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Metabolic Syndrome in Thai Renal Transplant Recipients: A Multicenter Study

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Background: Many renal transplant recipients develop complications such as obesity, posttransplantation diabetes mellitus, and dyslipidemia. There have been few studies of metabolic syndrome (MS) in Asian renal transplant recipients.

Material/Methods: This cross-sectional study was performed in 303 patients in 5 transplant centers in Bangkok, Thailand. The diagnosis of MS was based on the criteria of the modified NCEP-ATPIII, and chronic allograft dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

Results: Of 303 recipients, MS was diagnosed in 94 cases (31.0%) and the prevalence of MS in the first 3 years and after 3 years posttransplantation were 21.4% and 34.7% (P=0.042), respectively. There was an association between advanced age and chronic allograft dysfunction and higher prevalence of MS. Regarding non-anti-hypertensive and non-hypoglycemic medications, m-TOR inhibitor (odds ratio [OR], 2.14; 95% CI, 1.02–4.5) was associated with the prevalence of MS. Multivariate analysis revealed MS was associated with the use of beta-blockers (OR, 3.17; 95% CI, 1.88–5.32). Patients with no MS components had 26.9% prevalence of chronic allograft dysfunction and patients with higher numbers of MS components had 87.5% prevalence of chronic allograft dysfunction, which was significantly different (P=0.022).

Conclusions: Our study revealed that the prevalence of MS was higher in patients with higher numbers of MS components, especially after 3 years posttransplantation. Presence of more components of MS was associated with worse renal function in renal transplant recipients.

MeSH Keywords: Allografts • Diabetes Mellitus • Glomerular Filtration Rate • Metabolic Syndrome • Obesity

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Background

Renal transplantation (RT) is one of the renal replacement therapy modes for end-stage renal disease. The most common cause of late graft loss is recipient death with a functioning allograft, mainly due to cardiovascular diseases [1]. Metabolic syndrome (MS) is characterized by a constellation of abdominal obesity, high blood pressure (BP), high fasting plasma glucose (FPG), high triglyceride, and low high-density lipoprotein (HDL) cholesterol. MS increases the risk for development of cardiovascular and chronic kidney disease (CKD) [2–5]. In addition, the prevalence of MS is quite common after RT in Western countries [6].

Previous studies of renal transplant recipients (RTRs) have shown that MS is associated with renal disease and albuminuria. The data on these metabolic complications are limited in Asian populations. The association between the MS and the risk of chronic allograft dysfunction has not been studied in Thai RTRs who have a low prevalence of obesity. The objectives of this study were to determine the prevalence of MS in Thai RTRs and to study whether there was an association between MS and risk of chronic allograft dysfunction in Thai RTRs who were patients at several transplant centers in Bangkok, Thailand.

Material and Methods

A cross-sectional study was performed at the renal transplant clinics between January and September 2013 in 5 kidney transplant centers in Bangkok, Thailand. This study was approved by the institutional review board of each transplant center. Written informed consent for participation in the study was obtained from all patients. The study was conducted in accordance with the ethics standards of the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008. The recipient charts were reviewed for age, sex, time after renal transplantation, and clinical and laboratory data.

Treatment data were collected, including immunosuppressive regimens, hypoglycemic agents, and anti-hypertensive medications. The number of anti-hypertensive medications used in each RTR was recorded. BP was measured twice by using an automated, validated device, in the arm of seated participants. Each BP variable was the average of 2 readings. At each examination, weight, height, and waist circumference were measured. The value of body mass index (BMI) was determined using the weight in kilograms divided by the square of the height in meters.

Fasting blood samples were collected in the morning and sent for testing of FPG, blood urea nitrogen (BUN) level, and serum creatinine (SCr), as well as total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and serum uric acid. All values were measured by standardized methods. Renal function or estimated glomerular filtration rate (eGFR) was calculated by using the CKD-EPI equation [7]. Chronic allograft dysfunction was defined as estimated GFR (eGFR) <60 mL/min/1.73 m^2, irrespective of proteinuria.

The diagnosis of MS was based on the modified Asian criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) [8]. MS was diagnosed based on the presence of any 3 of the following 5 metabolic risk factors: abdominal obesity, high BP, high FPG, high triglyceride, and low HDL cholesterol. In the modified Asian criteria, the waist circumference cutoff points to identify abdominal obesity were >90 cm in men and >80 cm in women.

Statistical analysis

The significance of baseline differences was estimated between subjects with and without MS with the use of independent-sample *t*-tests for continuous variables and chi-square tests for categorical variables. Multivariate logistic regression was performed to correct for confounders. These variables were sex, age, systolic BP (SBP), diastolic BP (DBP), FPG, triglyceride, total cholesterol, oral hypoglycemic agents or insulin, m-TOR inhibitors, renin-angiotensin-aldosterone system (RAS) inhibitor, beta-blocker, alpha-blocker, and anti-hypertensive medication numbers. The prevalence of chronic allograft dysfunction was determined in RTR (with and without MS) by the number of metabolic syndrome components present. All analyses were performed with the use of Windows statistical software (STATA version 11). The data are expressed as means ± standard deviation (SD). *P* value of less than 0.05 was considered to be significant.

Results

Of 303 recipients studied, 179 (59.1%) were male. Their mean age was 46.22±10.92 years. Mean SBP was 125.52±14.97 mmHg, mean DBP was 73.77±9.46 mmHg, mean SCr level was 1.48±0.77 mg/dL, eGFR by CKD-EPI formulae was 60.23±21.75 mL/min/1.73 m^2 after a median follow-up time of 68 months (IQR 34-120).

MS by NCEP ATP III (modified Asian) criteria was diagnosed in 94 RTRs (31.0%). Of these, 52 patients (55.3%) were male. The prevalence of MS in the first 3 years was 21.4% and increased to 34.7% after 3 years posttransplantation (P=0.042). There were 60 patients (63.8%) who met the criteria to have MS with 3 components, 26 patients (27.7%) had 4 components, and 8 patients (8.5%) had 5 components of MS. The most prevalent

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Table 1. Demographic data of renal transplant recipients.

Variables	Total (N=303)	MS (n=94)	Non MS (n=209)	RR (95%CI)	p-value[a]
Age (yrs); Mean ±SD	46.22±10.92	48.31±12.25	45.27±10.16	1.03 (1, 1.05)	0.026*
Male	179 (59.1%)	52 (55.3%)	127 (60.8%)	0.8 (0.49, 1.31)	0.373
Pretransplantation DM	16 (5.3%)	13 (13.8%)	3 (1.4%)	11.02 (3.06, 39.69)	<0.001**
PTDM	31 (10.8%)	20 (24.4%)	11 (5.3%)	5.72 (2.6, 12.59)	<0.001**
Time from transplantation to the last visit					
≤12 mo	32 (10.6%)	8 (8.5%)	24 (11.5%)	Ref	1.000
13–36 mo	52 (17.2%)	10 (10.6%)	42 (20.1%)	0.71 (0.25, 2.05)	0.532
>36 mo	219 (72.3%)	76 (80.9%)	143 (68.4%)	1.59 (0.68, 3.72)	0.280
Mean ±SD.	80.96±60.24	81.17±58.09	80.87±61.32	1 (1, 1)	0.968
Median (Q1, Q3)	68 (34,120)	66 (40,108)	68 (26,123)	–	0.738
BMI (kg/m^2)	23.63±4.32	26.28±4.23	22.44±3.81	1.27 (1.18, 1.37)	<0.001**
SBP (mmHg)	125.52±14.97	129.5±16.53	123.73±13.89	1.03 (1.01, 1.04)	0.002**
DBP (mmHg)	73.77±9.46	74.03±10.41	73.65±9.03	1 (0.98, 1.03)	0.750
MAP (mmHg)	91.02±9.73	92.52±10.52	90.35±9.29	1.02 (1, 1.05)	0.073
Central obesity (Asia); M>90, F>80 cm	104 (34.3%)	64 (68.1%)	40 (19.1%)	9.01 (5.18, 15.68)	<0.001**
Hypertriglyceridemia; ≥150 mg/dL or drug use	82 (27.1%)	62 (66%)	20 (9.6%)	18.31 (9.77, 34.31)	<0.001**
Low HDL-C; M<40, F<50 mg/dL	49 (16.2%)	7 (7.4%)	42 (20.1%)	3.13 (1.37, 7.09)	0.001
High blood pressure; BP ≥130/85 mmHg or drug use	263 (86.8%)	93 (98.9%)	170 (81.3%)	21.34 (2.88, 157.8)	0.003**
FPG; ≥100 mg/dL or drug use	89 (29.4%)	63 (67%)	26 (12.4%)	14.3 (7.89, 25.93)	<0.001**
HbA1C (%)	5.5±1.94	6.11±2.03	5.22±1.83	1.36 (1.1, 1.7)	0.005**
HDL-C (mg/dL)	60.36±18.1	50.97±17.03	64.54±16.99	0.95 (0.93, 0.97)	<0.001**
LDL-C (mg/dL)	104.86±33.75	108.93±44.68	103.21±28.14	1 (1, 1.01)	0.197
Triglyceride (mg/dL)	126.1±64.85	176.33±73.38	103.75±45.54	1.02 (1.02, 1.03)	<0.001**
BUN (mg/dL)	20.29±10.83	24.39±14.81	18.45±7.8	1.06 (1.03, 1.09)	<0.001**
Creatinine (mg/dL)	1.48±0.77	1.63±0.92	1.41±0.69	1.43 (1.04, 1.96)	0.029*
GFR: CKD EPI (mL/min/1.7 3m^2)	60.23±21.75	52.58±18.9	63.67±22.1	0.98 (0.96, 0.99)	<0.001**
GFR <60 mL/min/1.73 m^2	150 (49.5%)	57 (60.6%)	93 (44.5%)	1.92 (1.17, 3.15)	0.010*

Values presented as mean ±SD. or n (%).* P<0.05; ** P<0.01. DM – diabetes mellitus; PTDM – posttransplantation diabetes mellitus; SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; HDL-C – high-density lipoprotein cholesterol; HbA_1C – hemoglobin A_1C; LDL-C – low-density lipoprotein cholesterol; BUN – blood urea nitrogen; GFR – glomerular filtration rate; CKD-EPI – Chronic Kidney Disease-Epidemiology Collaboration. [a] Analysis of variance tests for continuous factors and Pearson chi-square tests for categorical factors.

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component of MS was elevated BP (86.8%), followed by central obesity (34.3%), impaired FPG (29.4%), and hypertriglyceridemia (27.1%). The least prevalent component of the MS was low HDL cholesterol (16.2%). In addition, significantly advanced age and chronic allograft dysfunction were detected in the MS patients (Table 1).

Compared to the 209 patients without MS, MS patients had lower eGFR (52.58±18.9 *vs.* 63.67±22.1 mL/min/1.73 m^2; P<0.001, Table 1). In further analysis, the prevalence of chronic allograft dysfunction was calculated in RTR with 3, 4, and 5 components of MS compared to in RTR with 0, 1, and 2 components of MS. There was a significant association between the number of metabolic components and the prevalence of chronic allograft dysfunction in the RTRs, as shown in Figure 1.

Regarding current non-anti-hypertensive and non-hypoglycemic medications in the RTRs, m-TOR inhibitor was significantly associated with the prevalence of MS (Table 2). Multivariate analysis demonstrated that beta-blocker was independently associated with MS. Of note, steroid use was lower among MS patients because 1 center used a prednisolone withdrawal protocol for the diabetic patients.

Posttransplantation diabetes mellitus (PTDM) was diagnosed in 31 RTRs (10.8%) after the exclusion of 16 patients who had pre-transplant diabetes [9]. The prevalence of PTDM in the first 3 years and after 3 years posttransplantation were 12.7% and 10.1% (P=0.528), respectively.

Finally, the association between each of the components of MS and chronic allograft dysfunction in the RTRs was also examined (Table 3). High triglyceride, high BP, and low HDL cholesterol were independently associated with chronic allograft dysfunction in the RTRs.

Discussion

In this study, the prevalence of MS in the first 3 years was 21.4% and increased to 34.7% after 3 years posttransplantation (P=0.042), which is consistent with the study of Porrini et al., who found the prevalence of MS was dynamic and increased with time – 22.6% at 12 months, 37.7% at 36 months, and 64% at 6 years after transplantation [10]. In contrast, Israni et al. demonstrated the relatively stable risk of MS after 6 months posttransplant [11]. Their patients had the high prevalence of MS 39.8% at 12–24 months posttransplantation and 35.4% at 36–48 months. The prevalence of MS in this study was similar to the Arab RTRs (28.6%) but, in contrast, MS was more common in females than males in the study of Elkehili et al. [12].

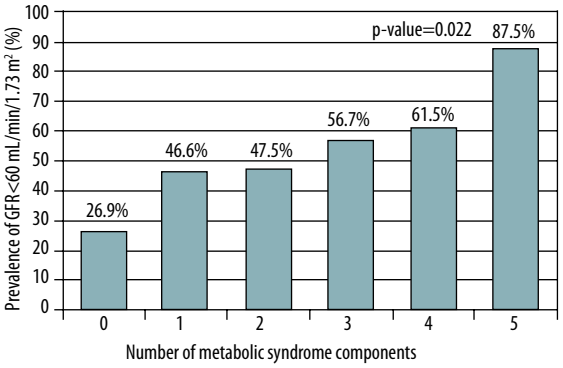

Figure 1. Prevalence of chronic allograft dysfunction (eGFR <60 mL/min/1.73 m^2) in renal transplant recipients by the number of metabolic syndrome components.

It has been shown that there is an association between the MS and CKD in Thai population. The prevalence of the MS in Thai RTRs was 31% in this study compared to 30.1% in Thai CKD (n=2228) and 24.4% Thai non-CKD population (n=13 129) [13]. This study demonstrated a significant association between MS and risk of chronic allograft dysfunction in RTRs in Thailand. The risk of chronic allograft dysfunction progressively increased with increased numbers of MS components, similar to the meta-analysis of 11 studies, which included 30 146 non-transplant patients [14]. Patients with MS had higher SBP and required more antihypertensive medications. Of note, the use of beta-blocker is associated with MS, similar to the study of Teixeira et al. [15]. Therefore, the choice of antihypertensive medication should be considered in RTRs especially those with variable components of MS.

In addition, environmental factors also affect the development of MS. Brazilian individuals of Japanese ancestry residing in Brazil were twice as likely to develop MS compared with native Japanese. The prevalence of MS was significantly higher in male Brazilians of Japanese ancestry residing in Brazil (37.5%) compared with those residing in Japan (25.3%) or native Japanese (21.4%) [16].

MS is the strongest risk factor for the development of PTDM [OR 5.26 (95%CI 2.06–13.43)]. It has been well recognized that both PTDM and MS are contributing factors of allograft dysfunction, cardiovascular morbidity, and patient death after RT [17–20]. Recipient death with a functioning allograft is the most common cause of late allograft failure in the Western world. In contrast, according to a report of the Thai Transplant Registry, recipient death with a functioning allograft was the third most common cause of all allograft losses (only 15%) and cardiovascular disease was a relatively rare cause of death (12%) among Thai RTRs [21]. However, Stępień et al. demonstrated a significant negative correlation between renal function (eGFR) and

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Table 2. Current medication use in renal transplant recipients.

Variables	Total (N=303)	MS (n=94)	Non MS (n=209)	RR (95%CI)	p-value
Oral hypoglycemic agent	16 (5.3%)	11 (11.7%)	5 (2.4%)	5.41 (1.82, 16.04)	0.002*
Insulin use	21 (6.9%)	15 (16%)	6 (2.9%)	6.42 (2.41, 17.15)	0.001**
Oral hypoglycemic agent or Insulin use	29 (9.6%)	22 (23.4%)	7 (3.3%)	8.82 (3.61, 21.52)	0.001**
Cyclosporine	122 (40.3%)	37 (39.4%)	85 (40.7%)	0.95 (0.58, 1.56)	0.830
Tacrolimus	137 (45.2%)	36 (38.3%)	101 (48.3%)	0.66 (0.4, 1.09)	0.106
MMF or MPA	238 (78.5%)	78 (83%)	160 (76.6%)	1.49 (0.8, 2.79)	0.209
Azathioprine	36 (11.9%)	7 (7.4%)	29 (13.9%)	0.5 (0.21, 1.19)	0.115
Sirolimus or everolimus	32 (10.6%)	15 (16%)	17 (8.1%)	2.14 (1.02, 4.5)	0.044*
Prednisolone	249 (82.2%)	72 (76.6%)	177 (84.7%)	0.59 (0.32, 1.09)	0.091
ACEI or ARB	95 (31.4%)	39 (41.5%)	56 (26.8%)	1.94 (1.16, 3.23)	0.011*
Beta-blocker	92 (30.4%)	45 (47.9%)	47 (22.5%)	3.17 (1.88, 5.32)	<0.001*
Calcium channel blocker	175 (57.8%)	55 (58.5%)	120 (57.4%)	1.05 (0.64, 1.71)	0.858
Diuretic	11 (3.6%)	5 (5.3%)	6 (2.9%)	1.9 (0.57, 6.39)	0.299
Alpha-blocker	46 (15.2%)	21 (22.3%)	25 (12%)	2.12 (1.12, 4.02)	0.022*
Aspirin	71 (23.4%)	18 (19.1%)	53 (25.4%)	0.7 (0.38, 1.27)	0.239
Number of anti-HTN medication use	1.39±0.96	1.77±0.89	1.22±0.95	1.84 (1.4, 2.41)	<0.001*

Values presented as mean ±SD. or n (%), RR (Relative risk). P-value corresponds to Logistic regression analysis. MMF – mycophenolate mofetil; MPA – mycophenolic acid; ACEI – angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; HTN – hypertension.

Table 3. Logistic regression analysis of the association between components of metabolic syndrome and chronic allograft dysfunction (eGFR <60 mL/min/1.73 m^2) in renal transplant recipients.

Variables	Chronic allograft dysfunction (n=150)	Non-chronic allograft dysfunction (n=153)	RR (95%CI)	p-value
FPG ≥100 mg/dL or drug use	47 (31.3%)	42 (27.5%)	1.21 (0.74, 1.98)	0.458
High blood pressure; BP ≥130/85 mmHg or drug use	137 (91.3%)	126 (82.4%)	2.26 (1.12, 4.57)	0.023*
Low HDL-C; M<40, F<50 mg/dL	31 (20.7%)	18 (11.8%)	1.95 (1.04, 3.67)	0.037*
Hypertriglyceridemia; ≥150 mg/dL or drug use	54 (36%)	28 (18.3%)	2.51 (1.48, 4.26)	0.001*
Central obesity; M>90, F>80 cm	56 (37.3%)	48 (31.4%)	1.3 (0.81, 2.1)	0.275

Values presented as number (%), and chronic allograft dysfunction was defined by eGFR <60 mL/min/1.73 m^2. FPG – fasting plasma glucose; HDL-C– high-density lipoprotein cholesterol; M – male; F – female.

body adiposity index [22]. With the increasing prevalence of obesity and MS after 3 years posttransplantation, we speculate that in the future there will be more cardiovascular morbidity and mortality, as well as late allograft loss [23].

Diet control and regular exercise leading to weight loss can reverse the processes of the MS and obesity. Greater interest of physicians in weight reduction and reducing body mass index could be the motivating factor for patients to enhance self-efficacy and perform weight loss measures [24]. Because there is a significant correlation between the number of metabolic components and the prevalence of chronic allograft dysfunction, and because chronic allograft dysfunction is a potent predictor of cardiovascular events and patient death, physicians

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and healthcare personnel as a team must use multidisciplinary approaches to aggressively control modifiable cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia, as well as encouraging smoking cessation. The present study had several limitations. First, we could not identify the causal relationship between MS and renal function because this was a cross-sectional study. Second, data on ultrasonography of the kidneys, the amount of proteinuria, and the microscopic examination of the urine (especially hematuria) were unavailable. As a result, participants with eGFR ≥60 mL/min/1.73 m^2 and non-GFR-based evidence of kidney damage were classified into the non-allograft dysfunction group in analysis.

Conclusions

Our study demonstrated that the prevalence of MS was high, especially after 3 years posttransplantation, in Thai RTRs. MS was associated with worse renal function and there was a significant correlation between the number of metabolic components and the prevalence of chronic allograft dysfunction in Thai RTRs. Lifestyle modification, dietary counseling, and increased physical activity or regular exercise should be emphasized at every clinic visit for RTRs.

Conflict of interest

None declared.

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