independent continuous characteristics, including total steroid dose and the TAC trough levels for immunosuppressive drugs ($P = 0.33$ and 0.59 respectively). On the other hand, in categorical characteristics, the post-transplant serum adiponectin level in patients administered TAC was significantly lower than that in patients administered CyA (14.3 vs. 18.7 μg/ml, $P = 0.01$). Further, the adiponectin level in patients treated with ARB was significantly higher than that in patients without ARB treatment (17.9 vs. 14.7 μg/ml, $P = 0.01$).

Pre- and post-transplant adiponectin levels in patients treated with TAC or CyA

The post-transplant serum adiponectin level in patients administered TAC was significantly decreased as compared with the pre-transplant level (pre: 19.4 vs. post: 14.3 μg/ml, $P = 0.0006$), whereas no significant difference was found between those in CyA-treated patients (pre: 19.9 vs. post: 18.7 μg/ml, $P = 0.25$). Further, the pre-transplant adiponectin level in patients administered TAC who developed NODAT was significantly lower than that in non-NODAT patients (13.7 vs. 20.5 μg/ml, $P = 0.02$), while there was no significant difference for post-transplant adiponectin level in those who developed NODAT as compared with the non-NODAT group (17.2 vs. 18.8 μg/ml, $P = 0.13$) (Fig. 2a). In addition, the post-transplant adiponectin level was significantly decreased as compared with the pre-transplant level in non-NODAT patients treated with TAC (20.5 vs. 14.9 μg/ml, $P = 0.0007$) (Fig. 2a). As for non-NODAT patients treated with TAC, there was no significant difference between the post-transplant adiponectin level for those with IGT ($n = 7$) and NGT ($n = 36$) (14.0 vs. 15.1 μg/ml, $P = 0.77$). In addition, there were no significant differences between the pre- and post-transplant adiponectin levels in CyA-treated patients (Fig. 2b).

Table 2. Continuous characteristics associated with adiponectin level in serum.

Continuous characteristic	*P*-value
Post-transplant age	0.59
Post-transplant BW	0.34
Post-transplant BMI	0.48
Nadir creatinine	0.9
Post-transplant C-peptide	0.36
Post-transplant hsCRP	0.9
Total steroid dosage	0.33
TAC trough	0.59

BW, body weight; BMI, body mass index; HsCRP, high-sensitivity C-reactive protein; TAC, tacrolimus; SD, standard deviation.
Statistics: age- and gender-adjusted partial Spearman's correlation.

Pre- and post-transplant adiponectin levels in patients treated with or without ARB

There was no significant difference between the pre- and post-transplant adiponectin levels in patients administered ARB (20.7 vs. 17.9 μg/ml, $P = 0.09$), while the post-transplant adiponectin level in patients without treatment of ARB was significantly decreased as compared with the pre-transplant level (pre: 19.7 vs. post: 14.7 μg/ml, $P = 0.01$). Further, there was no significant difference in regard to pre-transplant adiponectin level in patients treated with ARB who developed NODAT as compared with non-NODAT patients (14.7 vs. 21.6 μg/ml, $P = 0.07$), though the post-transplant level for patients who developed NODAT was lower than that for non-NODAT patients (11.7 vs. 18.9 μg/ml, $P = 0.02$) (Fig. 3a). Additionally, in patients without treatment of ARB, there were no significant differences for adiponectin levels between the NODAT and non-NODAT groups in both pre- and post-transplant measurements (pre: 11.2 vs. 20.6 μg/ml

Table 3. Categorical characteristics associated with adiponectin level in serum.

Categorical characteristic	No. with characteristic		Mean adiponectin ± SD (μg/ml)		*P*-value
	Yes	No	Yes	No	
Hypertension	51	47	17.8 ± 9.2	14.9 ± 6.8	0.09
Hyperlipidemia	9	89	17.5 ± 5.7	16.3 ± 8.5	0.28
Living donor	64	34	15.0 ± 6.6	19.0 ± 10.3	0.11
HCV	9	89	20.6 ± 15.5	15.9 ± 7.1	0.94
TAC	52	46	14.3 ± 6.7	18.7 ± 9.2	0.01
ARB	51	47	17.9 ± 8.4	14.7 ± 7.9	0.01

HCV, hepatitis C virus; ARB, angiotensin receptor blockers; SD, standard deviation.

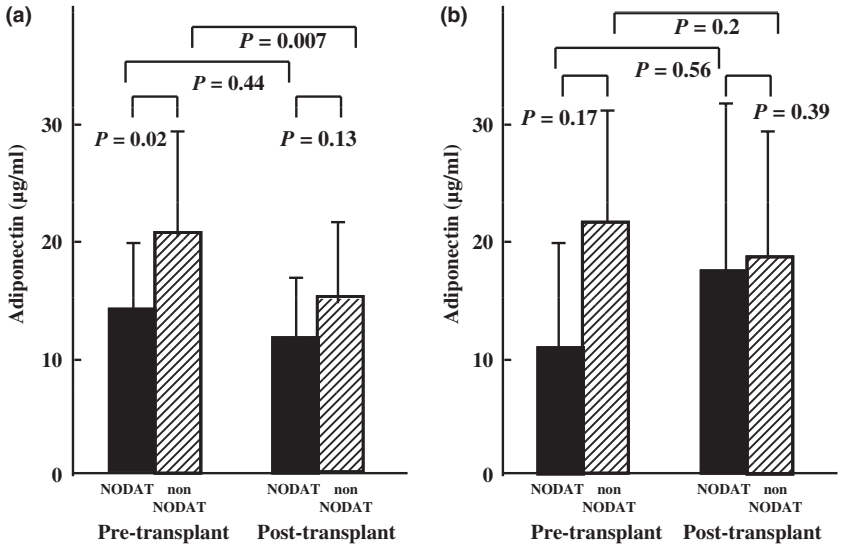

Figure 2 Comparisons of serum adiponectin levels between NODAT and non-NODAT patients treated with tacrolimus (a) or cyclosporine (b). a: NODAT; *n* = 9, non-NODAT; *n* = 43. b: NODAT; *n* = 3, non-NODAT; *n* = 43. Values are shown as the mean ± standard deviation.

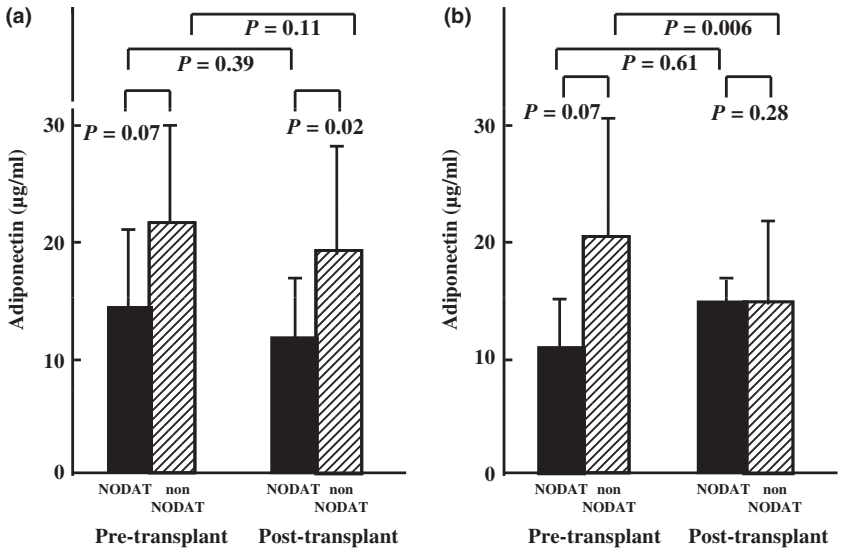

Figure 3 Comparisons of serum adiponectin levels between NODAT and non-NODAT patients treated with (a) or without (b) angiotensin receptor blockers. a: NODAT; *n* = 7, non-NODAT; *n* = 44. b: NODAT; *n* = 5, non-NODAT; *n* = 42. Values are shown as the mean ± standard deviation.

and post: 14.8 vs. 14.7 μg/ml, $P = 0.07$ and 0.28 respectively), whereas, the post-transplant adiponectin level in non-NODAT patients without treatment of ARB was significantly decreased as compared with the pre-transplant level (20.6 vs. 14.7 μg/ml, $P = 0.0006$) (Fig. 3b).

Discussion

New-onset diabetes after transplantation is a form of type 2 diabetes mellitus, thought to develop in response to relative insulin deficiency resulting from insulin resistance or impaired insulin production, or a combination of both [17]. Adiponectin has been proposed as a factor that mediates insulin resistance and β-cell dysfunction in the pathogenesis of type 2 diabetes [18,19]. In regard to the regulation of insulin secretion, a recent study showed that adiponectin significantly stimulated insulin secretion *in vitro* and *in vivo* at low glucose concentrations [20]. In this study, we confirmed the presence of increased insulin resistance and decreased insulin secretion in NODAT patients based on HOMA-IR and I-index values. In addition, our results revealed a significant inverse correlation between adiponectin level and HOMA-IR value, and a positive correlation between follow-up duration after transplantation and HOMA-IR value, whereas none was seen between I-index value and adiponectin level or follow-up duration. Therefore, the novel finding in this study is that a decreased serum adiponectin level after

transplantation is associated with insulin resistance, but not with insulin secretion, in the development of NODAT.

Transplant recipients have a particularly high risk of developing NODAT, which is induced by increased insulin resistance as a consequence of various factors in addition to those that affect the general population. Of those factors, we initially focused on the associations between adiponectin levels in blood and administrations of immunosuppressive drugs. Recent evidence has demonstrated a positive relationship between glucocorticoid dosage and adiponectin concentration [11], whereas no significant difference was observed between them in this study. Although the adverse effects of steroids on insulin sensitivity and glucose tolerance have been widely reported [1–3], the relationships between steroids and adiponectin remain controversial [11]. With regards to the effects of calcineurin inhibitors, which impair glucose homeostasis by a combination of effects, on both islet toxicity and insulin sensitivity [1], the diabetogenic potential of TAC has been reported to be associated with a greater risk than that of CyA [21]. In this study, the pre-transplant adiponectin level in patients treated with TAC who developed NODAT was significantly lower than that in non-NODAT patients, which supports the notion that adiponectin is a strong predictor for the development of NODAT in patients treated with TAC, as reported by Bayés *et al.* [12]. In addition, we found that the post-transplant adiponectin level in patients administered TAC was significantly decreased as compared with the pre-transplant level, while that in non-NODAT patients treated with TAC was also significantly decreased as compared with the pre-transplant level, which are novel and important findings.

A possible explanation for the higher risk of TAC administration as compared with CyA for the development of NODAT is that TAC-based regimens are associated with more marked β-cell morphologic changes and inhibit insulin secretion to a greater extent than CyA-based regimens [22]. Based on our present findings, another diabetogenic potential of TAC may be associated with decreased adiponectin levels in serum, though scant information is available regarding the mechanism associated with decreased adiponectin levels in patients treated with TAC. A recent investigation of the incidence of NODAT associated with TAC pharmacokinetics and related genetic polymorphisms revealed that the frequency of NODAT was higher in patients with the *adiponectin T45G* genotype, though the difference did not reach the level of significance [23]. Additional examinations are needed to fully elucidate the mechanisms of the effects of TAC in regard to adiponectin levels on the development of NODAT.

Another important and novel finding of obtained from our analysis is that ARB administration reduces the decrement of adiponectin and may lessen the risk of NODAT development in renal transplant recipients. Recently, Hjelmesæth *et al.* [11] demonstrated that treatment with β-blockers was independently associated with lower adiponectin levels, however, no significant relationship between treatment with other antihypertensive drugs, including angiotension-converting enzyme inhibitor, and adiponectin levels were shown in renal transplant recipients. In this study, the post-transplant adiponectin level in patients treated with ARB who developed NODAT was significantly lower than that in non-NODAT patients. Furthermore, in non-NODAT patients without treatment of ARB, the post-transplant adiponectin level was significantly decreased as compared with the pre-transplant level. A large body of evidence suggests that ARB can prevent new-onset type 2 diabetes [24]. It is possible that modulation of adiponectin production by ARB is one of the explanations for how blockade of the renin-angiotensin system leads to a diminished incidence of type 2 diabetes [25]. In renal transplant recipients, ARB is used for the treatment of hypertension and post-transplant erythrocytosis, and reduction of proteinuria; however, data supporting the superiority of ARB over other antihypertensive drugs in regard to graft improvement and patient survival are lacking [26]. The present findings suggest that ARB administration is effective for not only treatment of hypertension or proteinuria, but also for reducing the risk of NODAT in renal transplant recipients.

A negative correlation between BMI and adiponectin level in patients who underwent renal transplantation was previously reported [27]. In addition, increased body weight and BMI have been shown to be associated with the development of NODAT in a number of studies [3], while significant negative correlations were found between plasma adiponectin concentration and BMI or HOMA-IR in kidney transplant patients [28]. In this study, NODAT patients also had higher pre-transplant BMI values. Together, these results suggest that BMI is an important factor that influences adiponectin levels and insulin resistance in NODAT patients.

A recent study demonstrated that adiponectin is a better predictor for the development of NODAT than inflammatory markers (hsCRP, interleukin-6, tumor necrosis factor-alpha and pregnancy-associated plasma protein A) [12]. In this study, the mean post-transplant serum adiponectin level in all patients was significantly lower than the pre-transplant level, while mean pre- and post-transplant serum adiponectin levels in NODAT patients were significantly lower than those in the non-NODAT group. In contrast, there were no significant differences between NODAT and non-NODAT patients for both pre- and post-transplant levels of serum hsCRP. Thus, our results support those presented in that study.

Another report noted that no significant relationships were observed between adiponectin and hsCRP in renal transplant patients [11], which finding also agrees with our results that revealed no significant correlation between serum adiponectin and hsCRP levels in all of the patients in this study. Meanwhile, obesity was found to be positively correlated with insulin resistance and increases in vascular inflammatory markers [29]. In addition, adiponectin is believed to have an anti-inflammatory property [30]. Therefore, the relationship between adiponectin and inflammatory markers in regards to the development of insulin resistant NODAT in relation to obesity requires further study.

We acknowledge several limitations in this study. First, there was a small number of subjects enrolled, all of whom were Japanese. Further, adiponectin measurements are not covered by national insurance in Japan, thus for reasons of expense we could not obtain a sufficient number of samples. Finally, our subjects were not chosen in a randomized fashion and the time periods from transplantation to entry varied. Despite these limitations, we consider that our results will contribute to a better understanding of the association between adiponectin and development of NODAT, and provide useful information about prevention of the disease.

In conclusion, we found that serum adiponectin levels are decreased after transplantation and have a significant association with insulin resistance, but not with insulin secretion, in the development of NODAT in patients who undergo renal transplantation. TAC administration decreased serum adiponectin levels, while that of ARB reduced the decrement of adiponectin. These preliminary findings regarding insulin and glucose metabolism in relation to adiponectin levels are important for future development of NODAT prevention strategies.

Authorship

KN: designed study, collected data, analysed results, wrote manuscript. HK, TK, YK, NF, ST: performed study. YI: designed study, edited manuscript.

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