ORIGINAL ARTICLE

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Graft function and cardiovascular risk in renal transplantation

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SUMMARY

Despite progress over the last decade, morbidity and mortality in renal transplantation remains high, and several studies have highlighted the role of chronic graft dysfunction in the development of atherosclerosis.

Aim: To evaluate the prevalence of risk factors and cardiovascular disease in transplant recipients with good graft function.

Methods: We retrospectively evaluated 106 patients who received a kidney transplant from a cadaveric heart-beating donor prior to December 1999 and who had a good graft function in December 2009. In this study, a good graft function was defined by a glomerular filtration rate greater than 60 ml/min/1.73 m^2, estimated by the Nankivell equation. Demographic, anthropometric, clinical and laboratory variables with known impact on cardiovascular disease were recorded.

Results: The mean age of the renal transplant recipients in December 2009 was 55.8±11.8 years. The overall mean time of follow-up was 14.4±3.7 years. Most patients´ immunosuppression regimen consisted of corticosteroids (62.3%) and ciclosporin (84.9%). At the final evaluation, 80% of patients had hypertension, 65% had a body mass index above 25 kg/m^2 and 79% did not have a recommended LDL-cholesterol value. The prevalence of smoking and hypertriglyceridaemia was 11% and 31%, respectively. Approximately 13% of patients in this study had clinical evidence of cardiovascular disease defined by the presence of ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or heart failure.

Conclusion: This population presented multiple cardiovascular risk factors. The prevalence of cardiovascular disease in these patients was, however, less than expected, which may suggest the presence of protective factors probably related to a good graft function.

Key-Words:
Cardiovascular disease; graft dysfunction; kidney transplantation.

INTRODUCTION

After the first successful kidney transplant in 1954, developments in immunosuppression regimens generated excellent short-term graft survival. However, there has been little or no improvement in long-term allograft survival.

According to literature, the main cause of renal graft loss is death with a functioning kidney, with cardiovascular disease (CVD) playing a leading role[1]. There is a scarcity of available data on the prevalence of CVD in renal transplant recipients, unlike in the population of haemodialysis patients, in which some studies show frightening prevalence rates, in the order of 30-60%[2].

In kidney transplantation, the major cardiovascular risk factors are similar to those of the general population:

diabetes mellitus, hypertension, obesity, dyslipidaemia and smoking. However, Ducloux *et al.*[3] showed that the Framingham score tends to underestimate the real cardiovascular risk in renal transplant patients, which suggests the influence of other factors. Some studies have identified factors related to uraemia, such as left ventricular hypertrophy, inflammation, hyperhomocysteinaemia, endothelial dysfunction and vascular stiffness, among others. While chronic renal graft dysfunction has been reported as an additional cardiovascular risk factor[4], its impact on the different cardiovascular events requires further characterisation.

PATIENTS AND METHODS

The aim of this study was to evaluate the prevalence of risk factors and CVD in kidney transplant recipients who had received a transplant more than ten years ago and who have good graft function, defined by an estimated glomerular filtration rate of more than 60 ml/min/1.73 m^2 (Nankivell equation). The data was collected from patients' clinical files in the last half of 2009. The selected patients are a part of several physicians´ patient lists. The authors evaluated each patient's demographic variables (gender, age), aetiology of chronic kidney disease, mean duration of renal transplant, immunosuppression, concomitant medication, proteinuria and cardiovascular risk variables (hypertension, posttransplant diabetes mellitus (PTDM), overweight, smoking and dyslipidaemia). The patients with a previous history of CVD prior to renal transplant were excluded (n=43). Hypertension was defined in this study by two blood pressure readings greater than 140/90 mmHg at the last visit and/or the taking of antihypertensive medication. A diagnosis of PTDM was based on fasting blood glucose levels exceeding 126 mg/dl and/or taking oral hypoglycaemic agents or insulin. Overweight was determined by a body mass index between 25 and 30 kg/m^2 and obesity by a value greater than or equal to 30 kg/m^2. The smoking variable corresponded to current or previous history of smoking. With regard to dyslipidaemia, the prevalence of high LDL-cholesterol and hypertriglyceridaemia was evaluated separately. Taking into account the American Heart Association recommendations, high LDL-cholesterol was defined by a value greater than 100 mg /dl and hypertriglyceridaemia by a level greater than 150 mg/dl.

The prevalence of CVD in this population was evaluated through the clinical evidence of ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or heart failure. For the detection of CVD, clinical records and results from additional diagnostic tests were used. All patients performed electrocardiography and echocardiography, according to the annual evaluation protocol of our Transplantation Unit. Additional tests were required based on more specific cardiovascular diseases symptoms and signs. Therefore, 16 patients underwent myocardial perfusion scintigraphy, 5 patients performed a lower limb Doppler ultrasound and a cerebral computed tomography was conducted in 3 patients.

The authors performed a descriptive analysis of the data using SPSS software (version 16.0, Chicago, IL, USA).

RESULTS

A total of 106 renal transplant recipients were enrolled with a mean follow-up of 14.4±3.7 years. There was a male predominance (56%). The overall mean age in the final evaluation was 55.8±11.8 years. All patients were on haemodialysis for an average time of 33.4±32.2 months (range: 4-136) prior to the renal transplant. At the final evaluation, most patients were treated with an immunosuppressive regimen that included prednisone (62%) and/or ciclosporin (85%). The median prednisone dose was 4.6±1.4 mg/day (min: 2.5; max: 10 mg/day). Prior to transplant, only one patient had type 2 diabetes mellitus (0.9%) and 29% were overweight or in obesity class I (Fig. 1). The long follow-up may explain some flaws in the patients' clinical data registration. For that reason, some variables such as hypertension, smoking and dyslipidaemia could not be assessed at the time of transplantation.

According to the criteria of the study, most patients (80%) were hypertensive, and only 44% had a controlled blood pressure at the final evaluation. Forty-eight patients (45%) were treated with an angiotensin converting enzyme inhibitor or an angiotensin II receptor antagonist. The majority of the patients (n=85) showed a proteinuria value less than 300 mg/24h. The mean 24h-proteinuria was 348±254 mg (range: 101-896 mg) for the subgroup of patients with cardiovascular disease and 255±411 mg (range:

10-2900 mg) in the subgroup without cardiovascular disease.

Being overweight was also significant, with only 34% of patients having appropriate weight for their height (Fig. 1).

In terms of lipid profile, 79% of patients had an increased LDL-cholesterol level, and 31% had hypertriglyceridaemia. Thirty-seven patients (35%) were treated with statins and one patient with fibrate. The prevalence of smoking was 12%. Twenty-one patients (19.8%) developed PTDM.

Fourteen patients (13%) developed clinically evident CVD, most of them with ischaemic heart disease (9 patients). There was no reported case of peripheral vascular disease (Fig. 2).

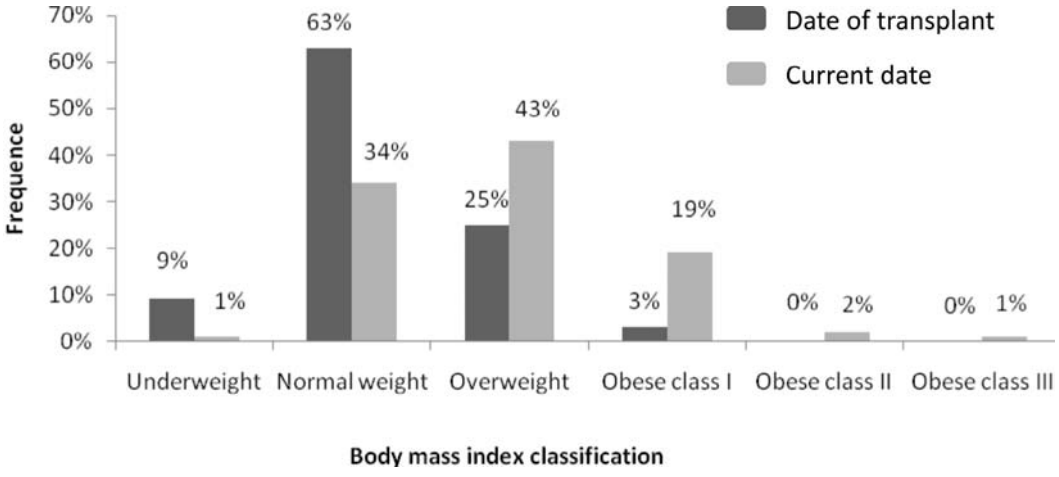

Figure 1

Body mass index classification at the time of transplant and at the current date.

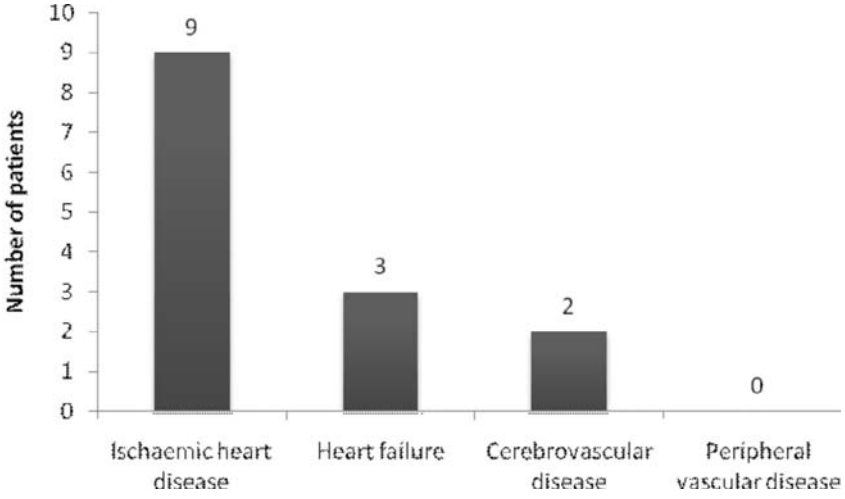

Figure 2

Clinical evidence of cardiovascular disease.

DISCUSSION

The relationship between renal graft dysfunction and the prevalence of CVD is well established in dialysis patients. The authors sought to assess the prevalence of cardiovascular risk factors in renal transplant recipients who had received the graft more than ten years ago and who have good graft function at present.

In the population studied, there was a high prevalence of hypertension, overweight and high LDL-cholesterol. These complications may be, in part, explained by the side effects of a prolonged immunosuppression time. Other studies have shown that ciclosporin is associated with hypertension and sodium and water retention through two mechanisms leading to a gain of body sodium: the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, and suppression of atrial natriuretic factor. This drug has also been implicated as a factor responsible for posttransplant dyslipidaemia, probably related to a retrocontrol change of the hepatic low density lipoprotein or to its receptor molecule occupation by ciclosporin[5].

In turn, corticosteroids also have well-known metabolic side effects. Corticosteroids lead to increased body weight by stimulating appetite, and, moreover, increase blood pressure by two distinct mechanisms. First, they promote renal sodium retention, leading to increased plasma volume, and also induce angiotensin II receptor, potentiating the vasoconstrictor effects of this hormone.

Systemic corticosteroid therapy is associated with insulin resistance, hyperinsulinaemia and increased hepatic lipoprotein synthesis. Previous studies have suggested that corticosteroids not only induce cardiovascular risk factors, but also act directly on the development and progression of atherosclerotic vascular disease. Some studies, such as Li Wei *et al.*[6] suggest that the proatherosclerotic effect is related to a dose of prednisolone (or equivalent) greater than 7.5 mg per day that is not regularly used in renal transplant patients as long-term maintenance therapy.

In 1979, the Framingham study showed the existence of an unequivocal association between diabetes mellitus and CVD in the general population. In renal transplantation, the new development of diabetes mellitus has a comparable impact as a cardiovascular risk factor[7].

In our study, the prevalence of PTDM was 19.8%, which is consistent with the experience of other renal transplantation centers (7.6-26.8%)[8]. With regard to dyslipidaemia, epidemiological studies that include renal transplant patients with and without renal graft dysfunction suggest a prevalence of hypertriglyceridaemia between 13 and 38%[9], which is similar to the prevalence value found in this population analysis.

Regarding the determination of the overall prevalence of CVD in other groups (general population, chronic renal failure in the early stages and transplant recipients), the authors cannot make comparisons, due to the scarcity of available data. In addition, the epidemiological studies published in this area focus selectively on each cardiovascular complication, which hampers an integrated and comprehensive assessment of the subject.

It was shown that in industrialised countries, CVD is strongly related to age, affecting approximately one quarter of the population over 65 years of age. With regard to ischaemic heart disease, European studies have found a prevalence in the general population between 40 and 70 years of age in the order of 7%[10,11].

In 1999, Mosterd *et al.*[12] calculated a prevalence of heart failure of 3.9% in the population over 55 years of age, while more recent studies, such as that of Sánchez *et al.*[13] in 2008, found prevalence rates of around 8%. For cerebrovascular disease, other epidemiological studies show a prevalence of 1.4-4.5% in the population over the age of 50 years, reaching 7.5% in individuals over 65 years old[14].

Other data from the literature points to prevalence rates of specific concern; in particular, data published in 2006 by the British Heart Foundation revealed a joint prevalence of ischaemic heart disease and cerebrovascular disease (in individuals between 45 and 64 years) of 17.1% in men and 7.1% in women, respectively. With regard to peripheral vascular disease, several studies report a prevalence of 2-5% in the population between 50 and 70 years of age, which could amount to 37% in diabetic patients[15].

It is accepted that the later stages of chronic kidney disease (CKD) are associated with a high prevalence of CVD[16]. In stages I and II of CKD, the work of Culleton, 1999[17], Henry, 2002[18] and Leoncini, 2004[19] and his collaborators has shown an association between these two entities. There is no data available in the literature on the prevalence of CVD in these stages.

Regarding renal transplant recipients, Marcén *et al.*[20] published in 2006 a retrospective analysis of 2382 recipients of cadaveric kidney (with and without renal dysfunction), with an immunosuppressive regimen that included ciclosporin, and a prevalence of ischaemic heart disease of about 7% was estimated, a rate similar to that found in our study. The prevalence of heart failure and cerebrovascular disease in our study was 2.8% and 1.9%, respectively.

This is clearly below the results of published series, which include patients with and without renal dysfunction, that suggest a ten-year prevalence of 12%[21] and 8%[22], respectively. Peripheral vascular disease is common in patients on renal function replacement therapy[23,24] and it is associated with an increased risk of death, regardless of the cause. Snyder *et al.*[25] reported a prevalence of 20% and 5% of peripheral vascular disease in renal transplant patients with and without diabetes mellitus, respectively. In our study, there was no evidence of peripheral vascular disease with clinical translation, which may suggest the importance of the relationship between graft function and progression of atherosclerotic disease.

The overall prevalence of CVD in our study was 13%, well below that found in the series of chronic renal failure patients on dialysis, but curiously similar to the estimated prevalence for the general population in the sixth decade of life. The low prevalence of CVD found in this study, which appears to be associated with a good graft function, confirms the reason we consider transplantation the best renal function replacement therapy. Given the combination of risk factors which are highly prevalent in the transplant population, associated with the side effects of immunosuppression, more cardiovascular complications could be expected. Rather, the lower prevalence of CVD suggests that a good graft function protects against the progression of atherosclerosis in these patients.

CONCLUSION

CVD is the leading cause of death in renal transplant recipients. The assessment of classic risk factors for this entity should be routine in these patients, regardless of the degree of graft function.

The present study focussed on a population with multiple cardiovascular risk factors, but in which the prevalence of CVD was lower than expected. The findings in this study suggest that graft function may be an independent factor that contributes decisively to the maintenance of cardiovascular status by influencing the progression of atherosclerosis.

This proposes the presence of protective factors probably associated with good renal graft function. The identification of these factors may contribute to the development of new therapeutic regimens (or a better adaptation of existing ones) to prolong the survival of transplant patients. Furthermore, the use of a regimen that includes cardiovascular protection may contribute to increasing the duration of the renal graft.

Conflict of interest statement. None declared.

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