ORIGINAL ARTICLE

Prevalence of metabolic syndrome in Chinese renal transplant recipients

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Objective To investigate the prevalence of metabolic syndrome in Chinese renal transplant recipients, using two different sets of diagnostic criteria.

Design Cross-sectional study.

Setting Regional hospital, Hong Kong.

Patients All Chinese patients who received solitary living–related or cadaveric kidney transplantation from 1 July 1997 to 31 December 2005 in our hospital with follow-up of more than 6 months were recruited. The diagnosis of metabolic syndrome was made according to the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) criteria and the International Diabetes Federation criteria.

Results Using the modified (Asian) NCEP-ATPIII criteria, a total of 39 (32%) of 121 patients had metabolic syndrome, which included 20/69 (29%) of the males and 19/52 (37%) of the females. Using the International Diabetes Federation criteria, metabolic syndrome was diagnosed in 26% of the patients, 22% in males and 31% in females. In our patients, the most common component of metabolic syndrome was hypertension and the least common was low high-density-lipoprotein–cholesterol level. Low high-density-lipoprotein–cholesterol levels were significantly more common in female patients.

Conclusion This study shows that there is a high prevalence of metabolic syndrome in our Chinese renal transplant recipients.

Introduction

The metabolic syndrome (MS) is a cluster of interrelated common clinical entities, which include: obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidaemia. It has been well recognised that MS is closely associated with atherosclerotic cardiovascular disease in the general population.[1] A community-based population study demonstrated that established cardiovascular disease risk factors are associated with the development of new-onset kidney disease.[2] Moreover, among US adults, MS increases the risk of chronic kidney disease.[3] Recently it has been found that MS is also common in renal transplant recipients.[4] As in the general population, in renal transplant recipients, MS is associated with an increased risk of renal dysfunction and cardiovascular mortality.[4-6] However, most of the published studies were based on Caucasians, there being a lack of data in Chinese renal transplant recipients. Interestingly, in the general population, the prevalence of MS differs widely among ethnic groups and according to the definition used.[7-9] In the present study, we investigated the prevalence of MS in Chinese renal transplant recipients using different diagnostic criteria.

Methods

Patients

This was a cross-sectional study. All Chinese patients who received solitary living–related or cadaveric kidney transplantation from 1 July 1997 to 31 December 2005 in Queen Elizabeth Hospital, Hong Kong with follow-up of more than 6 months were recruited. The study was performed in accordance with the Declaration of Helsinki. Written consent was obtained from each patient. Demographic and clinical data were extracted from patient records.

Key words
Kidney transplantation; Metabolic syndrome; Prevalence

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接受腎臟移植的華裔病人出現代謝綜合徵的現患率

目的 應用兩套不同的診斷準則，探討接受腎臟移植的華裔病人出現代謝綜合徵的現患率。

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患者 從1997年7月1日至2005年12月31日，所有在本醫院接受活體親屬腎移植或屍腎移植，以及隨訪期6個月以上的華裔病人均參加研究。代謝綜合徵的診斷則採用美國國家膽固醇教劃成人治療指南(NCEP-ATPIII)準則，以及國際糖尿病聯盟(IDF)準則。

結果 按修訂NCEP-ATPIII（亞洲）準則，121名病者中，39 (32%)位有代謝綜合徵，包括69名男性患者中的20位(29%)和52名女性患者中的19位(37%)。據IDF準則，診斷出26%患者有代謝綜合徵，男性患者中有22%，女性患者中有31%。在這批病人中最普遍的代謝綜合徵症狀是高血壓，最少見的是高密度脂蛋白脂膽固醇含量低，而後者又明顯地常見於女性病人。

結論 研究顯示，接受腎移植的華裔病人患上代謝綜合徵的情況相當普遍。

Immunosuppressive regimens

Our patients were basically put on triple immunosuppressive therapy with either tacrolimus (Prograf, Astellas, Japan) or cyclosporine A (Neoral, Novartis, Switzerland), prednisolone and azathioprine. All patients received 500 mg of methylprednisolone at induction, followed by intravenous hydrocortisone 100 mg every 6 hours for 3 days and then oral prednisolone 30 mg daily. The dose of prednisolone was gradually tapered after the first month at a rate of 2.5 mg every 2 weeks and maintained at 7.5 mg daily. Azathioprine was given at a dose of 1.5 mg/kg daily since day 1 after the transplant. Cyclosporine was initially administered orally as a loading dose of 10 mg/kg within 12 hours of surgery and continued as 5 mg/kg twice daily. In this study, an abbreviated formula based on a limited sampling strategy was used to estimate the cyclosporine area under the 12-hour concentration-time curve (AUC_{0-12}).

Calculation of cyclosporine AUC_{0-12} depended on the formula: 452.4 + C_0 x 17.5 + $C_{1.5}$ x 1.89 (C_0: cyclosporine trough level; $C_{1.5}$: 1.5-hour postdose cyclosporine level).[10] The dose of cyclosporine was gradually titrated to maintain an abbreviated AUC_{0-12} of around 6000-8000 ng x h/mL in the first 3 months post-transplant, and 4000-6000 ng x h/mL thereafter.[11] Tacrolimus was administered orally with a loading dose of 0.3 mg/kg within 12 hours of surgery and then 0.15 mg/kg twice daily. Abbreviated tacrolimus AUC_{0-12} monitoring was used. Calculation of tacrolimus AUC_{0-12} depended on the formula: 16.2 + C_2 x 2.4 + C_4 x 5.9 (C_2: 2-hour postdose tacrolimus level; C_4: 4-hour postdose tacrolimus level). Based on a previous pilot study in stable patients on tacrolimus in our centre, the AUC_{0-12} value was kept at around 100-150 ng x h/mL in the first 3 months and around 80-100 ng x h/mL thereafter.[12] Since 2001, some of our patients did receive an interleukin-2 receptor antagonist during induction therapy; patients on cyclosporine were given basiliximab (Simulect, Novartis, Switzerland) while those on tacrolimus were given daclizumab (Zenapax, Roche, NJ, US). Basiliximab was given at a dose of 20 mg around 2-hour pre-transplantation and a second dose after 4 days. Daclizumab was given as a 1 mg/kg infusion around 2 hours before transplantation and then every 14 days for four doses.

Acute rejection was defined as any episode with the relevant clinical and laboratory signs and symptoms and all such episodes were confirmed by renal biopsy. Our protocol for treating acute cellular rejection entailed 500 mg methylprednisolone given intravenously for 3 days. In case of steroid-resistant rejection, appropriate antibody therapy was started.

Measurements

Subjects came back to our centre at 8:00 am after an 8-to-12–hour overnight fast. Fasting blood samples were drawn to determine serum creatinine, triglyceride, and high-density-lipoprotein (HDL) cholesterol and plasma glucose concentrations. Low-density-lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula.[13] Hypertension was defined as (i) the administration of antihypertensive agents and/or a history of this disorder; (ii) a systolic blood pressure greater than 130 mm Hg; or (iii) a diastolic blood pressure greater than 85 mm Hg. Weight, height, and waist circumference (midway between the iliac crest and the 10th rib) were also measured.

Post-transplant diabetes mellitus (PTDM) was defined as a fasting blood glucose of more than 7 mM (126 mg/dL) on two occasions at any time after transplantation or associated with use of oral hypoglycaemic agents and/or insulin, in patients with no previous history of diabetes mellitus.

Diagnostic criteria for metabolic syndrome

The diagnosis of MS was made according to the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) criteria[14] and the International Diabetes Federation (IDF) criteria.[15] The five thresholds used were: (i) serum triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or specific treatment for this lipid abnormality, (ii) serum HDL-cholesterol level <1.04 mmol/L (<40 mg/dL) in men or <1.29 mmol/L (<50 mg/dL) in women or specific treatment for this lipid abnormality, (iii) systolic blood pressure

≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg (high blood pressure) or use of antihypertensive medication, (iv) fasting plasma glucose level ≥100 mg/dL (≥5.6 mmol/L) or use of antidiabetic medication, and (v) waist girth >102 cm for men or >88 cm for women (original NCEP-ATPIII criteria) and waist girth ≥90 cm for men or ≥80 cm for women (modified NCEP-ATPIII criteria for Asians). Because the original cut-off for abdominal obesity in the NCEP definition (waist circumference >102 cm for men and >88 cm for women) were shown to be inappropriate for Asian populations and the number of subjects who met these criteria was extremely low,[7,8,16] we used Asian cut-off limits.[7,8,15,16]

National Cholesterol Education Program–Adult Treatment Panel III criteria

Subjects who had three or more of the risk factors were judged as having MS (MS group), and those having two or less were judged as not having the condition (non-MS group).

International Diabetes Federation criteria

Subjects with central obesity (defined as waist circumference ≥90 cm for men or ≥80 cm for women in Chinese) plus two or more of the risk factors were judged as having MS.

Statistical analysis

The Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], US) was used to perform the analyses. Continuous data were expressed as means and standard deviations and categorical data as percentages. Continuous data were analysed by independent sample *t* tests to detect the differences between groups and categorical data by the Chi squared test. A P value of <0.05 was considered statistically significant.

TABLE 1. Demographic and transplant characteristics of patients with/without metabolic syndrome (MS) by modified (Asian) National Cholesterol Education Program–Adult Treatment Panel III criteria

Characteristic*	MS (n=39)†	Non-MS (n=82)†	P value‡
Age of recipient (years)	42±10	38±10	0.010
Male	20 (51)	49 (60)	0.379
Donor source			0.572
Living	3 (8)	9 (11)	
Cadaveric	36 (92)	73 (89)	
Diabetes mellitus			
Pre-transplant	11 (28)	1 (1)	<0.001
Post-transplant	12 (31)	10 (12)	0.013
Duration of transplant (years)	5.1±2.1	5.3±2.3	0.633
Waist circumference (cm)	90.3±9.6	78.1±10.0	<0.001
Body mass index (kg/m^2)	25±5	21±3	<0.001
Weight gain at 1-year post-transplant (kg)	6±7	3±6	0.017
Hepatitis B status	5 (13)	13 (16)	0.661
Calcineurin inhibitors			
Tacrolimus	19 (49)	34 (41)	0.452
Cyclosporine	20 (51)	48 (59)	
Use of interleukin-2 receptor antagonist	20 (51)	44 (54)	0.807
Prednisolone dosage (mg)	7.5	7.5	1.000
Use of ACEI or ARB	4 (10)	5 (6)	0.415
Triglyceride (mM)	2.0±1.1	1.5±1.1	0.026
HDL cholesterol (mM)	1.5±0.5	1.7±0.5	0.370
Fasting glucose (mM)	5.6±0.8	5.2±0.8	0.188
Hypertension	39 (100)	64 (78)	0.002
SCr at 6 months (μM)	160±60	162±66	0.792
SCr at 12 months (μM)	151±55	158±55	0.510
Proteinuria (g/day)	0.81±1.44	0.29±0.71	0.038
Albuminuria (mg/day)	62±76	52±75	0.680
CMV infection	7 (18)	11 (13)	0.512
Acute rejection	7 (18)	20 (24)	0.426

* ACEI denotes angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blockers, CMV cytomegalovirus, HDL high-density lipoprotein, and SCr serum creatinine

† MS denotes metabolic syndrome; values are expressed as mean±SD or No. (%)

‡ Continuous variables were analysed with the use of *t* tests, all categorical data were analysed with the use of Chi squared test

Results

Demographic and transplant characteristics of patients with and without metabolic syndrome (according to the National Cholesterol Education Program–Adult Treatment Panel III criteria for Asians)

Table 1 shows the background data for renal transplant patients with or without MS. The mean follow-up duration after kidney transplantation was 63 (standard deviation, 29) months. Using the modified (Asian) NCEP-ATPIII criteria, a total of 39 (32%) of 121 patients had MS. Compared to the non-MS group, in those with MS, the mean age was greater (P=0.01), PTDM and hypertension were more prevalent (P=0.013 and P=0.002 respectively), and body mass index and waist circumference were greater (P<0.001 in both cases). The MS group also had higher mean serum triglyceride levels (P=0.026), and more severe proteinuria (P=0.038). Other clinical variables did not differ significantly. Both groups were receiving similar doses of steroids during the study and the proportions receiving tacrolimus or cyclosporine were also similar (P=0.452). In all, 15 patients in this cohort were taking lipid-lowering agents.

Percentage of patients with metabolic syndrome according to different diagnostic criteria

Using the modified (Asian) NCEP-ATPIII criteria, 39 (32%) of 121 patients had MS including 20 (29%) of 69

TABLE 2. Percentage of patients with metabolic syndrome according to different diagnostic criteria

	Prevalence of metabolic syndrome (%)*		
	Modified (Asian) NCEP-ATPIII criteria: waist girth >80 cm in women or >90 cm in men	Original NCEP-ATPIII criteria: waist girth ≥88 cm in women or ≥102 cm in men	IDF criteria: waist girth ≥80 cm in women or ≥90 cm in men
Male (n=69)	29	16	22
Female (n=52)	37	21	31
Total (n=121)	32	18	26

* NCEP-ATPIII denotes National Cholesterol Education Program–Adult Treatment Panel III, and IDF International Diabetes Federation

TABLE 3. Crude prevalence of metabolic syndrome and its components as defined by the modified (Asian) National Cholesterol Education Program–Adult Treatment Panel III criteria

Component*	Crude prevalence (%)			P value
	Total (n=121)	Men (n=69)	Women (n=52)	
Central obesity	37	33	42	0.312
Low HDL-cholesterol	7	2	14	0.009
High TG	42	42	42	0.975
Hypertension	86	84	89	0.490
Hyperglycaemia	36	38	35	0.729
Metabolic syndrome	32	29	37	0.379

* HDL denotes high-density lipoprotein, and TG triglyceride

males and 19 (37%) of 52 females. Using the original NCEP-ATPIII criteria, MS was diagnosed in 18% of the patients: 16% of the males and 21% of the females. Using the IDF criteria, MS was diagnosed in 26% of the patients: 22% of the males and 31% of the females (Table 2).

Prevalence of metabolic syndrome and its components as defined by the modified (Asian) National Cholesterol Education Program–Adult Treatment Panel III criteria

In our Chinese renal transplant recipients, the most common component of MS was hypertension and the least common was low HDL-cholesterol. Low HDL-cholesterol was significantly more common in females (14% vs 2%, P=0.009). However, there was no significant gender difference in the occurrence of other MS components (Table 3).

Discussion

In the general population, the prevalence of MS differs widely among ethnic groups depending on the definition of MS used.[7-9] In a US study, its prevalence was 24.7 to 26.7% using the original NCEP-ATPIII criteria.[3,9] By contrast, in a Japanese population its prevalence was 12.4% using the same NCEP criteria and 21.2% according to the modified (Japanese) criteria.[17] de Vries et al[4] applied the consensus definition (NCEP-ATPIII) of MS to the kidney transplant population in the Netherlands, and reported that 63% of Caucasian renal transplant patients had MS. Porrini et al[5] reported that 37.7% of Spanish renal transplantation recipients had MS using modified NCEP criteria, while Armstrong et al[18] reported that 50% of Australian renal transplant recipients had MS according to the original NCEP criteria. These various reports suggest that MS is more prevalent in Caucasian renal transplant recipients than the general population. However, in Japan there was only a slight difference in the prevalence of MS between the general population and renal transplant patients.[19] This discrepancy may be related to differences in lifestyle, eating habits, or the prevalence and degree of obesity among Japanese and Caucasian populations. In the InterASIA study, Gu et al[20] showed that 15.1% of the Chinese adults aged 35 to 74 years had MS by the modified (Asian) NCEP criteria. In another study involving a Hong Kong Chinese working population, the crude prevalence of MS ranged from 8.9 to 13.4% depending on the criteria used.[21] In the present study, we showed that MS was more prevalent in our Chinese renal transplant recipients than that reported in the literature for the general population. To the best of our knowledge, this is the first study showing the prevalence of MS in Chinese renal transplant recipients.

In our study, body mass index and waist circumference of the MS group were significantly greater than those in the non-MS group. As in the general population, being overweight was a major clinical feature of MS in renal transplant recipients. Insulin resistance is the central pathophysiological feature underlying MS.[22] In renal transplant recipients, factors other than obesity may contribute to insulin resistance. High-dose immunosuppressive therapy in the early post-transplant period, namely steroids and calcineurin inhibitors, may play a major role. Indeed, early high-dose steroid usage, together with acute rejection, have been associated with insulin resistance.[23,24] In our study, all patients received the same immunosuppressive regimen as well as the same amount of maintenance steroids. Thus, we were unable to assess the relationship between steroid dosage and the occurrence of MS. However, acute rejection was not particularly associated with subsequent development of MS. Similarly, none of our patients were on a calcineurin inhibitor–free regimen, and thus we could not evaluate their role in the development of MS. Hjelmesaeth et al[24] have demonstrated an association between cytomegalovirus disease and insulin resistance,

possibly via inducing release of cytokines such as tumour necrosis factor–alpha.[25,26] Our data, however, could not demonstrate any independent relationship between this disease and the development of MS.

Our study revealed that MS was more prevalent in the females than males (37% vs 29%), which was consistent with the general adult population in China.[20] This difference might be due to a higher prevalence of low HDL-cholesterol in women compared to men, which may be due to different cut-off values used in men and women. de Vries et al[4] also reported that patients with MS were more often female. In contrast, some reports have shown that MS was more common in male renal transplant recipients,[5,19] indicating that gender predisposition of MS may differ widely between ethnic groups in renal transplant recipients.[3,7-9,16,17]

In our study, PTDM was more prevalent in the MS group, consistent with a previous report by Porrini et al.[5] In their longitudinal study, MS was a prominent risk factor for PTDM. Obesity and dyslipidaemia, which are components of MS, are associated with insulin resistance, one of the most important causative elements in the pathophysiology of type 2 diabetes.[27,28] Our approach to treating dyslipidaemias in renal transplant recipients conforms to that advocated by the NKF-K/DOQI working group.[29] There is a particular emphasis given to the high cardiovascular risks associated with kidney transplantation. Based almost entirely upon adverse results and benefits with therapy in the general population, three subgroups of renal allograft recipients with distinct lipid profiles are distinguished for particular attention. These are: (1) those with triglyceride levels >5.65 mmol/L (>500 mg/dL); (2) those with LDL levels >2.59 mmol/L (>100 mg/dL); and (3) those with LDL levels ≤2.59 mmol/L (≤100 mg/dL), triglycerides levels >2.26 mmol/L (>200 mg/dL) and non-HDL cholesterol levels >3.36 mmol/L (>130 mg/dL). They were all treated with lipid-lowering agents after failure of control with lifestyle modification.

In the present study, the diagnosis of MS was made according to the NCEP-ATPIII and IDF criteria, as they are easily applicable in a clinical setting and used widely. Our study showed that the prevalence of MS differed according to the criteria used, being slightly lower by IDF criteria (which recognises central obesity as an essential component). At present, there is no consensus on which diagnostic criteria for MS are best suited for renal transplant recipients. Further longitudinal studies of cardiovascular disease and renal allograft function are needed to clarify this issue.

It has been reported that MS is a risk factor for renal dysfunction in the general population.[2,3] In heart transplantation, Valantine et al[30] suggested that a 'metabolic milieu' may modify the process of chronic transplant dysfunction. In longitudinal studies, de Vries et al[4] and Porrini et al[5] suggested that MS is associated with impaired renal allograft function. Different mechanisms have been proposed for the association between MS and impaired renal function. Obesity may contribute to renal dysfunction in many ways, such as excess excretory load, renal sodium retention, hyperinsulinaemia, insulin resistance, and renal lipotoxicity.[31-34] Moreover, obesity is associated with worsening proteinuria in renal transplant recipients.[18] Finally, glucose intolerance, hypertension and dyslipidaemia (all components of MS) directly damage the kidneys through renal or systemic atherosclerosis.[35-38] Our series did not demonstrate a significant difference in renal function between patients with and without MS, probably because they were from a cross-sectional study and the sample size was small.

In conclusion, the present study showed a high prevalence of MS in our Chinese renal transplant recipients, more so in females than males, and varied according to the different diagnostic criteria used. By the IDF criteria, which cites central obesity as an essential component, its prevalence was slightly lower.

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