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Clinical diagnosis of metabolic syndrome: predicting new-onset diabetes, coronary heart disease, and allograft failure late after kidney transplant

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Summary

Metabolic syndrome is associated with coronary heart disease (CHD) and new-onset diabetes after kidney transplant (NODAT). Using data collected from transplant centers worldwide for the Patient Outcomes in Renal Transplantation study, we examined associations of metabolic syndrome ($n = 2253$ excluding recipients with diabetes pretransplant), CHD ($n = 2253$), and NODAT ($n = 1840$ further excluding recipients with diabetes in the first year post-transplant), with the primary outcome of allograft failure. We assessed risk factors associated with secondary outcomes of metabolic syndrome, NODAT, and CHD after adjusting for type of baseline immunosuppression and transplant center effects. Metabolic syndrome prevalence was 39.8% at 12–24 months post-transplant and 35.4% at 36–48 months. Metabolic syndrome was independently associated with NODAT (hazard ratio 3.46, 95% confidence interval 2.40–4.98, $P < 0.0001$), CHD (2.03, 1.16–3.52, $P = 0.013$), and allograft failure (1.36, 1.03–1.79, $P = 0.028$). Allograft failure occurred in 218 patients (14.6%). After adjustment for metabolic syndrome, NODAT (1.63, 1.18–2.24, $P = 0.003$) and CHD (5.48, 3.27–9.20, $P < 0.0001$) remained strongly associated with increased risk of allograft failure. Metabolic syndrome, NODAT, and CHD are risk factors for allograft failure. NODAT and CHD are risk factors for allograft failure, independent of metabolic syndrome.

Introduction

In the general, non-transplant population, metabolic syndrome has been recognized as an important risk factor for type 2 diabetes and cardiovascular disease [1–3]. Guidelines for treating individuals with metabolic syndrome recommend weight loss, increased physical activity, and reduced intake of foods with saturated fats, trans fats, and cholesterol. In addition to lifestyle modification, guidelines recommend management of metabolic factors such as dyslipidemia, elevated blood pressure, elevated glucose, and prothrombotic state. For high-risk patients, low dose aspirin is recommended [2,3].

As in the general population, metabolic syndrome has also been associated with increased risk of cardiovascular disease and new-onset diabetes mellitus after kidney transplant (NODAT; Table 1) [4–13]. Cardiovascular disease is a major cause of morbidity and mortality after kidney transplant [14–16], and NODAT is a risk factor for cardiovascular disease events and death [17–20]. Immunosuppressive medications such as steroids, calcineurin inhibitors, and mTOR inhibitors can produce risk factors common to metabolic syndrome, NODAT, and coronary heart disease (CHD) [7,21–23].

However, the relative risk of allograft failure for transplant recipients with metabolic syndrome, compared with

risk for NODAT and CHD, is not known. Such information can further clinicians' understanding of the risks of allograft failure. There are no specific guidelines for managing metabolic syndrome in transplant recipients, but there are guidelines for managing its individual risk factors [24].

In this study, we used a subset of data collected from transplant centers around the world as part of the Patient Outcomes in Renal Transplantation (PORT) study [4]. We compared the association of metabolic syndrome with NODAT, CHD, and allograft failure. We also examined the association of NODAT with allograft failure, after adjusting for presence of metabolic syndrome.

Materials and methods

Study population

The data source was the PORT study, an observational data collaboration from 14 transplant centers worldwide, with recipients who underwent kidney transplant from 1990 to 2007 [4]. We used a subset of 2253 nondiabetic recipients, who underwent transplants in 1996 to 2006,

Table 1. Incidence of metabolic syndrome in published studies and association with outcomes.

Study	*n*	Time post-transplant	Incidence, percent	Metabolic syndrome associated with outcomes
De Vries 2004 [26]	606*	Median 6 years	63	Only blood pressure and triglycerides associated with renal dysfunction
Rogers 2005 [12]	241†	Pretransplant	59	Metabolic syndrome and non-functioning pancreas allograft associated with renal dysfunction
		1 year	19	
Ducloux 2005 [11]	292	1 year	32	Not associated with graft loss‡
Porrini 2006 [10]	230	1.5 years	38	Increased risk of NODAT, renal function, allograft loss, patient death
Courivaud 2007 [9]	337	1 year	32	Associated with atherosclerotic events
Faenza 2007 [8]	298	1 year	17	Associated with increased risk of CVD¶
Adeseun 2008 [6]	112§	<0.5 years	55	MS and components not associated with CAC
Wilson 2009 [28]	234**	At transplant	19	Associated with increased risk of LVH
		1 year	37	
Rike 2007 [7]	397	2 years	38	Associated with increased risk of CVD††
Kishikawa, 2009 [4]	94	Mean 3.9 years	15	N/A
Bellinghieri 2009 [5]	182	6 years	Men 20, Women 30	N/A
Ozdemir 2009 [29]	112	Mean 5.8 years	11% pretransplant 29% at 1 year	Associated with increased risk of allograft loss
Soveri 2009 [39]	1706	7–8 years	32%	Associated with increased risk of MACE‡‡ and cardiac death
Bayer 2010 [40]	640¶¶	At transplant	57% at transplant	Associated increased risk of NODAT
Luan 2010 [30]	203§§	Median 10.3 weeks	48%	N/A
Luan 2010 [27]	591***	Median 4 years	53%	Associated with increased risk of NODAT and renal dysfunction

CAC, coronary artery calcification; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; N/A, not available; MACE, major adverse cardiac events; NODAT, new-onset diabetes after transplant.

*Cross-sectional study of the Netherlands kidney transplant recipients.

†Included only simultaneous kidney-pancreas transplants in a prospective, multicenter trial of daclizumab.

‡French study showed that metabolic syndrome had no association with graft loss after adjusting for creatinine clearance, urinary protein excretion, C-reactive protein, post-transplant change in body mass index, delayed graft function, cytomegalovirus disease, and acute rejection. Association present in unadjusted analysis.

¶Retrospective Italian study in which cardiovascular disease was not explicitly defined.

§Cross-sectional study of kidney transplant patients with no prior history of coronary artery revascularization or myocardial infarction.

**Pediatric transplants only.

††Defined as sudden death, myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack. Two groups studied, one with steroid withdrawal and the other receiving long-term corticosteroid therapy.

‡‡In this ALERT study dataset, major adverse cardiac events defined as cardiac death, nonfatal myocardial infarction, or coronary revascularization procedure.

¶¶Included only nondiabetic patients from 3 academic centers.

§§Included only nondiabetic patients.

***Included only nondiabetic patients.

from five North American and two European centers that routinely collected information on risk factors that define metabolic syndrome. Quality control measures to ensure data validity have been described previously [4]. Metabolic syndrome and its defining risk factors were described during the following post-transplant intervals: 6–12, 12–24, 24–36, 36–48, and 48–60 months. Eligibility criteria for inclusion in each interval were: (i) alive with a functioning kidney allograft at the end of the interval, (ii) no evidence of diabetes at time of transplant, and (iii) data present for at least four of five risk factors that define metabolic syndrome during the interval.

Defining exposure and outcomes

Metabolic syndrome was defined based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III definition. Patients were defined as having metabolic syndrome if at least three of the following five risk factors were present during the interval: (i) body mass index (BMI) ≥30 kg/m^2, (ii) triglycerides ≥150 mg/dl, (iii) high-density lipoprotein (HDL) cholesterol <40 mg/dl in men or <50 mg/dl in women, (iv) fasting glucose ≥100 mg/dl or diagnosis of diabetes, and (v) blood pressure ≥130/85 mmHg or use of anti-hypertensive medications. To describe incidence of NODAT during post-transplant years 1 through 5 by metabolic syndrome group, we additionally limited the analysis to 1840 patients with no evidence of NODAT in the first post-transplant year and with data on hypoglycemic medication use.

The date for development of NODAT after the first year post-transplant was defined for patients with no evidence of diabetes in the first post-transplant year as the earliest of: (i) initiation of hypoglycemic medications or (ii) any glucose measurement >200 mg/dl. CHD was defined as fatal and nonfatal acute myocardial infarction, coronary revascularization, and sudden cardiac death. Coronary revascularization included angioplasty, coronary stenting, and coronary artery bypass grafting. Estimated glomerular filtration rate (eGFR) [25] at 12 months post-transplant was calculated according to the Modification of Diet in Renal Disease Study equation. Allograft failure was defined as return to dialysis, retransplant, or death.

Analysis

We identified independent predictors of metabolic syndrome using multivariate logistic regression. We examined the univariate association between metabolic syndrome and demographic, clinical, and transplant characteristics known at baseline and immediately post-transplant. Covariates univariately associated with metabolic syndrome were considered in the multivariate logistic model. A backward selection process was used to retain covariates in the final multivariate model. Age was modeled as a second-degree polynomial. Type of calcineurin inhibitor (CNI) agent was forced to remain in the final model. Incidence of NODAT and CHD after the first year post-transplant was estimated using separate Kaplan-Meier models. Separate multivariate Cox proportional hazards models were developed to determine whether or not metabolic syndrome was independently associated with subsequent NODAT, CHD, and allograft failure. Another Cox proportional hazards model was used to assess the association of NODAT and CHD with subsequent allograft failure, after adjusting for metabolic syndrome 6–12 months post-transplant. NODAT and CHD were included as time-varying covariates. Type of CNI agent was forced to remain in each of the final models.

All analyses were performed using SAS v9.1.3 (SAS, Cary, NC, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

Metabolic syndrome after kidney transplant

The baseline characteristics of kidney transplant patients at risk for metabolic syndrome are shown in Table 2. Prevalence of metabolic syndrome ranged from 39.8% at 12–24 months post-transplant to 35.4% at 36–48 months ($P > 0.05$ by McNemar test) (Fig. 1). Prevalence of risk factors that define metabolic syndrome varied little across time. The most common were elevated blood pressure, triglycerides, glucose, and BMI, in order of decreasing prevalence. The least common was low HDL cholesterol (Fig. 1). Given the transient physiologic changes seen with the high doses of steroids prescribed postoperatively, we focused on metabolic syndrome at 6–12 months post-transplant. Independent baseline predictors of metabolic syndrome at 6–12 months post-transplant, after adjustment for transplant center, were recipient age, baseline BMI, history of coronary revascularization, and absence of pretransplant dialysis (Table 3).

New onset diabetes after transplant

To examine the effects of metabolic syndrome on NODAT, incidence of metabolic syndrome was calculated during the first year post-transplant, and incidence of NODAT was calculated after the first year post-transplant. Cumulative incidence of NODAT by 60 months post-transplant was 13%. Metabolic syndrome in the 6–12 month interval was associated with an increased risk of NODAT (Fig. 2). NODAT incidence by 60 months post-transplant was 23% in kidney transplant recipients with metabolic syndrome occurring 6–12 months post-transplant, compared with

Table 2. Baseline characteristics of all patients (n = 2253) and of patients eligible for analysis of new-onset diabetes after transplant (n = 1840).

	All		Eligible for NODAT analysis	
Characteristics	*n*	Percent	*n*	Percent
Age, years				
18–34	421	18.7	365	19.8
35–49	802	35.6	680	37.0
50–64	771	34.2	608	33.0
≥65	259	11.5	187	10.2
Gender				
Men	1337	59.3	1088	59.1
Women	916	40.7	752	40.9
Race				
White	1926	85.5	1609	87.4
Black	144	6.4	115	6.3
Asian	92	4.1	58	3.2
Other	30	1.3	15	0.8
Unknown	61	2.7	43	2.3
Region				
North America	1523	67.6	1265	68.8
Europe	730	32.4	575	31.3
Body mass index, kg/m^2				
<30	1707	75.8	1418	77.1
≥30	432	19.2	330	17.9
Unknown	114	5.1	92	5
Cause of end-stage kidney disease				
Hypertension	254	11.3	192	10.4
Glomerular disease	815	36.2	669	36.4
Cystic disease	401	17.8	345	18.8
Other	752	33.4	607	33.0
Unknown	31	1.4	27	1.5
HLA mismatches				
0	262	11.6	233	12.7
1–3	914	40.6	759	41.3
4–6	658	29.2	544	29.6
Unknown	419	18.6	304	16.5
Recipient hepatitis C positive	73	3.2	54	2.9
Panel reactive antibodies				
<10	1836	81.5	1567	85.2
≥10	213	9.5	175	9.5
Unknown	204	9.1	98	5.3
History of acute myocardial infarction	56	2.5	43	2.3
History of congestive heart failure	40	1.8	33	1.8
History of revascularization	69	3.1	60	3.3
History of stroke	95	4.2	71	3.9
History of peripheral arterial disease	36	1.6	28	1.5
History of cancer	123	5.5	104	5.7
Pretransplant dialysis time, years				
None	310	13.8	262	14.2
≤1	851	37.8	724	39.3
>1 to <2	298	13.2	228	12.4
2 to <3	205	9.1	163	8.9
≥3	418	18.6	312	17
Unknown	171	7.6	151	8.2
Transplant number				
First	1936	85.9	1580	85.9
Subsequent	317	14.1	260	14.1
Donor age, years				
<18	128	5.7	108	5.9
18–34	371	16.5	320	17.4
35–49	480	21.3	402	21.8
50–64	407	18.1	319	17.3
≥65	79	3.5	60	3.3
Unknown	788	35.0	631	34.3
Donor gender				
Men	1017	45.1	853	46.4
Women	824	36.6	686	37.3
Unknown	412	18.3	301	16.4
Donor race				
White	1309	58.1	1111	60.4
Black	38	1.7	26	1.4
Other/unknown	906	40.2	703	38.2
Donor hepatitis C positive	10	0.4	8	0.4
Donor type				
Living	799	35.5	657	35.7
Deceased	1454	64.5	1183	64.3
Recipient/donor cytomegalovirus status				
R-/D-	389	17.3	344	18.7
R+/D-	399	17.7	326	17.7
R+/D+	455	20.2	368	20.0
R-/D+	268	11.9	227	12.3
Either unknown	742	32.9	575	31.3
Cold ischemia time, h				
0 to <12	920	40.8	762	41.4
12 to <24	668	29.6	535	29.1
≥24	159	7.1	124	6.7
Unknown	506	22.5	419	22.8
Delayed graft function	263	11.7	203	11.0
Transplant era				
1995–1999	324	14.4	291	15.8
2000–2006	1929	85.6	1549	84.2
Azathioprine	20	0.9	17	0.9
Mycophenolate mofetil	1496	66.4	1219	66.3
mTor inhibitor	283	12.6	241	13.1
Steroid	2140	95.0	1754	95.3
Calcineurin inhibitor agent				
Cyclosporine	1146	50.9	971	52.8
Tacrolimus	725	32.2	539	29.3
None reported	382	17.0	330	17.9

NODAT, new onset diabetes after transplant.

7% in recipients without metabolic syndrome. In an adjusted analysis, metabolic syndrome occurring 6–12 months post-transplant was associated with an increased

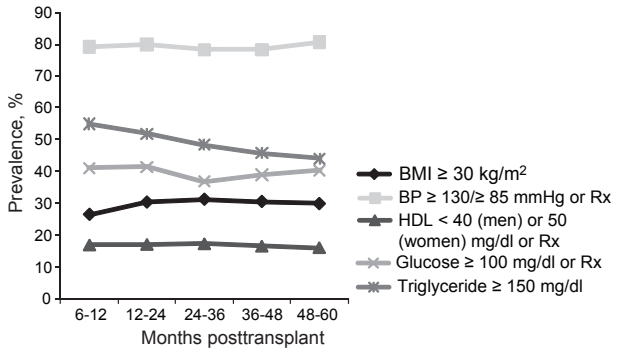

Figure 1 Prevalence of risk factors that define metabolic syndrome across time. BMI, Body mass index; BP, blood pressure; HDL, high-density lipoprotein cholesterol.

risk of subsequent NODAT [adjusted hazard ratio (HR) for NODAT 3.46, 95% confidence interval (CI) 2.40–4.98, $P < 0.0001$).

Risk factors independently associated with NODAT were recipient age, recipient race, eGFR, and baseline BMI (Table 3).

Coronary heart disease

Between 12 and 60 months post-transplant, 56 recipients experienced CHD events, including 25 nonfatal acute myocardial infarctions, 28 coronary revascularizations, and 3 fatal acute myocardial infarctions and sudden deaths. Metabolic syndrome in the 6–12 month post-transplant interval was associated with increased risk of subsequent CHD (Fig. 3). Cumulative incidence of CHD events by 60 months post-transplant was 5.9% in transplant recipients with metabolic syndrome occurring 6–12 months post-transplant, compared with 2.3% in recipients without metabolic syndrome ($P = 0.001$). In an adjusted analysis, metabolic syndrome occurring 6–12 months post-transplant was associated with increased risk of subsequent CHD events (HR 2.03, 95% CI 1.16–3.52, $P = 0.013$).

Risk factors independently associated with CHD were metabolic syndrome 6–12 months post-transplant, CHD in the first year post-transplant, recipient age, gender, race, pretransplant history of coronary revascularization, pretransplant history of stroke or cerebrovascular accident, and non-use of mycophenolate mofetil at 12 months post-transplant (Table 3).

Association with allograft failure

By 60 months post-transplant, allograft failure occurred in 218 patients (14.6%); 166 (11.3%) returned to dialysis or underwent retransplant and 52 (3.8%) died with function. In an unadjusted analysis, metabolic syndrome 6–12

Table 3. Independent baseline predictors of metabolic syndrome 6–12 months post-transplant and new-onset diabetes and coronary heart disease after 12 months post-transplant*.

Metabolic syndrome			New onset diabetes after transplant			Coronary heart disease		
Factors	OR (95% CI)	*P*	Factors	HR (95% CI)	*P*	Factors	HR (95% CI)	*P*
Dialysis duration, years			6–12 m MS	3.46 (2.40–4.98)	<0.0001	6–12 m MS	2.03 (1.16–3.52)	0.013
≥3	1.05 (0.74–1.49)	0.781	Age (per 10 years)	1.33 (1.16–1.52)	<0.0001	0–12 m CHD	4.03 (1.72–9.46)	
2–<3	1.27 (0.85–1.91)	0.246	eGFR (per 10)	1.10 (1.00–1.22)	0.049	Age (per 10 years)	1.56 (1.23-1.98)	0.001
1–<2	1.09 (0.77–1.55)	0.618	Black (versus white)	2.12 (1.23–3.65)	0.01	Female	0.52 (0.28–0.97)	
<1	1		BMI ≥ 30 kg/m^2	1.69 (1.19–2.40)	0.00	Black (versus white)	3.11 (1.43–6.79)	0.0002
No dialysis	0.57 (0.42–0.78)	0.0004				Pretransplant CVA	2.93 (1.23–7.00)	
						Pretransplant revascularization	4.21 (1.99–8.92)	0.041
Pretransplant revascularization	2.01 (1.16–3.47)	0.013				12 m MMF	0.50 (0.28–0.88)	0.004
BMI ≥30 kg/m^2	7.67 (5.94–9.89)	<0.0001						0.016
Age squared (age in years/10)	0.94 (0.9–0.99)	0.017						0.0002
Age in years/10	1.85 (1.18–2.89)	0.008						0.017

BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); HR, hazard ratio; MMF, mycophenolate mofetil; MS, metabolic syndrome; OR, odds ratio.
*Additionally adjusted for type of calcineurin inhibitor agent used at baseline and transplant center.

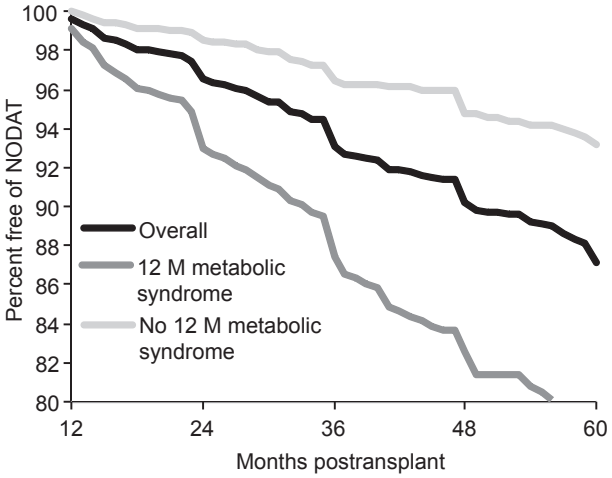

Figure 2 Kaplan Meier curve showing the increased risk of new-onset diabetes after transplant in kidney transplant recipients with metabolic syndrome. Unadjusted hazard ratio for new-onset diabetes after the first year post-transplant, 3.80 (95% CI, 2.73–5.29, $P < 0.001$). NODAT, new-onset diabetes after kidney transplant.

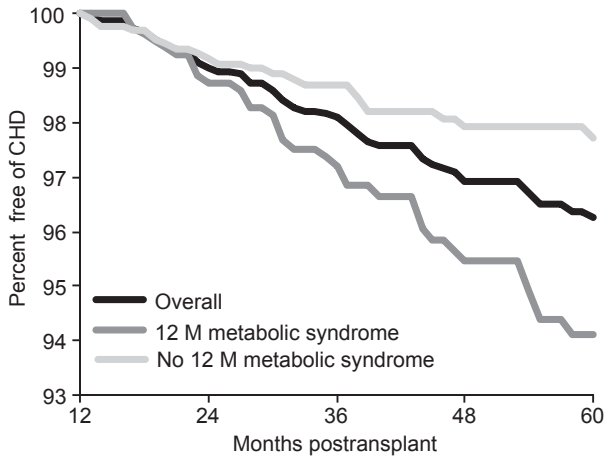

Figure 3 Kaplan Meier curve showing the increased risk of coronary heart disease in kidney transplant recipients with metabolic syndrome. Unadjusted hazard ratio for coronary heart disease after the first year post-transplant, 2.35 (95% CI, 1.37–4.02, $P < 0.0018$). CHD, coronary heart disease.

months post-transplant was associated with an increased risk of graft failure within 60 months post-transplant (HR 1.64 95% CI 1.26–2.14, $P = 0.0003$; Fig. 4). This association of metabolic syndrome with subsequent allograft failure persisted in the multivariate model (Table 4), and in an analysis in which graft failure was limited to death with a functioning allograft (HR 2.55, 95% CI 1.40–4.66, $P < 0.002$). Metabolic syndrome was not associated with death-censored graft failure (HR 1.10, 95% CI 0.81–1.51, $P = 0.54$). In this model, other factors independently associated with allograft failure were eGFR at 12 months post-transplant, recipient race, primary cause of end-stage kidney disease, panel reactive antibodies at time of transplant, number of HLA mismatches, pretransplant history of revascularization, absence of pretransplant dialysis, and delayed graft function. After adjustment for metabolic syndrome in a multivariate model, both NODAT and CHD were associated with an increased risk of graft failure (NODAT HR 1.63, 95% CI 1.18–2.24, $P = 0.003$; CHD HR 5.48, 95% CI 3.27–9.20, $P < 0.0001$; Table 5). In this analysis, younger age was associated with higher risk of graft failure. This is consistent with the higher risk of death-censored graft failure observed among younger recipients (data not shown). When graft failure was limited to death with a functioning graft, this association was appropriately reversed (data not shown).

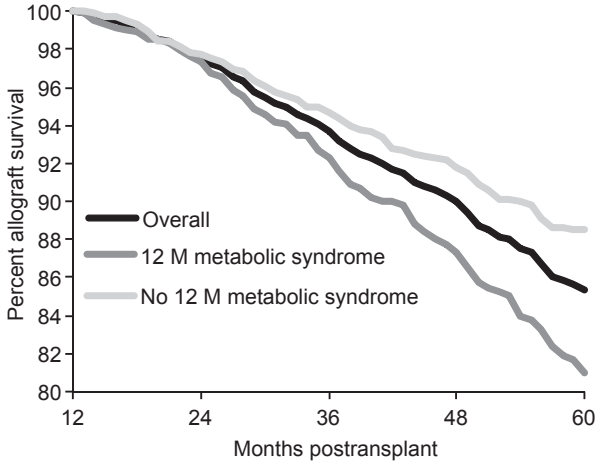

Figure 4 Kaplan–Meier curve showing the increased risk of allograft failure in kidney transplant recipients with metabolic syndrome. Unadjusted hazard ratio for allograft failure after the first year post-transplant, 1.64 (95% CI, 1.26–2.14, $P < 0.0003$).

Discussion

This study notes several important findings: (i) Prevalence of metabolic syndrome varied little across time after 6 months post-transplant; (ii) metabolic syndrome was independently associated with subsequent NODAT, CHD, and allograft failure; (iii) NODAT and CHD were associated with allograft failure, independent of metabolic syndrome in a multivariate model.

Incidence of metabolic syndrome varies based on the kidney transplant population being studied [12,26,27]. We found that frequency of metabolic syndrome was similar to frequency described by previous studies [7,10,28]. One would anticipate that levels of steroids, CNIs, and other agents would be lower with longer time after the peri-operative period. This could translate to a better

Table 4. Association of metabolic syndrome with allograft failure 12–60 months post-transplant, adjusted for transplant center*.

Factor	HR (95% CI)	*P*
Metabolic syndrome (versus no)	1.36 (1.03–1.79)	0.028
CNI at 12 months post-transplant		
Cyclosporine	1.00	Ref
Tacrolimus	1.17 (0.82–1.66)	0.397
Both	0.91 (0.39–2.11)	0.825
None	1.03 (0.61–1.74)	0.907
Age in years/10, continuous	0.91 (0.81–1.02)	0.109
eGFR/10, continuous	0.73 (0.66–0.81)	<0.0001
Race		
White	1.00	Ref
Black	1.24 (0.78–1.96)	0.360
Other/unknown	0.37 (0.15–0.93)	0.034
Cause of end-stage kidney disease		
Hypertension	1.80 (1.20–2.70)	0.005
Glomerular disease	1.00	Ref
Cystic disease	0.76 (0.48–1.19)	0.231
Other/unknown	1.09 (0.78–1.51)	0.626
HLA mismatches		
0	0.81 (0.47–1.37)	0.428
1–3	1.00	Ref
4–6	1.48 (1.06–2.06)	0.021
PRA at transplant		
<10%	1.00	Ref
≥10%	1.75 (1.22–2.49)	0.002
Unknown	1.30 (0.65–2.60)	0.459
Pretransplant history of revascularization (versus no)	2.62 (1.51–4.55)	0.001
Pretransplant dialysis, years		
None	0.39 (0.22–0.70)	0.001
≤1	1.00	Ref
1 to <2	0.94 (0.53–1.64)	0.813
2 to <3	1.03 (0.52–2.05)	0.934
≥3	1.61 (0.94–2.74)	0.082
Delayed graft function (versus no)	1.58 (1.11–2.24)	0.011

CI, confidence interval; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PRA, panel reactive antibodies.

*Metabolic syndrome determined at 6–12 months post-transplant.

Table 5. Association of new onset diabetes and coronary heart disease with allograft failure 12–60 months post-transplant*.

Factor	HR (95% CI)	*P*
New onset diabetes (versus no)	1.63 (1.18–2.24)	0.003
Coronary heart disease (versus no)	5.48 (3.27–9.20)	<0.0001
CNI at 12 months post-transplant		
Cyclosporine	1.00	Ref
Tacrolimus	1.14 (0.80–1.63)	0.470
Both	1.02 (0.44–2.37)	0.969
None	1.09 (0.64–1.84)	0.759
Age in years/10, continuous	0.86 (0.77–0.97)	0.011
eGFR/10, continuous	0.72 (0.65–0.80)	<0.0001
Race		
White	1.00	Ref
Black	1.09 (0.69–1.72)	0.725
Other/unknown	0.37 (0.15–0.92)	0.032
Cause of end-stage kidney disease		
Hypertension	1.70 (1.13–2.56)	0.011
Glomerular disease	1.00	Ref
Cystic disease	0.76 (0.48–1.20)	0.242
Other/unknown	1.03 (0.74–1.44)	0.849
HLA mismatches		
0	0.86 (0.51–1.48)	0.593
1–3	1.00	Ref
4–6	1.51 (1.08–2.10)	0.015
Hepatitis C (versus no)	1.78 (0.99–3.18)	0.053
PRA		
<10%	1.00	Ref
≥10%	1.64 (1.15–2.35)	0.007
Unknown	1.35 (0.68–2.70)	0.392
Pretransplant history of revascularization (versus no)	2.15 (1.22–3.82)	0.009
Pretransplant dialysis, years		
None	0.38 (0.21–0.67)	0.001
≤1 year	1.00	Ref
1 to <2	0.87 (0.49–1.52)	0.615
2 to <3	1.03 (0.51–2.05)	0.938
≥3	1.47 (0.86–2.53)	0.158
Delayed graft function (versus no)	1.56 (1.10–2.23)	0.013
Metabolic syndrome (versus no)	1.17 (0.88–1.57)	0.280

CI, confidence interval; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PRA, panel reactive antibodies.

*Adjusted by transplant center; new onset diabetes and coronary heart disease included as time-varying covariates.

metabolic risk profile due to the role of these medications in inducing risk factors that are part of metabolic syndrome. However, the present analysis shows that risk of metabolic syndrome remains relatively stable after the first 6 months post-transplant.

Previous studies have shown that metabolic syndrome is associated with allograft dysfunction [10,12,26,29,30]. In one previous study, the association of metabolic syndrome with allograft failure was not present after adjustment for other clinical risk factors [11]. The present study showed that metabolic syndrome was associated with all-cause graft failure and with death with a functioning graft. This suggests that metabolic syndrome leads to decreased allograft failure due to increased risk of death. Previous studies have not evaluated the association of NODAT and CHD with allograft failure, after adjusting for metabolic syndrome. Therefore, our analysis is the first to show the relatively higher risk of allograft failure with NODAT and CHD, even after adjusting for metabolic syndrome (Table 3). This would suggest that NODAT and CHD are associated with allograft failure independent of mechanisms that lead to metabolic syndrome. Other studies have also shown an association of

NODAT [17–20] and CHD [31–33] with allograft failure and patient death. Some baseline risk factors associated with metabolic syndrome, NODAT, and CHD overlapped in the present analysis (Table 3). For example, increasing recipient age was associated with increased risk of all 3 outcomes. Recipient race (black versus white) was associated with increased risk of both NODAT and CHD. Pretransplant revascularization was a risk factor for both metabolic syndrome and CHD. BMI higher than 30 kg/m^2 at the time of transplant, a modifiable risk factor, was a risk factor for both metabolic syndrome and NODAT. Other potentially modifiable risk factors were pretransplant time on dialysis (a risk factor for metabolic syndrome), eGFR (a risk factor for NODAT), and CHD in the first year post-transplant (a risk factor for CHD after the first year post-transplant) (Table 3). Interventional trial data related to modifying risk factors of CHD are quite limited in the end-stage kidney disease and kidney transplant populations. Therefore, aggressive treatment of these risk factors for metabolic syndrome, NODAT, and CHD in these populations is based on extrapolation from the general non-transplant population [34].

This study is limited in several important ways. First, it was retrospective and therefore subject to the limitations associated with a retrospective, observational study approach. Second, our definition of metabolic syndrome required use of a modified NCEP ATP III definition. Because the present study did not collect waist circumference data, obesity was defined for men and women as BMI higher than 30 kg/m^2. Hypertriglyceridemia was defined based on laboratory values, and not on medication data, because data on medications that exclusively treat hypertriglyceridemia were limited. Statin use did not necessarily indicate treatment for hypertriglyceridemia. In the analysis of NODAT, we excluded patients with pre-existing diagnoses of overt diabetes in the first post-transplant year. However, some patients may have had subclinical diabetes, and these patients were not excluded. In the analysis of CHD, we did not collect information on mycophenolate mofetil and CNI blood levels. If non-use of mycophenolate mofetil was associated with higher levels of CNIs, this may help explain the association of non-use of mycophenolate mofetil with higher risk of CHD.

In summary, this study demonstrates the association of metabolic syndrome with increased risk of NODAT, CHD, and allograft failure. Prevalence of metabolic syndrome is relatively stable after the first 6 months post-transplant. Future clinical trials are needed to study the impact of interventions that reduce the risk of CHD, NODAT, and also metabolic syndrome. Such trials could study the impact of steroid avoidance [35], CNI withdrawal [36], switching from CNIs to mTOR inhibitors [37], and higher doses of mycophenolate mofetil along with lower levels of CNIs, on modifying the risks of CHD, NODAT, and metabolic syndrome. Trials studying new agents that increase HDL cholesterol could test whether or not these agents modify the risks of CHD and metabolic syndrome [38]. Successful interventions may lead to reduced risk of allograft failure.

Authorship

AKI: research design, data analysis, preparation of manuscript. JJS: research design, data analysis, preparation of manuscript. MAS: data analysis, preparation of manuscript. BK: research design, preparation of manuscript. All authors approved the manuscript for submission.

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