TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Renal resistive index as a new independent risk factor for new-onset diabetes mellitus after kidney transplantation

Prisca Mutinelli-Szymanski,[1] Agnès Caille,[2] François Tranquart,[3,4] Azmi Al-Najjar,[1] Matthias Büchler,[1,5] Christelle Barbet,[1] Jean-Frédéric Marlière,[1] Philippe Gatault,[1] Julie Réault,[6] Christopher Boin,[6] Valérie Chatelet,[1] Inass Laouad,[1] Hubert Nivet,[1,5] Yvon Lebranchu[1,5] and Jean-Michel Halimi[1,5]

1 Service de Néphrologie-Immunologie Clinique, Hôpital Bretonneau, CHRU Tours, Tours, France
2 INSERM CIC 202, France and Université François Rabelais Tours, France and CHRU de Tours, Tours, France
3 Service d'Imagerie Médicale, Hôpital Bretonneau, CHU Tours, Tours, France
4 Bracco Suisse SA, Research Centre, Switzerland
5 Université François Rabelais Tours, Tours, France
6 Pharmacy Department, Hôpital Bretonneau, CHRU Tours, Tours, France

Keywords
aortic stiffness, diabetes mellitus, pulse pressure, renal transplantation, resistance index, vascular disease.

Correspondence
Jean-Michel Halimi MD, PhD, Service de Néphrologie-Immunologie Clinique, Hôpital Bretonneau, 2, Bd Tonnellé 37044 Tours Cedex, France.
Tel.: (33) 2 47 47 37 46;
fax: (33) 2 47 47 38 02;
e-mail: halimi@med.univ-tours.fr

Conflicts of Interest
The authors have declared no conflicts of interest.

Received: 20 November 2011
Revision requested: 15 January 2012
Accepted: 23 January 2012
Published online: 24 February 2012

doi:10.1111/j.1432-2277.2012.01445.x

Summary

Pulse pressure and urinary albumin excretion were recently identified as risk factors of new-onset diabetes after renal transplantation (NODAT), suggesting that microvascular injury may be implicated in NODAT. However, the relationship between of microvascular injury and NODAT is unknown. In the present long-term (median follow-up: 5.7 years; observation period: 4908 patient-years) retrospective study in 656 renal transplant recipients, the association between baseline renal resistance index (RI, used as a marker of widespread microvascular damage) and the incidence of NODAT was assessed. The incidence of NODAT was 11.2% and 14.6% at 5 and 10 years, respectively, after transplantation. RI at 3 months was a risk factor for NODAT [hazard ratio (HR) per 0.1: 2.19 (1.55–3.09), $P < 0.0001$]. RI >0.75 (vs. $0 \leq 0.75$) was a potent a predictor of NODAT [HR: 3.29 (1.91–5.67), $P < 0.0001$], even after adjustments [HR: 3.29 (1.50–7.24), $P = 0.0030$] on age, weight, glucose, nephropathy, and arterial pressure. Similar results were observed when RI was measured at 1 month [HR per 0.1:1.74 (1.33–2.27), $P < 0.0001$] and 12 months [HR per 0.1:1.74 (1.33–2.27), $P < 0.0001$] after transplantation. High RI early after renal transplantation is a long-term risk factor for NODAT, and could be used to refine the individual risk of NODAT.

Introduction

New-onset diabetes after transplantation (NODAT) is a serious complication after organ transplantation. It contributes to the risk of cardiovascular disease and infection, thus reducing graft and patient survival [1–3]. Risk factors include recipient age, obesity, sirolimus and tacrolimus, steroids, beta-blocker use, low-grade proteinuria, urinary albumin excretion (UAE), and elevated arterial pressure [1–5].

In a previous report, we demonstrated that high pulse pressure (PP) is an independent risk factor of NODAT in kidney transplant recipients [4]. High PP represents a marker of aortic stiffness [6] and was associated with further renal dysfunction because of microvascular kidney damage [6]. Aortic stiffness could also impair pancreas microcirculation and thus insulin secretion, explaining, at least partly, the greater risk of NODAT with high PP in renal transplant recipients [4]. Interestingly, both pancreas and kidneys (unlike the heart) are perfused throughout systole and diastole by pulsatile flow [6]. Pancreas microcirculation is not routinely measured in humans; however, the microcirculation of the renal

allograft can be estimated with the intrarenal resistive index (RI) measured in segmental arteries of transplanted kidneys by color Doppler sonography [7,8]. Altered intrarenal Doppler indices of the grafts are associated with PP in kidney transplant recipients [9–11], which may indicate that high PP is associated with microvascular dysfunction in renal transplantation. In the present study, we used elevated RI as a marker of widespread microvascular damage, and assessed whether early intrarenal RI value after transplantation could predict the long-term risk of NODAT in a large cohort of renal transplant recipients.

Patients and methods

Selection of the population

Overall, 1309 patients received a renal transplant between October 1985 and March 2009 in our center. In the present retrospective study, we excluded 653 patients because of known diabetes mellitus before transplantation ($n = 123$), no RI evaluation at the 3-month visit ($n = 368$), graft loss or death ($n = 57$) or new-onset diabetes ($n = 48$) within the first 3 months after transplantation, recipient age ≤16 years ($n = 56$), or no diabetes status at the date of transplantation ($n = 1$). Finally, 656 patients were included. Initial immunosuppression included methylprednisolone, 250 mg, pre- and postoperatively; anti-interleukin 2 receptor antibodies (Basiliximab, Simulect®; Novartis, Rueil-Malmaison, France) at days 0 and 4; or antithymocyte antibodies (Thymoglobuline®; Genzyme, Lyon, France) usually for 5 days [12]. Maintenance immunosuppressive treatment included prednisone with a gradual tapering and mycophenolate mofetyl or azathioprine associated with cyclosporine, tacrolimus or sirolimus in most patients. Target trough levels at 3 months were 150–250 ng/ml for cyclosporine and 8–12 ng/ml for tacrolimus and sirolimus [13]. Steroids were withdrawn in half of the patients (most in the first year after transplantation). Visits in our ward were organized as followed: three visits per week during the first 2 weeks; two visits per week until day 60; weekly visits until day 120; monthly visits during the first year; one visit every other month during the second year; and three visits per year thereafter until death or end-stage renal disease (ESRD) (i.e., dialysis or retransplantation).

Clinical and biochemical measurements

At the time of transplantation, the following variables were recorded: for the donor, we recorded type of donor (living or deceased), age, gender, and cause of death, and for the recipient, graft rank, age, gender, panel reactive antibodies, cytomegalovirus (CMV) status, hepatitis C virus status, cause of renal failure and immunosuppressive induction treatment. At the 3-month visit after transplantation, the following variables were recorded: systolic, diastolic and pulse arterial pressure; acute rejection episodes; body mass index (BMI); biochemical parameters including fasting glucose, serum cholesterol and triglycerides; serum creatinine level (measured by the Jaffe method); estimated creatinine clearance (by the Cockcroft formula) [14]; proteinuria (by a 24-h urine collection, measured by the pyrogallol method [15]; and antihypertensive and immunosuppressive medications.

Resistive index measurement

Graft volume measured with length, width and depth, and peak systolic and end-diastolic velocities and RI measured in renal segmental arteries were evaluated by Doppler ultrasonography [7]. The RI was calculated with the peak systolic velocity (S) and the end-diastolic velocity (D) and the percentage reduction of the end-diastolic flow as compared with the systolic flow $(((S - D)/S) \times 100)$. The mean of three consecutive RI measurements was used. Three ultrasound systems were Toshiba Aplio 55A-770A, Esaote Technos MPX or Siemens Antares Premium Edition [7]. RI was measured at 1, 3, and 12 months after transplantation. Most Doppler measurements were performed by the same operator (FT). Renal artery stenosis was ruled out in all of our patients at the time of measurement [16] (Doppler sonogram is performed in our patients very early during follow-up [7], and we previously reported that the incidence of renal artery stenosis in around 6% in our center [16]).

In our analysis, high resistive index was defined as a RI >0.75, in accordance with the literature (usual reported cut-off values are 0.75 [17] and 0.80 [8]); to strengthen our results, the 0.80 cut-off value was also used.

Definition of NODAT

NODAT was defined according to the American Diabetes Association (ADA) [18]: symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mM, casual being defined as any time of day without regard to time since last meal; or fasting glucose ≥7 mmol/l, fasting being defined as no caloric intake for at least 8 h (oral glucose tolerance tests were not usually performed in our center, because they are not recommended as routine practice) [4,13]. These criteria were confirmed by repeat testing on a different day.

Statistical analyses

Results are expressed as percentages, mean ± standard deviation or median [interquartile range (IQR)]. Cox

proportional-hazards analysis was used in univariate and multivariate analyses to assess the association of several explanatory parameters and the risk of NODAT during follow-up. The results are expressed as hazard ratio (HR), 95% confidence intervals (95% CI) and *P* values. We explored the relation between RI measured at the 3 month visit and subsequent incidence of NODAT. To strengthen our results, we performed sensitivity analyses with RI measured at 1 month and 12 months after transplantation. Pearson and partial correlation coefficients were used to explore parameters potentially linked with RI. Patients were censored at their date of death, graft loss or date of last visit. Several models were used in the multivariate analyses; adjustments on age, BMI, and plasma fasting glucose were systematically used. No stepwise or other ad hoc procedures were used. Analyses involved use of SAS v9.1 (SAS Inst., Cary, NC, USA). A $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Donor and recipient characteristics at the time of transplantation and the 3-month visit are in Table 1. Recipients' mean age was 45.9 ± 13.3, and most of the patients were male (61.9%). The transplantation was the first for 86.3% of patients. The first cause of renal failure was glomerulonephritis (32.3%). At the 3-month visit, mean arterial pressure was 137 ± 16/81 ± 10 mmHg and PP was 57 ± 14 mmHg; mean RI was 0.67 ± 0.07 (median 0.67). Of note, the beta-blocker most frequently used in our center was atenolol. RI was greater than 0.75 in 12.8% of patients.

Conventional risk factors of NODAT

The median duration of follow-up was 5.7 years (range: 0.3–21.4 years), and the total observation period was 4908 patient-years. The incidence of NODAT was 7.7% (95% CI 6.1–9.3%) at 12 months, 11.2% (9.2–13.2%) at 5 years and 14.6% (12.0–17.1%) at 10 years after transplantation. Potent risk factors of NODAT were recipient age [HR per 1 year: 1.04 (95% CI 1.02–1.06), $P < 0.0001$], BMI at 3 months [HR per 1 kg/m^2: 1.15 (1.08–1.21), $P < 0.0001$], and fasting glucose at 3 months [HR per 1 mmol/l: 1.95 (1.65–2.31), $P < 0.0001$] (Table 2).

Other factors associated with risk of NODAT were nephrosclerosis as the cause of initial nephropathy [HR: 3.52 (1.74–7.12), $P = 0.001$], triglycerides level [HR: 1.43 (1.12–1.83), $P = 0.004$] and use of beta-blockers [HR: 1.93 (1.18–3.14), $P = 0.009$] but not creatinine level [HR per 1 μmol/l: 1.00 (0.99–1.01), $P = 0.326$] or estimated creatinine clearance at 3 months [HR per 1 ml/min/1.73 m^2: 0.99 (0.98–1.01), $P = 0.383$]. Among the immunosuppressive treatments at 3 months, tacrolimus [HR: 1.92 (1.07–3.45), $P = 0.028$] and cyclosporine [HR: 0.47 (0.27–0.83), $P = 0.0091$] were significantly associated with NODAT {sirolimus use did not reach statistical significance [HR: 2.47 (0.77–7.95), $P = 0.131$]}. The following

Table 1. Baseline characteristics of patients undergoing kidney transplantation and their donors.

Donor characteristics (n = 656)	
Living donor (%)	1.7
Age (years)	42.9 ± 15.8
Male sex (%)	64.6
At transplantation	
Recipient clinical characteristics	
Second/third (%)	12.5/1.2
Gender (% male)	61.9
Age (years)	45.9 ± 13.3
Panel reactive antibodies >75% (%)	6.4
Cytomegalovirus infection (%)	50.3
Hepatitis C virus infection (%)	6.6
Cause of renal failure	
Glomerulonephritis (%)	32.3
Autosomal-dominant polycystic kidney disease (%)	17.4
Uropathy (%)	6.0
Nephrosclerosis (%)	5.3
Unknown nephropathy (%)	31.5
Immunosuppressive drugs	
Anti-interleukin 2 receptor (%)	27.0
Antithymocyte antibody	71.8
3-month visit	
Clinical characteristics	
Body mass index (kg/m^2)	23.9 ± 3.9
Systolic/diastolic arterial pressure (mmHg)	137 ± 16/81 ± 10
Pulse pressure (mmHg)	57 ± 14
Acute rejection (%)	23.6
Biochemical parameters	
Glucose (mmol/l)	5.3 ± 0.9
Total cholesterol level (mmol/l)	5.7 ± 1.4
Triglycerides level (mmol/l)	1.9 ± 1.0
Creatinine level (**Li**mol/l)	133 ± 43
Estimated creatinine clearance (ml/min)	58.4 ± 18.2
Proteinuria (g/24 h) [median, (interquartile range)]	0.15 [0.00-0.34]
Medications	
Steroids (%)	96.0
Cyclosporine/tacrolimus (%)	71.5/25.2
Mycophenolate mofetyl/azathioprine (%)	64.2/31.9
Sirolimus (%)	3.1
ACEI/ARB (%)	6.6/2.6
Beta-blockers/diuretics (%)	50.0/9.4
Calcium-channel blockers (%)	53.8
Resistive index (at 3 months)	0.67 ± 0.07
Resistive index >0.75 (%)	12.8

Data are mean ± SD unless indicated.
ADPKD, autosomal dominant polycystic kidney disease; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

Table 2. Risk factors for new-onset diabetes mellitus after kidney transplantation: univariate analysis.

Recipient characteristics	Hazard ratio	95% CI	*P* value
At transplantation			
Clinical parameters			
Cytomegalovirus infection (yes versus no)	1.50	0.92–2.43	0.1045
Hepatitis C virus infection (yes versus no)	0.25	0.03–1.85	0.1739
Polycystic kidney disease (yes versus no)	1.44	0.81–2.56	0.2114
Renal vascular disease (yes versus no)	3.52	1.74–7.12	0.0005
Age (per 1 year)	1.04	1.02–1.06	<0.0001
3-month visit			
Clinical parameters			
Systolic arterial pressure (per 10 mmHg)	1.25	1.08–1.44	0.0018
Diastolic arterial pressure (per 10 mmHg)	1.10	0.86–1.41	0.4300
Pulse pressure (per 10 mmHg)	1.27	1.08–1.48	0.0025
Pulse pressure >60 mmHg (yes versus no)	1.97	1.21–3.21	0.0064
Acute rejection (yes versus no)	0.77	0.42–1.41	0.3966
Body mass index (per 1 kg/m^2)	1.15	1.08–1.21	<0.0001
Glucose (per 1 mmol/l)	1.95	1.65–2.31	<0.0001
Cholesterol level (mmol/l)	1.06	0.85–1.31	0.6209
Triglycerides level (mmol/l)	1.43	1.12–1.83	0.0038
Creatinine level (per 1 umol/l)	1.00	0.99–1.01	0.3261
Estimated creatinine clearance (ml/min)	0.99	0.98–1.01	0.3831
Medications			
Steroids (yes versus no)	1.01	0.36–2.81	0.9810
Beta-blockers (yes versus no)	1.93	1.18–3.14	0.0090
Cyclosporine (yes versus no)	0.47	0.27–0.83	0.0091
Tacrolimus (yes versus no)	1.92	1.07–3.45	0.0282
Sirolimus (yes versus no)	2.47	0.77–7.95	0.1309

CI, confidence interval.

were not risk factors for NODAT: hepatitis C virus [HR: 0.25 (0.03–1.85), $P = 0.174$] and CMV infection [HR: 1.50 (0.92–2.43), $P = 0.105$] (only 6.6% had hepatitis C virus in our cohort).

Hemodynamic factors associated with risk of NODAT at 3 months were PP [HR per 10 mmHg: 1.27 (1.08–1.48), $P = 0.003$] and systolic arterial pressure [HR per 10 mmHg: 1.25 (1.08–1.44), $P = 0.002$].

RI as an independent risk factor of NODAT

Determinants of RI

Univariate analysis revealed PP, systolic arterial pressure, recipient age and BMI correlated with RI at the 3-month visit (Table 3). PP but not systolic arterial pressure was significantly correlated with RI after adjustment for age and BMI (Table 3). Of note, donor age also correlated with RI measured at 3 months [r = +0.38 (0.31–0.44) $P < 0.0001$ (Table 3)]. However, the interpretation of this finding is questionable since donor age and recipient age are usually matched in our center.

Table 3. Pearson and partial correlation analyses of parameters associated with resistive index.

	RI	
	Correlation coefficient *r* (95% CI)	*P* value
Pearson correlation		
Pulse pressure (mmHg) (at 3 months)	+0.33 (0.26–0.40)	<0.0001
Systolic arterial pressure (mmHg) (at 3 months)	+0.15 (0.08–0.23)	<0.0001
Body mass index (BMI) (kg/m2) (at 3 months)	+0.20 (0.13–0.28)	<0.0001
Recipient age (years) (at the time of transplantation)	+0.56 (0.51–0.61)	<0.0001
*Partial correlation**		
Pulse pressure (mmHg) (at 3 months)	+0.17 (0.10–0.25)	<0.0001
Systolic arterial pressure (mmHg) (at 3 months)	+0.01 (–0.07–0.09)	0.7985

*Adjusted for body mass index and age.
CI, confidence interval; RI, resistive index.

High RI as a risk factor of NODAT

Resistive index (as a continuous variable) at the 3-month visit was associated with increased risk of NODAT [HR per 0.1: 2.19 (1.55–3.09), $P < 0.0001$] (Table 4). RI remained significant even after multiple adjustments [HR per 0.1: 1.61 (1.06–2.44), $P = 0.026$] (Table 4).

High RI was a potent a predictor of NODAT [HR for >0.75 vs. 0 ≤ 0.75: 3.29 (1.91–5.67), $P < 0.0001$], even after multiple adjustments [for age, body mass index, glucose, initial nephropathy and systolic arterial pressure: HR: 3.29 (1.50–7.24), $P = 0.0030$] (Table 4). Many models including other covariables were used: resistive index remained a significant predictor of NODAT. Of note, resistive index remained a risk factor of NODAT after adjustment on tacrolimus use [HR: 2.09 (1.47–2.96), $P < 0.0001$] and systolic arterial pressure [HR: 2.01 (1.41–2.84), $P < 0001$].

Patients with the highest RI (>0.80) had the greatest risk of NODAT [HR for >0.80 vs. 0 ≤ 0.80: 5.54 (2.81–10.92), $P < 0.0001$].

To strengthen our results, we performed sensitivity analyses using RI measured at 1 month and 12 months after transplantation: RI measured at 1 month [HR per 0.1: 1.74 (1.33–2.27), $P < 0.0001$] and at 12 months [HR

Table 4. High resistive index as a risk factor of new-onset diabetes mellitus after kidney transplantation.

	Hazard ratio per 0.1 (resistive index used as a continuous variable)	95% CI	*P* value	Hazard ratio (>0.75 vs. ≤0.75)	95% CI	*P* value
Univariate analysis						
Resistive index (RI)	2.19	1.55–3.09	<0.0001	3.29	1.91–5.67	<0.0001
Multivariate analysis						
Model 1	1.61	1.06–2.44	0.0264	2.06	1.06–3.98	0.0328
Model 2	1.56	1.03–2.36	0.0372	1.99	1.03–3.87	0.0419
Model 3	1.56	1.03–2.36	0.0359	1.93	0.98–3.80	0.0578
Model 4	2.16	1.27–3.67	0.0045	3.29	1.50–7.24	0.0030
Sensitivity analysis						
RI at 1-month visit	1.74	1.33–2.27	0.0001	2.31	1.40–3.84	0.0012
RI at 12-month visit	1.63	1.11–2.41	0.0139	1.19	0.47–3.00	0.7189

95% CI=95% confidence interval.
Resistive index was measured at 3 months following transplantation.
Model 1: Adjustment for age, BMI, fasting glucose.
Model 2: Model 1 + pulse pressure.
Model 3: Model 1 + nephrosclerosis (as the cause of initial nephropathy) + systolic arterial pressure.
Model 4: Model 1 + triglycerides.

per 0.1: 1.63 (1.11–2.41), $P = 0.014$] was significantly associated with NODAT; results were qualitatively unchanged when RI was used a binary variable (although the relationship was less strong at 12 months) (Table 4).

To determine whether microvascular damage (assessed by RI) could mediate the effect of aortic stiffness on NODAT, we evaluated the risk of NODAT associated with PP after adjustment for RI: PP was no longer associated with NODAT after adjustment for RI [HR per 10 mmHg: 1.00 (0.96–1.14), $P = 0.1328$].

Discussion

Pulse pressure, a marker of aortic stiffness, is an independent risk factor of NODAT, but the exact link between pulse pressure and NODAT is unknown [3]. We used elevated RI as a marker of widespread microvascular damage, and we assessed whether early intrarenal RI measurement could predict the long-term risk of NODAT in a large cohort of renal transplant recipients. At 3 months after transplantation, RI was a long-term risk factor of NODAT in our cohort (4908 patient-years of observation). Moreover, high RI (>0.75) was a potent a predictor of NODAT, even after multiple adjustments. PP was correlated with RI and was a risk factor of NODAT on univariate analysis but not after adjustment for RI. Sensitivity analyses revealed RI a predictor of NODAT even at 1 month and 12 months after transplantation. Therefore, high RI early after transplantation can be considered as a long-term risk factor for NODAT, and could be used to refine the individual risk of NODAT in renal transplantation. Aortic stiffness leading to microvascular injury within the pancreas circulation (leading to impaired insulin secretion) may be one of the mechanisms of NODAT.

Renal RI was previously linked to renal and patient survival in renal transplantation [8]; however, the relation between RI and NODAT was not assessed [8]. To our knowledge, the relationship between renal RI and the incidence of diabetes mellitus has not been reported. In previous studies, RI was shown to be associated with systemic atherosclerosis in kidney transplant recipients [9–11]. High RI was found mostly in patients with older age and increased carotid intima-media thickness [19]. In another study, RI was associated with age and PP but not renal function [11]. In nontransplanted patients, renal RI was associated with central PP [20]. Interestingly, hypertension was found to be a risk factor of diabetes mellitus in the general population [21]. This association suggests a link between vascular damage and the onset of diabetes [22]. Ultrastructural alterations of vascular pancreatic islets with loss of endothelial cell homeostasis have been suggested to play a key role in the pathogenesis of beta-cell dysfunction [23]. Moreover, endothelial dysfunction precedes the onset of hyperglycemia and has been proposed to contribute to the development of type 2 diabetes mellitus [24]. The relation between RI and the incidence of diabetes may be because of increased central pressure associated with aortic stiffness leading to pancreatic microvascular damage (but pancreatic microvascular damage was not assessed in the present study). Other mechanisms may be discussed. First, high RI may a marker of insulin resistance: recently, renal RI was found higher in type 1 diabetic children than in controls and even higher in children with insulin

resistance [25]. This relationship was also observed in patients with newly diagnosed type 2 diabetes mellitus [26]. Thus, high RI as a marker of insulin resistance could explain the relation with risk of NODAT but is unlikely: we found RI correlated with BMI but still a significant risk factor of NODAT after adjustment for triglycerides level and BMI (excellent markers of insulin resistance). Second, the relation between RI and NODAT could be mediated by inflammation [27]. In effect, high RI was more frequently found in nontransplanted patients with elevated UAE than in those with normal excretion of urinary albumin [28]. Moreover, two recent studies from our group confirmed that elevated UAE or microalbuminuria was a risk factor for diabetes in renal transplant recipients [4] and in subjects from the general population [29]. In this latter report, UAE was correlated with C-reactive protein (CRP) level [29]. This hypothesis is also supported by the positive significant correlation found between CRP level and RI in untreated hypertensive patients [30]; of note, RI was also correlated with PP and UAE in this study [29]. Unfortunately, we did not collect CRP values for our patients.

Our study has several limitations. It is a retrospective study, and our findings need to be confirmed in large long-term prospective studies. However, our analysis is based on a close follow-up of our cohort, and the total duration of observation (4908 patient-years of observation) is greater than that for most epidemiological studies of renal transplantation. The 5- and 10-year incidences of NODAT were 11.2% and 14.6%, respectively. In the literature, the short-term incidence of NODAT was highly variable (2–50% at 1 year) depending on the diagnostic criteria [1]; however, the long-term incidence of NODAT is less clear because studies with long-term follow-up are scarce. The incidence of NODAT being lower in our study than in other studies [1,30] probably reflects our strict diagnostic criteria: NODAT was defined according to the ADA [18], these criteria were systematically confirmed by repeat testing on a different day, and patients with transient elevation of fasting glucose were not classified as having NODAT. Some parameters such as waist circumference were not available for our patients, but BMI was used as a surrogate, as was done in other studies [31]. In the present study, the association between steroid use and NODAT did not reach the significant threshold; however, we did find an association with steroids in a previous paper when all patients from our center were included in the analysis [4].

Finally, elevated RI was used as a marker of widespread microvascular damage as a result of arterial stiffness. The use of this marker is supported by recent findings of increased arterial stiffness (measured by brachial–ankle pulse wave velocity) strongly correlated with cerebrovascular resistance (measured in the anterior cerebral blood flow) in nontransplanted patients [32] (because pancreas, kidneys, and brain – unlike the heart – are perfused throughout systole and diastole by pulsatile flow [6]). Pancreas function or vascularisation was not assessed, so that the association between RI and pancreas microvascularisation is putative. High resistive index values in renal transplant recipients should prompt frequent glucose monitoring and correction of other modifiable risk factors for NODAT; however, it is presently unknown whether correcting risk factors for NODAT could be associated with a decrease in resistive index. The association of elevated RI (or high PP) and further development of diabetes should now be assessed in other cohorts of renal transplant recipients and in the general population.

In conclusion, our findings indicate that renal RI is an independent predictor of new-onset diabetes in kidney transplant patients. High RI be used to refine the individual risk of NODAT early after renal transplantation: from a practical point of view, patients with high RI early after transplantation should be considered at high risk of NODAT: in such patients, early therapeutic changes (adequate use of CNI or sirolimus, steroid withdrawal, diuretics and beta-blockers avoidance, body weight reduction…) can be discussed in order to reduce the risk of NODAT.

Authorship

PM-S: wrote the paper, collected data. AC: performed statistical analyses. FT: performed Doppler studies. AA, MB, CB, J-FM, PG, JR, CB, VC, IL: collected data. HN: analyzed data. YL: analyzed data, wrote the paper; J-MH: designed the study, analyzed data and wrote the paper.

Funding

The authors have declared no funding.

Acknowledgements

None.

References

1. Davidson J, Wilkinson A, Dantal J, *et al.* New-onset diabetes after transplantation: 2003 international consensus guidelines. *Transplantation* 2003; **75**(suppl 10): S3.
2. Sulanc E, Lane J, Puumala S, Groggel G, Wrenshall L, Stevens RB. New-onset diabetes after kidney transplantation: An Application of 2003 International Guidelines. *Transplantation* 2005; **80**: 945.
3. Montori V, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Post-transplantation diabetes, a systematic review of the literature. *Diabetes Care* 2002; **25**: 583.

4. Roland M, Gatault P, Al Najjar A, *et al.* Early pulse pressure and low grade proteinuria as independent long-term risk factors for new-onset diabetes mellitus after kidney transplantation. *Am J Transplant* 2008; **8**: 1.
5. Marin M, Renoult E, Bondor CI, Kessler M. Factors influencing the onset of diabetes mellitus after kidney transplantation: a single French center experience. *Transplant Proc* 2005; **37**: 1851.
6. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney. *Hypertension* 2005; **46**: 200.
7. Ba S, Halimi JM, Al-Najjar A, *et al.* Prognostic value of absent end-diastolic flow within the first week following transplantation. *Transplant Proc* 2009; **41**: 645.
8. Radermacher J, Mengel M, Ellis S, *et al.* The renal arterial resistance index and renal allograft survival. *N Engl J Med* 2003; **349**: 115.
9. Bude RO, Rubin JM. Relationship between the resistive index and vascular compliance and resistance. *Radiology* 1999; **211**: 411.
10. Schwenger V, Keller T, Hofmann N, *et al.* Color Doppler indices of renal allografts depend on vascular stiffness of the transplant recipients. *Am J Transplant* 2006; **6**: 2721.
11. Krumme B, Grotz W, Kirste G, Schollmeyer P, Rump LC. Determinants of intrarenal Doppler indices in stable renal allografts. *J Am Soc Nephrol* 1997; **8**: 813.
12. Halimi JM, Buchler M, Al-Najjar A, *et al.* Respective predictive role of urinary albumin excretion and nonalbumin proteinuria on graft loss and death in renal transplant recipients. *Am J Transplant* 2007; **7**: 2775.
13. Roland M, Gatault P, Doute C, *et al.* Immunosuppressive medications, clinical and metabolic parameters in new-onset diabetes after kidney transplantation. *Transplant Int* 2008; **21**: 523.
14. Cockcroft DM, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31.
15. Halimi JM, Laouad I, Buchler M, *et al.* Early low-grade proteinuria: causes, short-term evolution and long-term consequences in renal transplantation. *Am J Transplant* 2005; **5**: 2281.
16. Halimi JM, Al-Najjar A, Buchler M, *et al.* Transplant renal artery stenosis: potential role of ischemia/reperfusion injury and long-term outcome following angioplasty. *J Urol* 1999; **161**: 28.
17. Kirkpantur A, Yilmaz R, Baydar DE, *et al.* Utility of the Doppler ultrasound parameter, resistive index, in renal transplant histopathology. *Transplant Proc* 2008; **40**: 104.
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; **27**: S5.
19. Heine GH, Gerhart MK, Ulrich C, Köhler H, Girndt M. Renal Doppler resistance indices are associated with systemic atherosclerosis in kidney transplant recipients. *Kidney Int* 2005; **68**: 878.
20. Raff E, Schwarz TK, Schmidt BM, Schneider MP, Schmieder RE. Renal resistive index – a valid tool to assess renal endothelial function in humans. *Nephrol Dial Transplant* 2010; **25**: 1869.
21. Gress T, Nieto J, Shahar E, Wofford M, Brancati F. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342**: 905.
22. Safar ME. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. *Curr Opin Nephrol Hypertens* 2001; **10**: 257.
23. Olsson R, Carlsson PO. The pancreatic islet endothelial cell: emerging roles in islet function and disease. *Int J Biochem Cell Biol* 2006; **38**: 492.
24. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk factor of type 2 diabetes mellitus. *JAMA* 2004; **291**: 1978.
25. Ghaffar AE, El Kaffas K, Mostafa M. Renal Doppler indices in diabetic children with insulin resistance syndrome. *Pediatr Diabetes* 2010; **11**: 479.
26. Afsar B, Elsurer R, Sezer S, Ozdemir FN. Insulin resistance is associated with increased renal resistive index independent of other factors in newly diagnosed type 2 diabetes mellitus and hypertensive patients. *Metabolism* 2010; **59**: 279.
27. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE. Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. *Diabetes Care* 2005; **28**: 2525.
28. Hamano K, Nitta A, Ohtake T, Kobayashi S. Associations of renal vascular resistance with albuminuria and macroangiopathy in type 2 diabetic patients. *Diabetes Care* 2008; **31**: 1853.
29. Halimi JM, Bonnet F, Lange C, Balkau B, Tichet J, Marre M. Urinary albumin excretion is a risk factor for diabetes mellitus in men, independently of initial metabolic profile and development of insulin resistance. *J Hypertens* 2008; **26**: 2198.
30. Ozelsancak R, Torun D, Koc Z, Sezer S, Ozdemir FN, Niron EA. Relationship between renal resistive index and inflammation in untreated hypertensive patients. *Int Heart J* 2009; **50**: 753.
31. Bayer ND, Cochetti PT, Kumar MSA, *et al.* Association of metabolic syndrome with development of new-onset diabetes after transplantation. *Transplantation* 2010; **90**: 861.
32. Robertson AD, Tessmer CF, Hughson RL. Association between arterial stiffness and cerebrovascular resistance in the elderly. *J Hum Hypertension* 2010; **24**: 190.