Endocrine Journal 2008, **55** (4), 677–683

The Impact of New-onset Diabetes on Arterial Stiffness after Renal Transplantation

KEN KATO, MUNEHIDE MATSUHISA, NAOTSUGU ICHIMARU*, SHIRO TAKAHARA**, YASUYUKI KOJIMA***, KAORU YAMAMOTO, TOSHIHIKO SHIRAIWA, AKIO KURODA, NAOTO KATAKAMI, KEN'YA SAKAMOTO, TAKA-AKI MATSUOKA, HIDEAKI KANETO, YOSHIMITSU YAMASAKI AND MASATSUGU HORI

Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Japan
**Department of Urology, Osaka University Graduate School of Medicine, Japan*
***Department of Advanced Technology for Transplantation, Osaka University Graduate School of Medicine, Japan*
****Department of Urology, Inoue Hospital, Japan*

Abstract. New-onset diabetes after renal transplantation (NODAT) is known to be a potent risk factor for cardiovascular events. We therefore investigated the incidence and risk factors for NODAT, and evaluated surrogate endpoints of atherosclerosis in Japanese patients with stable renal function after renal transplantation. Seventy-nine patients were enrolled in the study, and a 75 g oral glucose tolerance test (OGTT) was performed in subjects excluding patients with known NODAT. We evaluated the risk factors for NODAT and the degree of atherosclerosis, determined by brachial-ankle pulse wave velocity (baPWV), ankle-brachial blood pressure index (ABPI) and intima-media thickness (IMT) of the carotid artery. Eleven patients diagnosed as NODAT had significantly higher fasting plasma glucose before transplantation, blood pressure, and incidence of hepatitis C virus (HCV) infection than patients without NODAT. Multivariate regression analysis revealed that the independent determinant of NODAT was fasting plasma glucose pre-transplantation, HCV infection and systolic blood pressure. The baPWV in patients with NODAT was significantly higher compared to that in patients without NODAT. In addition, the independent determinant of baPWV evaluated by multivariate regression analysis was an increase in systolic blood pressure and age, and a decrease of adiponectin levels. In conclusion, we found that high fasting plasma glucose prior to transplantation, HCV infection and high blood pressure are risk factors for NODAT in Japanese patients after renal transplantation. Since NODAT patients have advanced arterial stiffness probably due to high blood pressure, strict control of blood pressure will be important for preventing the development of cardiovascular disease in NODAT.

Key words: New-onset diabetes after transplantation, Renal transplantation, PWV, Atherosclerosis
(*Endocrine Journal* **55**: 677–683, 2008)

SHORT-TERM renal allograft survival was dramatically enhanced with the improvement of immunosuppressive therapy, while long-term allograft survival remains problematic. Major complications of long-term allograft survival include cardiovascular disease as well as chronic allograft failure. Acute coronary syndrome is highly prevalent during the early post-transplant period and on average, cardiovascular disease mortality accounts for 30% and 75% of early and late post-transplant deaths, respectively [1–3]. Various risk factors for cardiovascular disease have been identified in renal transplant recipients, such as dyslipidemia, hypertension, hyperglycemia, smoking, renal allograft dysfunction, anemia, and an increase in inflammatory cytokines [4, 5]. Furthermore, new-onset diabetes after transplantation (NODAT) has recently been established as a potent risk factor for cardiovas-

Received: November 30, 2007
Accepted: December 3, 2007
Correspondence to: Munehide MATSUHISA, M.D., Ph.D., Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

cular disease in addition to diabetes prior to dialysis [6–8]. The incidence of cardiovascular disease was approximately three times higher in renal transplant recipients with NODAT than those without NODAT [9]. It is therefore very important to evaluate the degree of glucose tolerance and atherosclerosis of renal transplant recipients to improve allograft survival and mortality after renal transplantation.

Pulse wave velocity (PWV), ankle-brachial blood pressure index (ABPI) and intima-media thickness (IMT) of the carotid artery are accepted as strong independent predictors for cardiovascular events and mortality [10–12]. Recently, an instrument for measuring ABPI and brachial-ankle PWV (baPWV) by a volume-rendering method was developed [13]. These measurements are widely used to evaluate the degree of atherosclerosis, because the methods are easy, non-invasive and repeatable. A number of studies revealed that these surrogate endpoints were worsened in patients with end-stage renal failure [14, 15], and that renal transplantation could partially improve increased arterial stiffness [16]. However, it has not been fully evaluated whether NODAT affects these surrogate endpoints.

We therefore determined the impact of NODAT on baPWV, ABPI and IMT and the relationship between various risk factors and arterial function in renal transplant recipients in a single center cross sectional study.

Materials and Methods

Seventy-nine patients with renal transplants performed from 1998 to 2005 at Osaka University Medical Hospital were enrolled in this study. These subjects were stable renal transplant recipients without pre-existing diabetes. We excluded patients who had a plasma glucose concentration of greater than 7.0 mmol/L at the fasting state or 11 mmol/L 2 hours after a 75 g oral glucose load prior to transplantation. Immediately after transplantation, patients received immunosuppressant treatment composed either of anti-lymphocyte globulin or basiliximab with corticosteroids. The immunosuppressant treatment was based on calcineurin inhibitors (48 mg/day of tacrolimus and 31 mg/day of cyclosporine) with prednisolone and mycophenolate mofetile after the renal function was stabilized.

The study was approved by the Ethical Committee for Human Studies at Osaka University Hospital. After giving a detailed explanation of the study using a document, written informed consent was obtained from each subject. The oral glucose tolerance test (OGTT) was performed on all subjects excluding patients with known NODAT who had insulin therapy post-transplantation upon enrollment in the study. Plasma glucose and serum insulin levels were measured at 0, 30, 60 and 120 min after commencement of the OGTT. Diagnosis of NODAT has been clarified by the International Consensus Guidelines, which recommends diagnostic criteria for NODAT to mirror that of type 1 and type 2 diabetes mellitus as based on the American Diabetes Association and World Health Organization guidelines [17–19]. The degree of insulin resistance and insulin secretion was evaluated as the homeostasis model assessment of insulin resistance (HOMA-IR) and insulinogenic index, respectively. We also measured serum creatinine, adiponectin, lipid profile and high sensitive C-reactive protein (hsCRP) levels in the fasting state on the day of the OGTT. HCV and CMV infections were determined at pre-transplantation [9, 20].

The baPWV and ABPI were determined by using a device (AT-form PWV/ABI; Nippon Colin, Komaki, Japan) that can simultaneously monitor bilateral brachial and ankle pressure wave forms by the volume plethysmographic method, with optional tonometry sensors for carotid arterial wave measurements. To evaluate baPWV, the time duration between the brachial wave form and ankle wave form was automatically calculated as the heart-ankle time duration minus the heart-brachial time duration. The ABPI was calculated by the ankle systolic pressure divided by the arm systolic pressure. To evaluate the IMT, ultrasonographic scanning of the carotid artery was performed using an echotomographic system (Aplio SSA-700A; Toshiba Medical Systems Corp., Japan) with an electrical linear transducer (midfrequency 7.5 MHz). Scanning of the extracranial common carotid artery, the carotid bulb, and the internal carotid artery in the neck was performed bilaterally from three different longitudinal projections (*i.e.*, anterior oblique, lateral, and posterior oblique) as well as the transverse projections, as reported in our previous studies [21–23]. All of the images were photocopied. The detection limit of this echo system using 7.5 MHz was 0.1 mm. The IMT was measured as the distance from the leading edge of the first echogenic line to the leading edge of

the second echogenic line [24]. The first line represents the lumen-intima interface, and the second line is produced by the collagen-containing upper layer of the tunica adventitia. At each longitudinal projection, the site of the greatest thickness including a plaque lesion was sought along the arterial walls. Three determinations of IMT, one at the site of the thickest point, maximum IMT (Max-IMT), and two at adjacent points (located 1 cm upstream and 1 cm downstream from this site) were conducted. These three determinations were averaged (Mean-IMT). Higher values of IMT and baPWV, and the lower value of ABPI between both sides were used as representative values of the individuals for analysis.

Data are represented as means ± SD. Statistical comparisons between the patients with and without NODAT were assessed using ANOVA. The χ^2 test for trend was used to determine the relationship between the incidence of NODAT and risk factors such as HCV infection, family history of diabetes, and immunosuppressive treatments. Multivariate logistic regression analysis was performed to estimate the factors independently correlating with NODAT. Multivariate regression analyses were performed to evaluate the relationship between surrogate markers of cardiovascular disease and various risk factors for atherosclerosis. For multivariate regression analyses, the *F* value for the inclusion and exclusion of variables was set at 2.0. A p value of less than 0.05 was considered statistically significant. Analyses were performed with HALBAU statistical software (Gendai Sugaku-sha, Kyoto, Japan) on a personal computer. The threshold of statistical significance was defined as $p<0.05$.

Results

A total of 79 renal stable transplant recipients consented to the study and 77 subjects excluding patients with known NODAT underwent the OGTT. Clinical characteristics and metabolic parameters of the renal transplant recipients used in this study were as follows: 44 men and 35 women, age 44.6 ± 11.9 years, duration after transplantation 39.9 ± 23.2 months, body mass index (BMI) 21.2 ± 3.8, serum creatinine levels 124.7 ± 37.7 μmol/L, glycated hemoglobin A_{1C} (HbA_{1C}) 5.2 ± 0.6%, and fasting plasma glucose (FPG) 4.8 ± 0.9 mmol/L at the time of enrollment in the study. Prior to transplantation, BMI (20.7 ± 3.2) and FPG (4.8 ± 0.5 mmol/L) values were similar to those at the time of enrollment, although the HbA_{1C} (4.6 ± 0.5%) level was significantly lower than that at the time of enrollment.

Table 1. Metabolic parameters derived from oral glucose tolerance test with (NODAT) and without (Non-NODAT) new-onset diabetes after renal transplantation

	NODAT	Non-NODAT	P values
n	9	68	—
0-min glucose (mmol/L)	5.75 ± 2.08	4.63 ± 0.54	<0.05
30-min glucose (mmol/L)	9.60 ± 2.91	6.67 ± 1.80	<0.05
60-min glucose (mmol/L)	10.7 ± 4.19	6.20 ± 2.33	<0.05
120-min glucose (mmol/L)	10.0 ± 3.84	5.50 ± 1.52	<0.05
0-min insulin (pmol/L)	35.9 ± 12.0	29.1 ± 14.3	NS
30-min insulin (pmol/L)	157.7 ± 147.1	287.9 ± 247.0	NS
60-min insulin (pmol/L)	202.2 ± 112.2	208.8 ± 130.5	NS
120-min insulin (pmol/L)	203.1 ± 119.9	180.5 ± 99.5	NS
HOMA-IR	1.59 ± 0.88	1.00 ± 0.52	<0.01
HOMA-β	72.3 ± 48.0	103 ± 84.2	NS
Insulinogenic Index	0.43 ± 0.46	1.75 ± 2.49	<0.01

Data are given as means ± S.D. Data between the groups were compared by the one-way ANOVA followed by Scheffe's test.
NS: not significant

Eleven patients were diagnosed as NODAT, and 7 and 61 patients (Non-NODAT) were diagnosed to have impaired glucose tolerance and normal glucose tolerance, respectively. In NODAT patients, plasma glucose levels during the OGTT and HOMA-IR were significantly higher than those of Non-NODAT subjects, while the insulinogenic index was significantly lower than that in Non-NODAT subjects (Table 1). Patients with NODAT had a significantly higher age at transplantation, fasting plasma glucose concentration prior to transplantation, systolic blood pressure and low-density lipoprotein cholesterol (LDL-C) upon the OGTT compared with Non-NODAT subjects (Table 2). Among the other previously reported risk factors for NODAT, such as infection of HCV and CMV, family history of diabetes, class of calcineurin inhibitors, and treatment with high dose prednisolone at episodes of acute rejection, only the incidence of HCV infection was significantly higher in NODAT patients compared with Non-NODAT subjects. Multivariate logistic regression analysis revealed that the risk factors for NODAT were the incidence of HCV, high fasting plasma glucose levels prior to transplantation, and high systolic blood pressure (Table 3) at the time of enrollment.

Table 2. Clinical characteristics with (NODAT) and without (Non-NODAT) new-onset diabetes after renal transplantation

	NODAT	Non-NODAT	*P* values
n	11	68	—
Age (pre-transplant) (years)	45.7 ± 13.0	37.8 ± 11.6	<0.05
Age at OGTT (years)	50.5 ± 12.5	43.6 ± 11.6	NS
Gender (% male)	73	53	NS
Body mass index (pre-transplant)	22.1 ± 4.2	20.4 ± 3.0	NS
Body mass index at OGTT	22.5 ± 3.9	21.0 ± 3.7	NS
Duration after transplantation (months)	44.9 ± 24.2	39.1 ± 23.1	NS
Duration of dialysis (months)	43.7 ± 50.3	44.0 ± 48.2	NS
Fasting plasma glucose (pre-transplant) (mmol/L)	5.3 ± 0.8	4.8 ± 0.4	<0.01
HbA_{1C} (pre-transplant) (%)	4.6 ± 0.5	4.6 ± 0.5	NS
HbA_{1C} at OGTT (%)	5.7 ± 1.1	5.1 ± 0.3	<0.01
Serum creatinine (μmol/L)	133 ± 44	124 ± 35	NS
Systolic blood pressure at OGTT (mmHg)	135 ± 18	121 ± 15	<0.01
Total cholesterol (mmol/L)	5.61 ± 0.78	5.07 ± 0.96	NS
Triglyceride (mmol/L)	1.36 ± 0.35	1.38 ± 0.96	NS
Low-density lipoprotein cholesterol (mmol/L)	3.85 ± 0.72	3.26 ± 0.91	<0.05
Family history of diabetes (%)	9.1	34.3	NS[a]
Smoking (Brinkman index)	245 ± 455	202 ± 410	NS
Rejection episodes (%)	55	36	NS[a]
Cyclosporin (%)	27	41	NS[a]
Tacrolimus (%)	73	59	NS[a]
Adiponectin (μg/dL)	26.2 ± 13.1	21.4 ± 11.1	NS
High sensitive C-reactive protein (mg/dL)	0.14 ± 0.21	0.06 ± 0.15	NS
Hepatitis C virus infection (%)	18	0	<0.01[a]
Cytomegalovirus infection (%)	64	77	NS[a]
baPWV (m/s)	1.59 ± 0.34	1.34 ± 0.21	<0.01
ABPI	1.12 ± 0.06	1.13 ± 0.10	NS
Max-IMT (mm)	1.24 ± 0.87	1.08 ± 0.62	NS
Mean-IMT (mm)	0.68 ± 0.22	0.59 ± 0.27	NS

Data are given as means ± S.D. Data between the groups were compared by the one-way ANOVA followed by Scheffe's test, except for a = X^2 test. NS: not significant

Table 3. Factors related to new-onset diabetes after renal transplantation (NODAT) in renal transplant subjects

Variables	Odds ratio	(95% CI)	*P* values
Age (pre-transplant)	1.005	(0.932–1.083)	0.905
Fasting plasma glucose (pre-transplant)	1.098	(1.001–1.203)	0.047
Systolic blood pressure	1.053	(1.000–1.107)	0.048
Low-density lipoprotein cholesterol	1.027	(1.000–1.054)	0.051
Hepatitis C virus infection	1.222	(0.924–1.650)	0.0006
Rejection episodes	1.363	(0.861–2.247)	0.055
Tacrolimus	1.456	(0.548–4.888)	0.431

Multivariate logistic regression analysis was performed for 79 subjects with stable renal function after renal transplantation to select variables significantly associated with NODAT. Variables were considered for the multivariable models when their univariable *p*-value was less than 0.05.
CI: confidential interval

Furthermore, we assessed the surrogate endpoints for cardiovascular disease in NODAT and Non-NODAT subjects. As shown in Table 2, the baPWV in NODAT patients was significantly higher than that in Non-NODAT subjects, while there were no significant differences in Max-IMT, Mean-IMT and ABPI between the two groups. The baPWV was positively correlated with HbA_{1C}, age, systolic blood pressure, and Max-IMT levels, and negatively correlated with adiponectin levels. Multivariate regression analyses revealed that high blood pressure, age, and low adiponectin levels were independent determinants for developing arterial stiffness (Table 4).

Table 4. Correlation between baPWV and variables in renal transplant subjects

Variables	Univariate analysis* (95% CI)		Multivariate analysis†
	r value	*P* value	*F* value
Age at OGTT (years)	0.481	<0.001	9.699
Systolic blood pressure at OGTT (mmHg)	0.648	<0.001	32.378
Adiponectin (μg/dL)	–0.322	0.016	3.762
HbA_{1C} at OGTT (%)	0.379	0.006	0.910
High sensitive C-reactive protein (mg/dL)	0.077	NS	NE
Total cholesterol (mmol/L)	0.054	NS	NE
Triglyceride (mmol/L)	0.046	NS	NE
Low-density lipoprotein cholesterol (mmol/L)	0.111	NS	NE
Smoking (Brinkman index)	0.093	NS	NE

*Pearson's univariate correlation coefficients. †Multivariate regression analysis.
NS: not significant
NE: not entered

Discussion

In the present study, we firstly demonstrated that new-onset diabetes after renal transplantation induces arterial wall stiffening as determined by baPWV. Arterial stiffness is known to increase before dialysis in patients with chronic renal disease [14, 15], and renal transplantation improves this increased arterial stiffness [16]. In addition, hyperglycemia itself is known to be a potent promoter for developing arterial stiffness in patients with type 1 and type 2 diabetes [25, 26]. In this study, since the average baPWV level was within the normal range in the renal transplant recipients without NODAT, renal transplantation may have improved their arterial stiffness. Multivariate regression analyses demonstrated that the independent risk factors for arterial stiffening were an increase in blood pressure and age, and a decrease in adiponectin levels, but not an increase in hemoglobin A_{1C} levels, in all renal transplant patients. Since hypertension was a risk factor for NODAT, increased blood pressure, but not hyperglycemia, could be a major cause of arterial stiffness in NODAT. Hypertension is also known to be the most potent factor for developing arterial stiffness in end-stage renal disease [27]. Therefore, strict control of hypertension may be a key factor in preventing NODAT and atherosclerosis after renal transplantation. The HbA_{1C} level of 8 out of 11 patients with NODAT was within the normal range (less than 5.8%), and thus such mild hyperglycemia failed to contribute to increased arterial stiffness.

A previous report in patients with hypertension demonstrated that low serum adiponectin levels, as well as high arterial pressure and age, were independently related to arterial stiffness [28]. In the present study, we found a similar correlation between high baPWV and low serum adiponectin levels in renal transplant patients. Adiponectin is known to correlate directly with whole-body insulin sensitivity, which is a major cause of diabetes [29] and cardiovascular disease [30]. In the present study, however, plasma adiponectin levels were not correlated with the index of insulin resistance, HOMA-IR. Thus the effect of adiponectin on preventing arterial stiffness may be independent of the effect of insulin resistance after renal transplantation. In addition, the absolute levels of serum adiponectin in the subjects of the present study were elevated compared with those of Japanese subjects with various types of glucose tolerance in our previous report [31]. Several reports demonstrated similar findings that adiponectin levels were increased in subjects with end-stage renal disease and after renal transplantation [32]. Our results suggest that a lower adiponectin level may contribute to the development of atherosclerosis in renal transplant recipients.

We found that patients with NODAT have a higher HOMA-IR and lower insulinogenic index, indicating that the pathogenesis of NODAT involves an impairment of both insulin action and insulin secretory ability. Since the dosage and class of immunosuppressants used were identical between the patients with and without NODAT, impaired insulin secretion and ac-

tion were not due to the immunosupression therapy. Since plasma glucose levels prior to transplantation were significantly higher in patients with NODAT, evaluation of glucose tolerance by the OGTT may be beneficial for predicting the development of NODAT prior to transplantation. We should therefore treat renal transplant recipients that have fasting hyperglycemia or impaired glucose tolerance with strict intervention of their lifestyle prior to transplantation.

In addition to immunosuppressive drugs and previous glucose intolerance, age, race, and family history of diabetes were reported as non-modifiable risk factors for developing NODAT, whereas obesity, HCV and CMV infections [33, 34] were reported as modifiable risk factors. In this study, we found that HCV infection prior to transplantation was a risk factor for NODAT in renal transplant recipients. HCV infection is a well known risk factor for not only NODAT, but also type 2 diabetes, probably due to impaired insulin action in the liver [35]. In addition to these risk factors, lower adiponectin and higher high sensitive C-reactive protein (hs-CRP) levels were recently reported to be associated with NODAT [36], but we failed to observe such correlations.

In conclusion, we found that high fasting plasma glucose prior to transplantation, HCV infection and high blood pressure are risk factors for new-onset diabetes in Japanese patients after renal transplantation. Development of diabetes after transplantation induces increased arterial stiffness probably due to elevated blood pressure. Strict treatment for hypertension and mild fasting hyperglycemia will therefore be beneficial for the prevention of new-onset diabetes and cardiovascular disease after renal transplantation.

Acknowledgements

We appreciate the excellent technical assistance of M. Shinmei, K. Yamamoto and H. Kojima (Inoue Hospital) and the outstanding secretarial work of C. Yokogawa.

References

1. Aakhus S, Dahl K, Widerøe TE (1999) Cardiovascular morbidity and risk factors in renal transplant patients. *Nephrol Dial Transplant* 14: 648–654.
2. Humar A, Kerr SR, Ramcharan T, Gillingham KJ, Matas AJ (2001) Peri-operative cardiac morbidity in kidney transplant recipients: incidence and risk factors. *Clin Transplant* 15: 154–158.
3. Aakhus S, Dahl K, Widerøe TE (2004) Cardiovascular disease in stable renal transplant patients in Norway: morbidity and mortality during a 5-yr follow-up. *Clin Transplant* 18: 596–604.
4. Ojo AO (2006) Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 82: 603–611.
5. Kasiske BL, Chakkera HA, Roel J (2000) Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol* 11: 1735–1743.
6. Miles AM, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, Distant DA, Hong JH, Sommer BG, Friedman EA (1998) Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes. *Transplantaion* 65: 380–384.
7. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM (2002) Patient survival after renal transplantation. Impact of post-transplant diabetes. *Kidney Int* 62: 1440–1446.
8. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ (2003) Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 3: 178–185.
9. Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, Jenssen T (2006) The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 69: 588–595.
10. Khoshdel AR, Carney SL, Nair BR, Gillies A (2007) Better management of cardiovascular diseases by pulse wave velocity: combining clinical practice with clinical research using evidence-based medicine. *Clin Med Res* 5: 45–52.
11. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D (1999) Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol* 19: 538–545.
12. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 115: 459–467.
13. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y (2002) Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 25: 359–364.

14. Kitahara T, Ono K, Tsuchida A, Kawai H, Shinohara M, Ishii Y, Koyanagi H, Noguchi T, Matsumoto T, Sekihara T, Watanabe Y, Kanai H, Ishida H, Nojima Y (2005) Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kidney Dis* 46: 688–696.
15. Ekart R, Hojs R, Hojs-Fabjan T, Balon BP (2005) Predictive value of carotid intima media thickness in hemodialysis patients. *Artif Organs* 29: 615–619.
16. Zoungas S, Kerr PG, Chadban S, Muske C, Ristevski S, Atkins RC, McNeil JJ, McGrath BP (2004) Arterial function after successful renal transplantation. *Kidney Int* 65: 1882–1889.
17. Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, Jardine A, Levitt N, Marchetti P, Markell M, Naicker S, O'Connell P, Schnitzler M, Standl E, Torregosa JV, Uchida K, Valantine H, Villamil F, Vincenti F, Wissing M (2005) Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 19: 291–298.
18. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC (2003) New-onset diabetes after transplantation: 2003 International consensus guidelines. *Transplantation* 75: SS3–24.
19. Davidson JA, Wilkinson A (2004) New-Onset Diabetes After Transplantation 2003 International Consensus Guidelines: an endocrinologist's view. *Diabetes Care* 27: 805–812.
20. Hjelmesaeth J, Sagedal S, Hartmann A, Rollag H, Egeland T, Hagen M, Nordal KP, Jenssen T (2004) Asymptomatic cytomegalovirus infection is associated with increased risk of new-onset diabetes mellitus and impaired insulin release after renal transplantation. *Diabetologia* 47: 1550–1556.
21. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kajimoto Y, Morishima T, Kamada T (1994) Atherosclerosis in carotid artery of young IDDM patients monitored by ultrasound high-resolution B-mode imaging. *Diabetes* 43: 634–639.
22. Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, Maeda H, Handa N, Matsumoto M, Kamada T (1992) Prevalence of carotid atherosclerosis in diabetic patients: ultrasound high-resolution B-mode imaging on carotid arteries. *Diabetes Care* 15: 1290–1294.
23. Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, Hori M (2000) Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. *Diabetes Care* 23: 1310–1315.
24. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R (1986) Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 74: 1399–1406.
25. Lehmann ED, Gosling RG, Sönksen PH (1992) Arterial wall compliance in diabetes. *Diabet Med* 9: 114–119.
26. Gordin D, Rönnback M, Forsblom C, Heikkilä O, Saraheimo M, Groop PH (2007) Acute hyperglycaemia rapidly increases arterial stiffness in young patients with type 1 diabetes. *Diabetologia* 50: 1808–1814.
27. Wang MC, Tsai WC, Chen JY, Huang JJ (2005) Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis* 45: 494–501.
28. Mahmud A, Feely J (2005) Adiponectin and arterial stiffness. *Am J Hypertens* 18: 1543–1548.
29. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA (2001) Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86: 1930–1935.
30. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T, Matsuzawa Y (2003) Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 23: 85–89.
31. Matsuhisa M, Yamasaki Y, Emoto M, Shimabukuro M, Ueda S, Funahashi T, Matsuzawa Y (2007) A novel index of insulin resistance determined from the homeostasis model assessment index and adiponectin levels in Japanese subjects. *Diabetes Res Clin Pract* 77: 151–154.
32. Shen YY, Charlesworth JA, Kelly JJ, Peake PW (2007) The effect of renal transplantation on adiponectin and its isoforms and receptors. *Metabolism* 56: 1201–1208.
33. Reisaeter AV, Hartmann A (2001) Risk factors and incidence of posttransplant diabetes mellitus. *Trans Proc* 33: 8S-18S.
34. Rodrigo E, Fernández-Fresnedo G, Valero R, Ruiz JC, Piñera C, Palomar R, González-Cotorruelo J, Gómez-Alamillo C, Arias M (2006) New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 17: S291–295.
35. Lecube A, Hernández C, Genescà J, Simó R (2006) Glucose abnormalities in patients with hepatitis C virus infection: Epidemiology and pathogenesis. *Diabetes Care* 29: 1140–1149.
36. Bayes B, Granada ML, Pastor MC, Lauzurica R, Salinas I, Sanmartí A, Espinal A, Serra A, Navarro M, Bonal J, Romero R (2007) Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. *Am J Transplant* 7: 416–422.