Prevalência de síndrome metabólica e fatores associados em pacientes transplantados renais

Prevalence of metabolic syndrome and its associated factors in renal transplant recipients

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Resumo

Introdução: A população de pacientes submetidos ao transplante renal é considerada de alto risco para desenvolver obesidade e alterações no metabolismo lipídico e da glicose, devido ao uso de drogas imunossupressoras e da liberdade na alimentação no período pós-transplante. **Objetivo:** Este estudo foi desenhado para avaliar a prevalência da síndrome metabólica em receptores de transplante renal e para identificar os fatores associados com sua ocorrência. **Métodos:** Realizou-se um estudo transversal em pacientes transplantados renais com mais de seis meses de acompanhamento. A síndrome metabólica foi diagnosticada de acordo com os critérios do National Cholesterol Education Program Adult Treatment Panel III. **Resultados:** Entre os 87 pacientes inscritos, 39 (44,8%) apresentavam o fenótipo da síndrome metabólica. A idade média dos pacientes foi de 43,5 ± 12,1 anos, com predomínio do sexo masculino (69,0%) e brancos (66,7%). Os tempos médios e a mediana pós-transplante foram 64,2 ± 49,4 e 56 meses, respectivamente. Todos os 12 pacientes que desenvolveram diabetes mellitus pós-transplante também satisfizeram os critérios para a síndrome metabólica, o que comprometeu a inclusão desta variável na regressão logística. Na análise univariada, pacientes com síndrome metabólica apresentaram maior média de idade (p = 0,008), maior média no nível sérico de ciclosporina (p = 0,021), maior prevalência de história de doença coronariana (p = 0,023), e usaram com maior frequência beta-bloqueadores (p = 0,011) e bloqueadores do canal de cálcio (p = 0,039). Na análise multivariada, a idade (HR = 1,06; IC 95% 1,01 - 1,11, p = 0,006) e o uso de beta-bloqueadores (HR = 4,02; IC 95% = 1,41 - 11,4, p = 0,009) foram associados com risco aumentado de

Abstract

Introduction: The population of patients undergoing renal transplantation is considered at highrisk for developing obesity and changes in lipid and glucose metabolism, due to the use of immunosuppressive drugs and increased food freedom in the post-transplant period. **Objective:** This study was designed to assess the prevalence of metabolic syndrome in renal transplant recipients and to identify factors associated with its occurrence. **Methods:** A cross-sectional study was performed in renal transplant patients, with more than six months of follow-up. The metabolic syndrome was diagnosed according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III. **Results:** Among the 87 patients enrolled, 39 (44.8%) presented the phenotype of metabolic syndrome. The mean age of the patients was 43.5 ± 12.1 years-old, with a predominance of male (69.0%) and white (66.7%). The mean and median times of post transplant follow-up were 64.2 ± 49.4 and 56 months, respectively. All the 12 patients who developed post-transplant diabetes mellitus also met the criteria for metabolic syndrome, which compromised the inclusion of this variable in the logistic regression. In the univariate analysis, patients with metabolic syndrome had higher mean age (p = 0.008), higher median blood level of cyclosporine (p = 0.021), higher prevalence of history of coronary disease (p = 0.023), and they were more frequent users of beta (p = 0.011) and calcium- channel blockers (p = 0.039). In the multivariate analysis, age (HR = 1.06; 95% CI=1.01-1.11, p=0.006) and use of beta-blockers (HR = 4.02; 95% CI = 1.41 - 11.4, p = 0.009) were asso- ciated with increased

síndrome metabólica. Conclusão: A síndrome metabólica foi altamente prevalente na po- pulação de transplantados renais estudados, e foi asso- ciada com maior idade, uso de beta-bloqueadores e o diabetes mellitus pós-transplante.
Palavras-chave: Transplante de Rim. Dislipidemias. Diabetes Mellitus Tipo 2.

risk of metabolic syndrome. **Conclusion:** Metabolic syndrome was highly prevalent in the population of renal trans- plant recipients studied, and it was associated with older age, use of beta-blockers, and post-transplant diabetes mellitus.
Keywords: Kidney Transplantation. Dyslipidemias. Diabetes Mellitus, Type 2.

Introduction

The epidemiology of obesity recorded in recent decades has also been associated with the equally increased occurrence of metabolic syndrome (MS) in the general population.[1] In Brazil, the MS prevalence in the general adult population is around 20%.[2] MS is a cluster of cardiovascular risk factors (hypertension, dyslipidemia, obesity, and glucose homeostasis alterations), and insulin resistance is suggested to be a common pathogenic background.[3] The presence of MS increases the cardiovascular risk in the general population and in recipients of renal transplantation.[4]

The population of patients undergoing renal transplantation is considered at high-risk for developing obesity and changes in lipid and glucose metabolism, due to the use of immunosuppressive drugs and increased food freedom in the post-transplant period. For instance, high incidence of post-transplant diabetes mellitus (PTDM) and MS was observed among kidney transplant recipients treated with tacrolimus as the main immunosuppressive medication.[5]

According to few data available, the prevalence of MS in renal transplant patients increases with the post-transplant time and it is frequently associated with PTDM.[6] Some studies have confirmed the increased prevalence of MS after transplantation, implying its association with reduced renal allograft survival.[7,8]

Despite the association of MS with adverse outcomes, such as cardiovascular and impairment of renal function, so far only one study has documented the prevalence of MS in patients undergoing renal transplantation in Brazil.[9] In the present study, we assessed the prevalence of MS and the factors associated with its occurrence.

Patients and methods

This is a cross-sectional study, which was conducted between August, 2008, and January, 2009. The study included adults with renal transplant with more than six months of follow-up. Patients with MS and/or diabetes mellitus prior to transplantation, with cancer, and active inflammatory or infectious disease were not included in the analysis. Demographic and clinical information, measurement of weight, height, and blood pressure, in addition to the determination of serum creatinine, blood glucose, uric acid, total cholesterol, LDL-cholesterol, and triglycerides were obtained in the pre- and post-transplant periods. Value of LDL-cholesterol was calculated with the Friedewald's equation,[10] and the glomerular filtration rate (GFR) was estimated by using the formula of the study Modification of Diet in Renal Disease (MDRD).[11]

The MS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII),[12] which establishes the diagnosis by the presence of at least three of the following criteria: abdominal obesity characterized by waist circumference ≥ 102 cm in men, and ≥ 88 cm in women; triglycerides ≥ 150 mg/dL, or use of drugs for hypertriglyceridemia treatment; HDL < 40 mg/dL in men and < 50 mg/dL in women, or use of drugs for low HDL; fasting blood glucose ≥ 100 mg/dL, or drug therapy for hyperglycemia; and systolic blood pressure ≥ 130 mmHg, or diastolic ≥ 85 mmHg, or use of antihypertensive medication. Individuals taking hypoglycemic drugs or insulin were considered patients with PTDM.

The collected data were processed using the software SPSS, version 13.0. Values are expressed as means and standard deviation or percentage. For comparisons between groups, we used the *t*, chi-square, and Mann Whitney tests in univariate analysis, and we adopted the significance level of 0.05. The Odds Ratio and Spearman correlation were also calculated. Variables, which were significant at the level of 0.05 and were not criteria for MS, were included in the logistic regression model, the dependent variable in the model was MS.

Results

Of the 96 patients initially enrolled, 87 met the inclusion criteria and composed the study population.

The mean age of the patients was 43.5 ± 12.1 years-old. There was a predominance of male (69.0%) and white (66.7%) patients. The mean and median times of post-transplant follow-up were 64.2 ± 49.4 and 56 months, respectively. MS was diagnosed in 39 (44.8%) of the patients and 12 (30.8%) of them were diagnosed with PTDM. Table 1 shows that high blood pressure and hypertriglyceridemia were the most frequent components of MS identified among the patients. Even among the patients without MS, high-blood pressure was very frequent.

Table 2 shows the results of the univariate analysis. As it can be seen, patients with MS presented higher mean age (p = 0.008), higher median blood level of cyclosporine (p = 0.021), higher prevalence of pre-transplant history of coronary disease (p = 0.023), and usage of beta-blockers (p = 0.011) and calcium-channel blockers (p = 0.039). Besides the expected difference between the parameters directly related to the diagnosis of MS, all patients with PTDM met the criteria of MS, which compromised the inclusion of this variable in the logistic regression. There were no differences between the use of immunosuppressive medications – prednisone, azathioprine, ciclosporin, mycophenolate (mofetil or sodium), tacrolimus or sirolimus – and the occurrence of MS (Table 2).

In the multivariate analysis, age (HR = 1.06; 95% CI = 1.01 - 1.11, p = 0.006), and use of beta-blockers (HR = 4.02; 95% CI = 1.41 - 11.4, p = 0.009) were associated with increased risk of MS. Among the 39 patients with MS, 20 (51.3%) were treated with beta-blockers (p < 0.011). Individually, only treatment with propranolol (p = 0.044) was significantly associated with MS (Table 3).

The mean estimated GFR in mL/min./1.73 m^2 (± standard deviation) in patients without and with one, two, three, four, and five components of MS were, respectively, 49.5 (8.6), 57.4 (19.2), 50.1 (24.2), 50.2 (16.9), 53.0 (18.7), and 58.6 (14.8) and it was not statistically different (Sperman's correlation – r = 0.025, p = 0.818). As the patients were in different periods of post-transplant follow-up, we assessed the impact of MS on the GFR dividing them according the median time of follow-up (56 months). As it can be seen in the Figure 1, the GFRs were similar in patients with and without MS in the two time periods.

Discussion

It was Reaven, in 1988,[3] who first introduced the concept of MS. Soon, population studies reported an association between MS and renal disease.[12-15] However, so far, very little is known about the prevalence of this syndrome in renal transplant recipients. In the present study, MS was present in 44.8% of renal transplant recipients, a percentage higher than the one identified in some studies and lower in others. Porrini *et al*., in Spain, found MS in 37.7% of the patients.[4] In Japan, the prevalence of MS varied from 14.9 to 23.8%, according to the criteria used.[16] Moreover, in the Netherlands, 63% of the 606 renal transplant recipients evaluated presented MS.[7] A study in Brazil, to assess the prevalence of cardiovascular risk factors in renal transplantation, identified MS in 53% of the 192 patients studied.[9] The prevalence of MS in renal transplant recipients, as well as in the general population, seems to vary with the diagnostic criteria used, and the cultural habits of each population.

In nontransplanted individuals, age is an independent risk factor of MS, and the prevalence of each of the components of MS increases with age.[17] Depending on the criterion used, the prevalence of MS reaches

Table 1 Frequency of the components of metabolic syndrome defined according to the National Cholesterol Education Program Adult Treatment Panel III in renal transplant patients

Components of metabolic syndrome	Patients without metabolic syndrome (n = 48)	Patients with metabolic syndrome (n = 39)
Abdominal obesity (%)	6.3	51.3
High-blood pressure (%)	87.5	97.4
Hyperglycemia (%)	0	38.5
Hypertriglyceridemia (%)	31.3	92.3
Low level of HDL-Cholesterol (%)	21.3	81.6

Abdominal obesity was characterized by waist circumference =102 cm in men and = 88 cm in women; high-blood pressure was defined as systolic blood pressure = 130 mmHg or diastolic = 85 mmHg, or use of anti-hypertensive medication(s); hyperglycemia was defined as blood sugar = 100 mg/dL or drug therapy for hyperglycemia; hypertrigyceridemia was defined as triglycerides = 150 mg/dL or use of drugs for treatment of hypertriglyceridemia; low level of HDL was defined when < 40 mg/dL in men and < 50 mg/dL in women or use of drugs for lower HDL.

Table 2 Comparisons (univariate analysis) of demographic, laboratorial, and clinical parameters between patients with and without metabolic syndrome

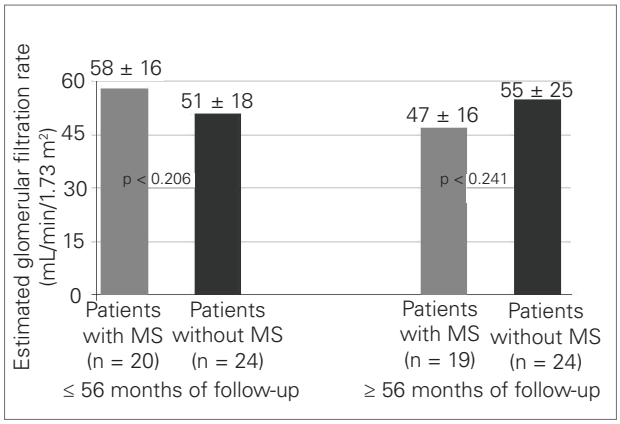
Parameters	Patients without metabolic syndrome (n = 48)	Patients with metabolic syndrome (n = 39)	p-value
Age (years) mean ± sd	40.5 ± 10.6	47.3 ± 13.0	0.008
Male gender, n (%)	35 (72.9)	25 (64.1)	0.377
Donor's age (years) mean ± sd	38.9 ± 1.7	40.4 ± 1.2	0.537
Time post-transplant (months) mean ± sd	63.2 ± 49.1	65.3 ± 50.4	0.843
Time to RRT (months) mean ± sd	28.2 ± 23.8	26.4 ± 30.5	0.762
Acute rejection episodes, n (%)	15 (31.3)	6 (15.4)	0.085
Menopause, n (%)	2 (42)	8 (20.5)	0.053
History of pre transplant CoDx, n (%)	0 (0)	4 (10.3)	0.023
Family history of DM, n (%)	13 (27.1)	16 (41)	0.202
Positivity for HCV, n (%)	3 (6.3)	2 (5.1)	0.823
Post-transplant diabetes, n (%)	0 (0)	12 (30.8)	< 0.0001
Systolic blood pressure (mmHg), mean ± sd	129.5 ± 23.4	136.0 ± 20.0	0.175
Diastolic blood pressure (mmHg), mean ± sd	79.1 ± 1.4	83.5 ± 10.9	0.072
Abdominal Circumference (cm), mean ± sd	82.8 ± 10.2	95 ± 12.6	< 0.0001
Blood glucose (mg/dL), mean ± sd	79.3 ± 1.4	95.9 ± 31	0.001
Triglyceride (mg/dL), mean ± sd	145.8 ± 84.7	209.0 ± 91.1	0.001
HDL-cholesterol (mg/dL), mean ± sd	50.8 ± 12.7	38.5 ± 10.8	0.001
Serum uric acid (mg/dL), mean ± sd	6.6 ± 1.5	6.4 ± 1.6	0.484
Serum creatinine (mg/dL), mean ± sd	1.7 ± 0.9	1.59 ± 0.7	0.438
Estimated GFR, mean ± sd	53.1 ± 21.5	52.6 ± 16.8	0.922
Beta-blocker usage (%)	12 (25)	20 (51.3)	0.011
Calcio-chanel blocker usage, n (%)	12 (25)	18 (46.2)	0.039
ACEI usage, n (%)	26 (54.2)	16 (41)	0.223
ARB usage, n (%)	13 (27.1)	13 (33.3)	0.527
Cyclosporine dose (mg/day), mean ± sd	216.7 ± 80.7	202.8 ± 87	0.710
Cyclosporine trough level (ng/mL), mean ± sd	109.8 ± 51.8	222.7 ± 144.2	0.021
Tacrolimus dose (mg/day), mean ± sd	5.0 ± 3.1	5.8 ± 2.6	0.384
Tacrolimus trough level (ng/mL), mean ± sd	7.1 ± 3.9	7.3 ± 3.6	0.862
Prednisone dose (mg/day), mean ± sd	4.5 ± 3.2	4.1 ± 1.8	0.585
Azatioprine dose (mg/day), mean ± sd	89.1 ± 41.8	102.3 ± 43.9	0.437
Sodium Mycophenolate (mg/day), mean ± sd	1000 ± 339.4	810 ± 372.3	0.182
Mycophenolate mofetil (mg/day), mean ± sd	1204.5 ± 458.5	1207.9 ± 498.4	0.987
Sirolimus dose (mg/day), mean ± sd	1.8 ± 0.6	2.1 ± 0.5	0.167
Sirolimus level (mg/dL), mean ± sd	5.3 ± 3.1	6.5 ± 2.7	0.261

sd: standard deviation; RRT: renal replacement therapy; CoDX: coronary disease; HCV: hepatitis C virus; HDL: high density lipoprotein; GFR: glomerular filtration rate (in mL/min/1.73 m^2); ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 3 Beta-blocker usage among renal transplant patients

Beta-blocker	Patients without metabolic syndrome (n = 48)	Patients with metabolic syndrome (n = 39)	p-value
Total (%)	12 (37.5)	20 (62.5)	0.011
Atenolol, n (%)	7 (41.2)	10 (58.8)	0.677
Propranolol, n (%)	2 (20)	8 (80)	0.044
Metoprolol, n (%)	2 (50)	2 (50)	0.439
Carvedilol, n (%)	1 (100)	0	-

Figure 1. Estimate glomerular filtration rate in patients with and without metabolic syndrome stratified according to median time of follow-up (56 months).



32% in patients in the age range of 45 to 54 years-old.[18] The mean age of our transplanted patients with MS was 47.3 years-old, which was significantly higher than in those (40.5 years-old) without the syndrome. A number of explanatory diet- and lifestyle-related risk factors are probably to be involved, affecting weight and multiple metabolic abnormalities and explaining the life course development of MS.

Hypertension represents the most common cardiovascular and renal risk factor, and it was found in 97.4 and 87.5% of our renal transplant recipients with and without MS, respectively. Beta-blockers have been used to treat hypertension for decades, either as monotherapy or combined with other anti-hypertensive agents. Beta-blockers are heterogeneous with respect to pharmacokinetic and pharmacodynamic effects.[19] In the most recent guidelines, the European Society of Hypertension / European Society of Cardiology[20] recommend that beta-blockers should not be preferred in hypertensives with multiple metabolic risk factors, including MS, abdominal obesity, high, normal or impaired fasting glucose, and impaired glucose tolerance. The use of beta-blockers is related to weight gain and dyslipidemia.[21] In our study, as a class of medication, beta-blockers were associated with MS. However, among the beta-blockers, only propranolol was independently associated with MS, a finding we did not identify in other studies associating the different beta-blockers and the development of MS in the renal transplantation arena. The recently introduced vasodilating beta-blocker carvedilol has attractive effects on insulin resistance and exhibits antioxidant effects, its use did not associate with MS in only one of our patients that were using it. Further studies are necessary to test whether the newer beta-blockers may overcome concerns about efficacy, adverse effects, and tolerability, while delivering cardiovascular protection, particularly in transplanted patients with the phenotype of MS.

Similarly as described in the general population, MS and PTDM were strongly associated in our patients. PTDM has been described in up to 25% of renal transplant recipients.[22] We found that among the 39 patients with MS, 12 (30.8%) developed PTDM, a finding that compromised the inclusion of this variable in the logistic regression. The nature of our study does not allow to establish any possible association of PTDM and renal and/or patient survival.

Most renal transplant recipients receive combinations or permutations of immunosuppressive drugs, including a calcineurin inhibitor (cyclosporine or tacrolimus), a mammalian target of rapamycin (mTOR) inhibitor (sirolimus or everolimus), an antiproliferative drug (mycophenolate mofetil and azathioprine), and corticosteroids. Cyclosporine and tacrolimus can induce glucose intolerance, hypertension, and hyperlipidemia. Sirolimus can induce hyperlipidemia. Corticosteroids can induce glucose intolerance, hypertension, hyperlipidemia, and weight gain. Thus, used alone or in combination, these medications likely contribute to MS in renal transplant recipients.[23,24]

The lack of association between the use of immunosuppressive medications and MS in this study is probably due to the inclusion of patients long after the renal transplant surgery (median time of follow-up was 56 months), a period of greater clinical stability and lower dosage of immunosuppressive drugs.

There are few data correlating MS and graft function in renal transplant recipients. De Vries *et al*. studied the association between MS and GFR in renal transplant recipients in two moments after transplantation: at the end of the first year (baseline) and at the mean time of six years. There was no significant difference between the GFR of groups, with and without MS at baseline, but more marked reduction of renal function in patients with MS was noted over time.[7]

Porrini *et al*. identified lower estimated GFR in renal transplant recipients from deceased donors in both the baseline (the end of the first year of transplantation) and at the end of follow-up (three years on average after the transplant).[4] In the present study, a single evaluation of GFR was performed at a median follow-up of 56 months, and there was no association between the occurrence of MS and worse renal graft function. This observation holds true even when we divide the sample into two groups, based on the median time of follow-up after transplantation. However, it is important to recognize that the cross-sectional nature of this study cannot evaluate the possible negative

impact of MS on graft renal function over time, as previously mentioned.[4,7] Besides, the use of creatinine or its blood clearance as surrogate endpoint may be misleading. Nankivell *et al*. showed that renal allograft function may underestimate the histological development of chronic renal allograft dysfunction.[25]

The present study has limitations. As the study was cross-sectional in design, directions of causality could not be inferred. Furthermore, the number of studied patients was relatively small. The assessment of renal function was based on estimated GFR using the MDRD equation, which has not yet been definitively validated in renal transplantation. In addition, the generalizability of our results to a broaden population of renal transplant recipients remains limited, as our study was confined to one transplant center. Finally, components of MS were weighed equally in the NCEP-definition, but both prevalence, impact, and even cut-off points of each component may vary substantially among racial groups, an aspect which was not explored in our study.

In summary, MS showed high prevalence in the population of renal transplant recipients studied, and it was directly associated with older age; use of beta-blockers, particularly propranolol; and PTDM. Further monitoring of these patients will allow assessment of the impact of MS on renal graft and patient's survivals.

References

1. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: Mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol 2007;2:550-62.
2. Salaroli LB, Barbosa GC, Mill JG, Molina MCB. Prevalence of metabolic syndrome in population-based study, Vitória, ES-Brazil. Arq Bras Endocrinol Metabol 2007;51:1143-52.
3. Reaven GM. Banting Lecture: Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
4. Porrini E, Delgado P, Bigo C, *et al*. Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. Am J Kidney Dis 2006;48:134-42.
5. Pérez-Flores I, Sánchez-Fructuoso A, Calvo N, Valga EF, Barrientos A. Incidence and risk factors for the metabolic syndrome and posttransplant diabetes in renal transplant recipients taking tacrolimus. Transplant Proc 2010;42:2902-4.
6. Luan FL, Stuckey LJ, Ojo AO. Abnormal glucose metabolism and metabolic syndrome in non-diabetic kidney transplant recipients early after transplantation. Transplantation 2010;89:1034-9.
7. de Vries AP, Bakker SJL, van Son WJ, *et al*. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. Am J Transplant 2004;4:1675-83.
8. Ozdemir FN, Karakan S, Akqul A, *et al*. Metabolic syndrome is related to long-term graft function in renal transplant recipients. Transplant Proc 2009;41:2808-10.
9. Souza FCM, Silva MI, Motta EM, *et al*. Prevalence of risk factors for cardiovascular disease in Brazilian renal transplant recipients. Transplant Proc 2007;39:446-8.
10. Friedewald WT, Levy RJ, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
11. Levey AS, Bosh JP, Lewis JB, *et al*. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
12. Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2006;112:2735-52.
13. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356-9.
14. Chen J, Munter P, Hamm LL, *et al*. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol 2003;14:469-77.
15. Pinto-Sietsma S, Navis G, Janssen W, *et al*. A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis 2003;41:733-41.
16. Naganuma T, Uchida J, Kinoshita Y, *et al*. The prevalence of metabolic syndrome in Japanese transplant recipients. Nephrology 2007;12:413-7.
17. Babio N, Bulló M, Martinez-González MA, *et al*. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. Nutr Metab Cardiovasc Dis 2009;19:563-70.
18. Buckland G, Salas-Salvado J, Lia Roure E, *et al*. Sociodemographic risk factors associated with metabolic syndrome in a Mediterranean population. Public Health Nutrition 2008;11:1372-8.
19. Black HR, Sica DA. A modern perspective on beta-blocker use in hypertension: clinical trials and their influence on clinical practice. J Clin Hypertens (Greenwich) 2007;9:10-8.
20. Mancia G, De Backer G, Dominiczak A, *et al*. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87.
21. Sharma AM, Pischon T, Hardt S, *et al*. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. Hypertension 2001;37:250-4.
22. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation 2006;82:603-11.
23. Yabu JM, Vincenti F. Kidney Transplantation: The Ideal Immunosuppression Regimen. Adv Chronic Kidney Dis 2009;16:226-33.
24. Padiyar A, Akoum FH, Hricik DE. Management of the kidney transplant recipient. Prim Care Office Pract 2008;35:433-50.
25. Nankivell BJ, Borrows RJ, Fung CL, *et al*. The natural history of chronic allograft nephropathy. N Engl J Med 2003;349:2326-33.