Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Effect of new-onset diabetes mellitus on arterial stiffness in renal transplantation

Anabelle Opazo Saez, Michaela Kos, Oliver Witzke, Andreas Kribben and Jens Nürnberger

Department of Nephrology, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Keywords
arterial stiffness, augmentation index, pulse wave velocity, renal transplantation diabetes mellitus.

Correspondence
PD Dr Jens Nürnberger, Department of Nephrology, University Hospital Essen, University Duisburg-Essen, Hufelandstrasse 55, 45147 Essen, Germany. Tel.: +49 201 723 3955; fax: +49 201 723 3393; e-mail: jens.nuernberger@uni-due.de

Received: 6 March 2008
Revision requested: 26 March 2008
Accepted: 5 May 2008

doi:10.1111/j.1432-2277.2008.00702.x

Summary

New onset diabetes (NODM) is a common and serious complication of kidney transplantation, and is associated with increased cardiovascular morbidity and mortality. Cardiovascular morbidity and mortality, in turn, are closely associated with arterial stiffening. We hypothesize that NODM may be associated with an increase in arterial stiffness in renal transplantation. We compared pulse wave velocity (PWV) and augmentation index in 318 renal transplant patients with (n = 57) and without NODM (n = 261). PWV was determined from pressure tracing over carotid and femoral arteries. Augmentation-index was derived by pulse-wave-analysis using radial applanation tonometry. PWV was significantly higher in transplant recipients with NODM (10.5 m/s) compared with transplant patients without NODM (8.7 m/s, P = 0.0002). There was no difference in augmentation index between patients with (27.7%) and without NODM (28.1%, P = 0.87). When analyzed by multiple regression analysis, PWV was only significantly correlated to age (P < 0.0001), NODM (P = 0.0325), and systolic blood pressure (P = 0.0081). NODM in renal transplant patients may accelerate arterial stiffening, thereby contributing to cardiovascular morbidity and mortality.

Introduction

Measuring arterial stiffness has become a major tool for assessing arterial function and cardiovascular mortality [1]. In particular, pulse wave velocity (PWV) and augmentation index have been proposed to be clinically useful stiffness markers on account of their noninvasiveness and ease of use [2]. Pulse wave velocity reflects the speed by which the primary pressure wave generated by ventricular ejection travels along the arterial tree. The augmentation index is determined from the pulse wave and reflects the degree to which central arterial pressure is increased by the reflected pulse wave [3]. Whereas PWV is the classic marker of arterial stiffness, augmentation index is a more complex parameter of arterial function depending on stiffness, endothelial function, and wave reflection [1]. Both parameters not only reflect the overall atherosclerotic load of the arterial tree but have also been shown to predict cardiovascular mortality in hypertension [4,5], chronic renal failure [6,7], and diabetes mellitus [7,8].

New onset diabetes (NODM) is a common and serious complication of kidney transplantation associated with increased cardiovascular morbidity and mortality [9]. Cardiovascular mortality, in turn, has been closely associated with arterial stiffening [1,2]). To date, it is not known whether NODM in renal transplantation contributes to arterial stiffening. In the present study, we evaluate the effect of NODM on arterial stiffness markers in renal transplant patients. We hypothesize that NODM contributes to arterial stiffening in renal transplantation, and that stiffness markers such as PWV and augmentation index may be increased in subjects with NODM.

Methods

Study population

In this cross-sectional study, 318 subjects with stable renal transplantation were recruited from our renal transplant outpatient clinic. In addition, data from 51 healthy controls and 35 nontransplant type II diabetics were

analyzed. Height and weight were measured, and body mass index (BMI) was calculated as weight to height squared. Laboratory measurements were measured with commercially available kits in our central laboratory. The study was performed in accordance with the principles laid down in the Declaration of Helsinki.

The diagnostic criteria for diabetes mellitus as recommended by the 2003 international consensus guidelines for new-onset diabetes after transplantation were used [10]. These criteria were symptoms of diabetes plus casual plasma glucose concentrations >200 mg/dl or fasting plasma glucose >126 mg/dl or 2-h plasma glucose >200 mg/dl during an oral glucose tolerance test.

Hemodynamic measurements

Measurements were performed in a quiet, temperature-controlled room after 10 min, in a supine position according to the recommendations for user procedures of clinical applications of arterial stiffness, task force III [11], using the SphygmoCor device (AtCor Medical, Sydney, Australia). Blood pressure and heart rate (mean of three readings) were measured with an automatic upper-arm oscillometric device (Omron *705IT*, Omron Medizintechnik, Mannheim, Germany). Pulse pressure (PP) was calculated by subtracting diastolic (DBP) from systolic blood pressure (SBP).

Aortic PWV was calculated from sequentially recorded pressure waveforms of the carotid and femoral artery as reported previously by our group [12,13]. With a simultaneous ECG recording of the R-wave as reference, the integral software calculated the pulse wave transit time. Anatomical measurements of the distance between the carotid and femoral artery were made on the surface of the body. The distance between carotid artery recording site and the suprasternal notch was subtracted from the distance from the suprasternal notch over the umbilicus to the femoral artery recording site. PWV [$m \times s^{-1}$] was calculated as ratio between the distance traveled by the pulse wave and pulse transmission time.

Augmentation index was calculated from pulse waves of the radial artery that were recorded by applanation tonometry, as previously described [12,14]. Data were collected directly into a portable computer; integral software was used to generate an averaged composite waveform (SphygmoCor) from which specially designed software derived an aortic blood pressure waveform using a validated transfer function algorithm [3]. The systolic part of the central arterial waveform is characterized by two pressure peaks. The first peak is caused by left ventricular ejection whereas the second peak is a result of wave reflection. Augmentation terms the difference between both pressure peaks, and augmentation index (%), which was calculated from augmentation divided by pulse pressure (expressed as a percentage), reflects the degree to which central arterial pressure is augmented by wave reflection.

Statistical analysis

Nonpaired, two-sided Student's *t*-test was used to analyze differences in anthropometric, hemodynamic or biochemical parameters between renal transplant patients with and without NODM. ANOVA was used to analyze the effect of potential confounders on the difference between stiffness markers between subjects with and without NODM.

Simple linear regression analysis (Pearson) was applied to further detect and describe strength and direction of correlations of stiffness markers to anthropometric, hemodynamic, clinical, and biochemical parameters. Those parameters that were significantly correlated to stiffness markers in simple regression analysis were further subjected to multiple regression analysis.

$P < 0.05$ was considered statistically significant. All values are shown as mean ± SEM. Statistical analysis was performed using GraphPad Prism 4.0 for MS Windows (GraphPad Software, Inc., San Diego, CA, USA).

Results

Characteristics of the study population are displayed in Table 1 (left column). Two hundred and eighty-eight subjects of the study population had a history of hypertension, 74 subjects had known coronary heart disease, and 24 subjects had a history of arterial occlusive disease. 53 patients had undergone parathyroidectomy, five patients had had a stroke in the past. The large majority was treated with antihypertensive drugs (234 subjects received beta-blockers, 167 subjects received calcium-antagonists, 201 subjects received ACE-inhibitor/angiotensin receptor-blockers, 211 subjects received diuretics, and 68 were treated with sympatholytic agents, respectively. The large majority received immunosuppressive therapy containing corticosteroids ($n = 283$) and calcineurin-inhibitors ($n = 284$; 120 with cyclosporine, 164 with tacrolimus). 152 subjects received mycophenolic acid; and 21 subjects received mTOR inhibitors.

From the 318 renal transplant patients, 57 subjects had NODM, whereas 261 transplant patients without diabetes served as controls (Table 1). Compared to nondiabetic transplant controls, transplant patients with NODM showed a significantly higher PWV ($P = 0.0002$).There was no difference in augmentation index between these two groups. As expected, parameters of glucose metabolism including glucose and HbA1 were also significantly

Table 1. Characteristics (mean ± SEM) of the transplant study population.

Parameter	Total (n = 318)	NODM (n = 57)	Controls (n = 261)	P-value
Age (years)	51.6 ± 0.76	57.4 ± 1.58	50.3 ± 0.85	0.0003
Gender (male/female)	156/162	26/31	136/125	0.3759
Height (cm)	169.9 ± 0.57	167.2 ± 1.29	170.4 ± 0.63	0.0311
Weight (kg)	73.4 ± 0.85	73.9 ± 1.81	73.4 ± 0.96	0.8036
Body mass index (kg/m^2)	25.4 ± 0.24	26.4 ± 0.26	25.1 ± 0.27	0.0403
History of hypertension	N = 288	N = 52	N = 236	0.9137
History of CHD	N = 74	N = 19	N = 55	0.0511
History of AOD	N = 24	N = 6	N = 18	0.3577
Cholesterol (mg/dl)	213.4 ± 2.8	218.3 ± 6.9	212.7 ± 3.0	0.4422
Glucose (mg/dl)	108.2 ± 1.83	133.4 ± 5.83	102.8 ± 1.67	<0.0001
HbA1c (mg/dl)	5.83 ± 0.064	6.46 ± 0.136	5.62 ± 0.059	<0.0001
Systolic blood pressure (mmHg)	149.3 ± 1.13	154.2 ± 2.82	148.2 ± 1.23	0.0419
Diastolic blood pressure (mmHg)	83.0 ± 0.63	80.4 ± 1.49	83.5 ± 0.69	0.0530
Pulse pressure (mmHg)	66.3 ± 0.98	73.8 ± 2.74	64.6 ± 1.02	0.0003
Heart rate (b.p.m.)	67.5 ± 0.70	70.7 ± 1.78	66.5 ± 0.80	0.0329
Pulse wave velocity (m/s)	9.04 ± 0.19	10.54 ± 0.56	8.67 ± 0.19	0.0002
Augmentation index (%)	27.9 ± 0.73	27.7 ± 1.71	28.1 ± 0.82	0.8728

CHD, coronary heart disease; AOD, arterial occlusive disease.
P-values for unpaired Student's t-test between subjects with NODM and controls without NODM.

higher in patients with NODM. Systolic blood pressure was higher in diabetics (P = 0.0419), whereas diastolic blood pressure tended to be lower the NODM group (P = 0.0530). Together, this resulted in a significantly greater pulse pressure in NODM subjects (P = 0.0003). Furthermore, NODM transplant patients were significantly older than transplant controls (P = 0.003).

Because age is a well-known determinant of PWV, we used ANOVA to analyze the confounding effect of age on the difference in PWV between NODM subjects and control transplants. Following ANOVA using age as co-variable, PWV remained significantly higher in NODM (P = 0.0115).

To further confirm that age does not significantly influence the observed difference in PWV between NODM subjects and controls, this analysis was repeated in subjects older than 45 years (Table 2). Even in these selected transplant cohorts of similar age, PWV remained significantly higher in subjects with NODM (P = 0.0073).

We further included a control group of healthy subjects and one control group of nontransplant diabetics to analyze the extent of the PWV increase in transplant subjects (Table 2). When compared with healthy subjects of similar age, PWV was significantly higher in NODM transplant patients (P < 0.0001) as well as in transplant controls (P = 0.045). PWV tended to be higher in nontransplant diabetics compared to healthy controls (P = 0.0705), but there was no significant difference in PWV between nontransplant diabetics and transplant patients without diabetes.

We additionally analyzed the impact of other potential determinants of PWV in this cohort of renal transplant patients. Table 3 shows the results of regression analysis between PWV and anthropometric, hemodynamic, clinical,

Table 2. Characteristics (mean ± SEM) of renal transplant subjects >45 years and control groups of healthy subjects and nontransplant diabetics.

Parameter	Transplant patients with NODM (n = 48)	Transplant patients Controls (n = 170)	Healthy controls (n = 51)	Nontransplant diabetics (n = 35)
Age (years)	61.0 ± 1.29	58.4 ± 0.65	61.2 ± 0.61	64.4 ± 0.61*
Gender (male/female)	21/27	88/82	38/41	19/16
Body mass index (kg/m^2)	26.5 ± 0.60	25.8 ± 0.31	27.0 ± 0.49	28.3 ± 0.53
Systolic blood pressure (mmHg)	152.5 ± 2.83	151.6 ± 1.48	136.0 ± 2.31***	142.1 ± 3.54*
Diastolic blood pressure (mmHg)	77.7 ± 1.23	82.5 ± 0.81**	81.5 ± 1.26*	78.7 ± 1.9
Pulse pressure (mmHg)	74.9 ± 3.00	69.1 ± 1.26*	54.5 ± 1.39***	63.4 ± 2.6**
Pulse wave velocity (m/s)	11.13 ± 0.62	9.61 ± 0.25**	8.53 ± 0.24***	9.21 ± 0.28*
Augmentation index (%)	28.4 ± 1.73	30.4 ± 0.88	27.5 ± 1.01	24.1 ± 1.66

*Indicates P < 0.05, **indicates P < 0.01, ***indicates P < 0.001 for comparison with NODM transplant subjects (Unpaired student's t-test).

Table 3. Results of simple and multiple regression analyses for anthropometric, hemodynamic, clinical, and biochemical parameters using pulse wave velocity as dependent variable. Correlation coefficients of simple (*r*) and multiple regression analysis (β) and *P*-values (*p*) are displayed.

	Simple regression		Multiple regression	
Pulse wave velocity	*r*	*p*	β	*p*
Age	0.602	<0.0001	0.516	<0.0001
Height	0.003	0.9649		
Weight	0.048	0.4157		
BMI	0.068	0.2494		
NODM	0.220	0.0002	0.401	0.0325
Hypertension	0.126	0.0343		
CHD	0.233	<0.0001	0.010	0.8563
AOD	0.141	0.0176	0.037	0.4678
Parathyroidectomy	0.024	0.7425		
Stroke	0.096	0.1843		
CNI	0.063	0.3840		
Corticosteroids	0.055	0.4475		
Mycophenolic acid	0.128	0.0749		
mTOR inhibitor	0.084	0.2462		
Beta-blocker	0.046	0.4443		
Ca-antagonist	0.125	0.0362	0.055	0.2641
ACE/ARB	0.179	0.0026	0.087	0.0679
Diuretics	0.037	0.5402		
Sympatholytics	0.016	0.7890		
Statins	0.114	0.0560		
Hemoglobin	0.018	0.7645		
Urea	0.044	0.4630		
Creatinine	0.065	0.2760		
Uric acid	0.027	0.6522		
Cholesterol	0.092	0.1949		
Glucose	0.251	<0.0001		
HbA1	0.212	0.0145		
Proteinuria	0.034	0.5698		
SBP	0.315	<0.0001	0.134	0.0081
DBP	0.001	0.9911		
PP	0.131	<0.0001		
Heart rate	0.075	0.2061		
Augmentation index	0.002	0.9716		

BMI, body mass index; CHD, coronary heart disease; AOD, arterial occlusive disease; CNI, calcineurin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

or biochemical parameters. Using simple regression analysis, PWV was significantly correlated to age, NODM, presence of coronary heart and arterial occlusive disease, treatment with Ca-antagonists and ACE-inhibitors/angiotensin receptor-blockers, glucose, HbA1, systolic blood pressure, and pulse pressure. Parameters that were significantly correlated to PWV (except for HbA1, glucose, and pulse pressure as they depend on diabetes and systolic blood pressure) were further submitted to multiple regression analysis, using PWV as dependent variable. After multiple regression analysis, PWV remained significantly correlated only to age ($P < 0.0001$), NODM ($P = 0.0325$), and systolic blood pressure ($P = 0.0081$).

Augmentation index was not analyzed by multiple regression analysis as it was not significantly correlated to NODM.

Discussion

In the present study, we evaluated the impact of new-onset diabetes mellitus on the arterial stiffness markers PWV and augmentation index. We found that PWV was significantly higher in subjects with NODM compared to controls. In contrast, augmentation index was not significantly different in the NODM group.

It has been shown that age is a strong predictor of NODM in renal transplantation [15]. Consistent with that report, patients with NODM in our study were significantly older than the control group without NODM. Because age is a major determinant of PWV, we additionally performed ANOVA to assess the potential effect of age on the observed difference in PWV between both the groups and found that PWV remained significantly higher in NODM. Furthermore, when only patients older than 45 years were analyzed to compare groups of similar age, PWV remained significantly higher in NODM patients. Consistent with these results, multiple regression analysis additionally showed that besides age and blood pressure, NODM remained significantly correlated to PWV. Together, our data provide new evidence that NODM is a strong determinant of PWV in renal transplant patients.

Patients with NODM were on transplant for 5 years (mean 5.4 years ± 5.7 SD). We believe that changes in the arterial wall may occur during such a time period. In fact, functional changes of the arterial wall such as an increase in PWV have been reported to occur over a short period of time [16]. Thus, we propose that NODM is an important contributor to arterial stiffening in subjects with renal transplantation. Optimizing glucose metabolism in renal transplant patients may improve cardiovascular morbidity and mortality in this patient group as arterial stiffening is not merely reflecting the overall atherosclerotic load but negatively affects hemodynamic function [2]. Further studies are required to investigate whether the use of such drugs can also slow down progression of arterial stiffening.

We compared the increase in PWV in our transplant groups with a control group of healthy subjects, and similar age. PWV in this control group was in the range previously reported for that age cohort [17]. Both transplant groups had a significantly higher PWV compared to the healthy controls, indicating that despite the reported beneficial effect of transplantation on arterial stiffness markers [18], arterial stiffening may be accelerated in these patients.

We also compared our PWV results in transplants with those of nontransplanted diabetic patients and found that transplant diabetics exhibited a significantly higher PWV compared to nontransplant diabetics. These results suggest that there may be an additive effect of renal failure and diabetes on the increase in PWV.

In addition to a higher PWV, subjects with NODM also exhibited a higher systolic blood pressure. Whereas diastolic blood pressure is a major determinant of PWV in younger individuals [13], systolic blood pressure (SBP) is more closely related to PWV in older individuals [1]. It is possible that SBP may contribute to the higher PWV observed in NODM subjects. However, when analyzed by multiple regression analysis, both NODM and SBP remained significantly correlated to PWV. Furthermore, aortic stiffening leads to characteristic changes of the blood pressure pattern with a rise of systolic and a fall of diastolic blood pressure resulting in a widening of the pulse pressure [2]. In our study, NODM patients indeed not only had higher PWV, but also exhibited higher systolic and lower diastolic blood pressure compared to the control group. As a result, NODM subjects exhibited a pulse pressure that was nearly 10 mmHg higher compared to controls. These findings are consistent with the idea that more pronounced aortic stiffening is responsible for the different blood pressure pattern observed in NODM transplant patients compared to control transplant subjects.

Interestingly, augmentation index was not associated with NODM. Augmentation index is a complex parameter of arterial function depending not only on stiffness and wave reflection but also on endothelial and cardiac function [3], and is not interchangeable with PWV [19]. We speculate that the lack of an association between NODM and augmentation index may result from such additional confounding factors. PWV and augmentation index may provide differential information on arterial function in renal transplant recipients.

It has been suggested that improving glucose metabolism may represent a significant target to lower cardiovascular mortality in renal patients with NODM [9,20]. In addition, pharmacological and nonpharmacological approaches to reduce arterial stiffness may be of particular importance for renal transplant patients who have NODM [2]. Further studies are required to evaluate the predictive value of PWV and augmentation index for cardiovascular mortality in renal transplant recipients.

Acknowledgements

We would like to thank Petra Höhner for her help in recruiting patients. We would also like to thank Christa Sittartz for her technical assistance.

Sources of funding

This study was supported, in part, by grants from the intramural research fund (IFORES) and the Jackstaedt foundation.

Authorship

AOS: Wrote paper/analyzed data. MK: Collected data. OW: Recruitment of patients, analyzed data. AK: Head of Department, recruitment of patients, analyzed data. JN: Designed study, wrote paper.

References

1. Laurent S, Cockcroft J, Van Bortel L, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588.
2. Opazo Saez AM, Mitchell A, Philipp T, Nürnberger J. Arterial stiffness: a potential therapeutic target to reduce cardiovascular mortality. *Curr Hypertens Rev* 2006; **2**: 97.
3. O'Rourke MF, Pauca A, Jiang XJ. Pulse wave analysis. *Br J Clin Pharmacol* 2001; **51**: 507.
4. Boutouyrie P, Tropeano AI, Asmar R, *et al.* Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* 2002; **39**: 10.
5. Laurent S, Boutouyrie P, Asmar R, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236.
6. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**: 2434.
7. Shoji T, Emoto M, Shinohara K, *et al.* Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 2001; **12**: 2117.
8. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; **106**: 2085.
9. Cosio FG, Kudva Y, van der Velde M, *et al.* New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 2005; **67**: 2415.
10. Davidson J, Wilkinson A, Dantal J, *et al.* New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003; **75**(Suppl. 10): SS3.
11. Van Bortel LM, Duprez D, Starmans-Kool MJ, *et al.* Clinical applications of arterial stiffness, Task Force III:

recommendations for user procedures. *Am J Hypertens* 2002; **15**: 445.
12. Nurnberger J, Opazo Saez A, Dammer S, *et al.* Left ventricular ejection time: a potential determinant of pulse wave velocity in young, healthy males. *J Hypertens* 2003; **21**: 2125.
13. Nurnberger J, Dammer S, Opazo Saez A, Philipp T, Schafers RF. Diastolic blood pressure is an important determinant of augmentation index and pulse wave velocity in young, healthy males. *J Hum Hypertens* 2003; **17**: 153.
14. Nurnberger J, Keflioglu-Scheiber A, Opazo Saez AM, Wenzel RR, Philipp T, Schafers RF. Augmentation index is associated with cardiovascular risk. *J Hypertens* 2002; **20**: 2407.
15. Joss N, Staatz CE, Thomson AH, Jardine AG. Predictors of new onset diabetes after renal transplantation. *Clin Transplant* 2007; **21**: 136.
16. Kameyama H, Takeda K, Kusaba T, *et al.* Augmentation of pulse wave velocity precedes vascular structural changes of the aorta in rats treated with N(omega)-nitro-L-arginine methyl ester. *Hypertens Res* 2005; **28**: 439.
17. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005; **46**: 1753.
18. Zoungas S, Kerr PG, Chadban S, *et al.* Arterial function after successful renal transplantation. *Kidney Int* 2004; **65**: 1882.
19. Sakurai M, Yamakado T, Kurachi H, *et al.* The relationship between aortic augmentation index and pulse wave velocity: an invasive study. *J Hypertens* 2007; **25**: 391.
20. Turk T, Pietruck F, Dolff S, *et al.* Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant* 2006; **6**: 842.