Original Article

Cardiovascular Disease and Risk Factors in Candidates for Renal Transplantation

Luís Henrique Wolff Gowdak, Flávio Jota de Paula, Dante Marcelo Artigas Giorgi, Marcelo Luís Campos Vieira, Eduardo Moacyr Krieger, José Jayme Galvão de Lima
São Paulo, SP - Brazil

Objective

To determine the prevalence of cardiovascular disease (CVD) and traditional risk factors in patients with chronic renal failure undergoing evaluation for inclusion on the renal transplantation list.

Methods

One hundred ninety-five patients with dialytic chronic renal failure underwent clinical evaluation and complementary tests and were compared with a group of 334 hypertensive patients paired for age. The Framingham equations were used for calculating the absolute risk (AR). The relative risk (RR) was calculated based on the absolute risk of the low-risk Framingham cohort.

Results

Thirty-seven percent of the patients had some sort of cardiovascular disease on the initial evaluation, peripheral vascular disease (23%) being the most prevalent. Patients with cardiovascular disease were excluded. Regarding traditional risk factors, a significant difference was observed in systolic blood pressure and total cholesterol (greater in the hypertensive group), and in the prevalence of men, diabetes, and smoking, which were greater in the chronic renal failure group. The latter had a greater degree of left ventricular hypertrophy, lower diastolic blood pressure, and a lower prevalence of familial history of cardiovascular disease and obesity. The relative risk for cardiovascular disease in patients with chronic renal failure was greater compared with that in the Framingham control population, but it did not differ from that observed in the group of hypertensive individuals.

Conclusion

The prevalence of cardiovascular disease and traditional risk factors is high among candidates for renal transplantation; the Framingham equations do not adequately quantify the real cardiovascular risk, and other risk factors specific for that population should contribute for their greater cardiovascular risk.

Key words

cardiovascular disease, risk factors, renal transplantation

InCor and Hospital das Clínicas of the FMUSP
Mailing address: Luís Henrique Wolff Gowdak - Av. Dr. Eneas de Carvalho Aguiar, 44 - 10º And. - Bl II - Cep 05403-000
São Paulo, SP, Brazil - E-mail: luis.gowdak@incor.usp.br
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Those who receive renal transplants have an extremely elevated rate of cardiovascular complications, particularly, those due to coronary artery disease [1]. This phenomenon may result from the combination of progression of the cardiovascular disease present on transplantation and the disease that precipitates after transplantation [2]. The relative importance of each mechanism has not been elucidated, but should undergo the influence of both clinical and epidemiological characteristics of the candidates for transplantation, and the care with the existence and extension of cardiovascular disease is investigated prior to surgery. Therefore, detailed cardiovascular investigation is currently considered one of the most important steps in pretransplantation evaluation and a fundamental measure for reducing morbidity and mortality associated with renal transplantation. It should necessarily include, in addition to the diagnosis of ongoing cardiovascular disease, the identification of the major determining factors of cardiovascular risk.

Regarding the last aspect, cardiovascular risk factors observed in chronic renal patients comprise the following: 1) the so-called traditional cardiovascular risk factors, ie, those also observed in the general population; 2) those peculiar to chronic renal patients, such as the increase in the calcium-phosphorus product, high levels of Lp(a), and hyperhomocysteinemia[3-5]; 3) those that, although present in the general population, acquire greater relevance in uremic patients. The prevalence of traditional risk factors in chronic renal patients undergoing dialytic treatment has already been reported [6]. However, data referring to the prevalence of those factors in patients already waiting on the transplantation list are scarce. These patients differ from the population of chronic renal patients because they had already been preselected by the transplantation teams that exclude the most severely ill patients. Consequently, conclusions derived from the former do not necessarily apply to the latter. Information about the risks of patients on waiting lists for transplantation are particularly important for those considered to have a greater probability of developing complications, such as older persons and those with diabetes.

Therefore, this study aimed at determining the prevalence of cardiovascular disease and traditional and nontraditional risk factors in a group of patients undergoing clinical evaluation for inclusion on the waiting list for renal transplantation.

Methods

The study protocol was approved by the scientific and ethics committees of the institutions involved. From January 1998 to October 2003, 273 patients with dialytic chronic renal failure

and age ≥ 50 years were referred to InCor for pretransplantation cardiovascular evaluation the Renal Transplantation Unit of the Hospital das Clínicas. All individuals had already undergone a preliminary investigation to eliminate those whose clinical conditions clearly contraindicated transplantation, such as neoplasia, active infection, or advanced stages of systemic diseases. The following patients were excluded from the study: those who refused to take part in the study (n=2); those who did not meet the specifications of the protocol (n=8); and those whose data were incomplete (n=68). After signing the written informed consent, 195 individuals were included in the study (fig. 1). The causes of chronic uremia were diabetes (n=69, 35%); nephrosclerosis (n=48, 26%); interstitial nephropathy (n=14, 7%); glomerulonephritis (n=8, 4%); polycystic disease (n=9, 4%); and undetermined (n=47, 24%). Patients had been undergoing hemodialysis for 48±30 (median, 39) months. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or both, or use of antihypertensive medication. Diabetes was defined as fasting glucose level > 126 mg% on at least 2 occasions or current use of antidiabetic agents.

In regard to pre-existing cardiovascular disease, all patients underwent clinical assessment, routine laboratory and radiological tests, in addition to electrocardiography and transthoracic echocardiography with color flow mapping. Clinical evidence or evidence deriving from complementary tests of current or previous cardiovascular disease (chronic coronary heart disease, or myocardial infarction, or both, heart failure, stroke, arteriopathy, as well as catheter or surgical procedures in the coronary, carotid, or peripheral vascular territory) were actively investigated.

For determining the absolute cardiovascular risk in 10 years, the Framingham equations [7], which consider age, sex, systolic blood pressure, total cholesterol, smoking, and diabetes, were used. The HDL-cholesterol levels were not included in the present study. The Framingham score is used for calculating the risk for individuals with no clinical manifestation of cardiovascular disease[7]; so, 72 patients in whom cardiovascular disease was identified were excluded.

The control group comprised 334 patients with primary arterial hypertension and no clinical evidence of cardiovascular disease, who were followed up in the hypertension unit of InCor during the same period. The control group was paired for age with the chronic renal group, but differed from the latter due to the presence of normal renal function (defined as serum creatinine < 1.5 mg/mL). These patients were chosen due to the observation that almost all chronic renal individuals are also hypertensive, and to the fact that all hypertensive individuals had undergone an equivalent clinical and laboratory evaluation by the same medical team. In addition, both groups were also analyzed and compared in regard to the prevalence of the following factors capable of influencing the occurrence of events, which are not taken into consideration by the Framingham score: creatinine; diastolic blood pressure; heredity (defined as history of early cardiovascular disease among first-degree family members); obesity (BMI ≥30); presence of left ventricular hypertrophy on the echocardiogram (defined as left ventricular mass index > 134 g/m^2 for men, and 110 g/m^2 for women [8]); and left ventricular mass index.

The relative risk was calculated dividing the absolute risk of each group of patients by the absolute values of the Framingham low-risk group [9]. Regarding the statistical analysis, the results were expressed as mean ± standard deviation, and, when necessary, median. The significance level adopted was $P<0.05$. The groups were compared by using the nonpaired 2-tailed Student *t* test or the chi-square test, as indicated.

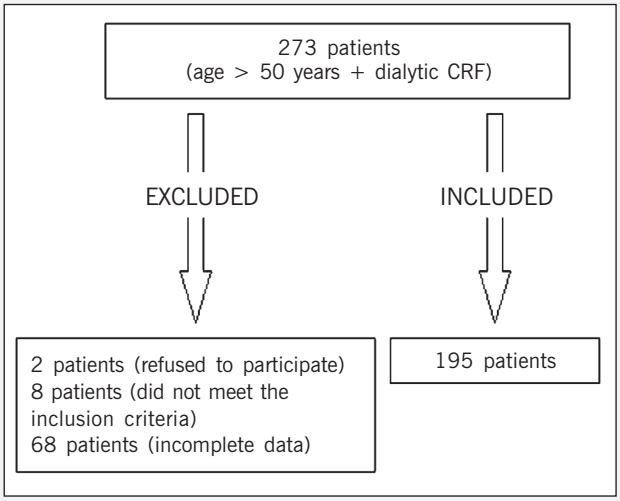

Fig. 1 - Selection of patients.

Results

Table I shows the prevalence of cardiovascular disease observed in the candidates for renal transplantation on the initial evaluation. Of the 195 patients, 72 (37%) were identified as having some sort of current or previous cardiovascular disease. The most frequent finding was peripheral vascular disease (23%). In our sample, the prevalence of history of myocardial infarction, stroke, and congestive heart failure did not exceed 10%. Eight (4%) patients had already undergone myocardial revascularization procedures before their inclusion in the study.

The remaining 123 candidates for renal transplantation with no clinical evidence of cardiovascular disease were compared with primary hypertensive patients regarding the prevalence of factors that could influence the occurrence of cardiovascular complications after transplantation (tab. II). Regarding the independent risk factors included in the Framingham equations, we observed that both groups had similar mean ages. They differed in systolic blood pressure and total cholesterol levels ($P<0.001$), which were more elevated in hypertensive individuals. The male sex, diabetes, and smoking ($P<0.001$) prevailed in chronic renal patients. In regard to other risk factors, we observed that the prevalence of hypertension was comparable in both groups. Body mass index, diastolic

Table I - Cardiovascular disease in candidates for renal transplantation (n=195)

Variables	n	%
Peripheral vascular disease	46	23
Stroke	19	10
Myocardial infarction	16	8
Heart failure	18	9
Myocardial revascularization	8	4
Patients with one or more alterations	72	37

blood pressure, and the prevalence of obesity and family history of early cardiovascular disease were significantly more elevated in hypertensive patients. On the other hand, serum levels of creatinine, left ventricular mass index, and the prevalence of left ventricular hypertrophy predominated in candidates for transplantation.

Tables III and IV show the estimates of absolute and relative cardiovascular risks in 10 years for 5 age groups in 2 groups of patients (men and women), respectively. The overall patients' risk was more elevated than that of the Framingham controls. The relative risk was not influenced by uremia, because chronic renal patients and hypertensive patients had similar relative risk independently of sex. On the other hand, sex influenced the risk over the different age groups. Among men, an approximate 80% increase in the absolute risk and a parallel reduction in the relative risk were observed in the 5 age groups in both groups of patients. On the other hand, in women, both the absolute and relative risks increased 3 times between the first and last quintiles in the chronic renal and hypertensive patients.

Discussion

Chronic renal failure is a very important public health problem. In the United States, a significant increase in the incidence and prevalence of that disease has been observed; the number of individuals treated with hemodialysis and transplantation exceeded 320,000 in 1998, and it is expected to reach 650,000 in 2010[10]. The finality of renal transplantation is to assure renal function normalization and prolonged complication-free survival. This objective has been partially frustrated by the elevated incidence of cardiovascular disease in transplanted individuals, which is considered of epidemic proportions. Recent data have shown that death with preserved renal transplant function is the most frequent cause of graft loss, and cardiovascular disease is the most frequent cause of death after renal transplantation[10]. Specialists have agreed that the existence of cardiovascular disease before transplantation is an important risk factor for the appearance of cardiovascular disease after transplantation. However, cardiovascular disease is often asymptomatic, especially in diabetic patients, a group particularly at risk for developing chronic renal failure. Therefore, the detection of cardiovascular disease and its risk factors in patients with chronic renal failure is mandatory before the patients' inclusion on the waiting lists for renal transplantation[11].

In the present study, in accordance with the concept that chronic renal disease is a risk factor for the development of cardiovascular disease[12], some sort of cardiovascular disease was found in more than one third of the individuals older than 50 years referred for cardiological evaluation before transplantation, with a predominance of peripheral occlusive arterial disease. In the Wave 2 Dialysis Morbidity and Mortality Study[13] with more than 4 thousand patients initiating dialytic therapy, 52% had some form of preexisting cardiovascular disease at the beginning of the dialytic program. A recently published study[14] by our team showed that obstructive coronary artery disease was present in 42% of the candidates for renal transplantation undergoing protocol coronary angiography indicated independently of the presence of symptoms. In that same cohort (unpublished data), we observed that 15 of 28 individuals with peripheral vascular disease also had coronary artery obstruction ≥ 70% on coronary angiography, a particularly important observation given the high occurrence of peripheral vascular disease in the current sample. As already mentioned, these data suggest that the events that occur after transplantation may be the result of either complications of cardiovascular disease present on the occasion of the surgery, or progression of preexisting disease. Due to the lack of studies on primary preven-

Table II - Traditional cardiovascular risk factors (numbers from 1 to 6) and others not considered by the Framingham score in candidates for renal transplantation and in individuals with primary hypertension with no evidence of cardiovascular disease

Variable	Candidates for renal transplantation (n=123)	Primary hypertensive individuals (n=334)	P
1. Age (years)	58±6	60±6	NS
2. Male sex (%)	67	32	<0.0001
3. Systolic blood pressure (mmHg)	173±29	180±30	<0.05
4. Smoking (%)	25	16	0.05
5. Total cholesterol (mg%)	187±48	217±43	<0.001
6. Diabetes (%)	28	15	<0.001
7. BMI (kg/m^2)	26±4	30±6	<0.001
8. Obesity (%)	15	34	<0.001
9. Familial history (%)	28	41	<0.05
10. High blood pressure (%)	95	100	NS
11. Diastolic blood pressure (mmHg)	100±16	113±18	<0.001
12. Left ventricular hypertrophy (%)	80	51	<0.0001
13. Creatinine (mg%)	8.6±2.3	1.0±0.2	<0.0001
14. LV mass index (g/m^2)	180±42	131±42	<0.0001

Table III - Estimates of absolute (%) and relative coronary risk in 10 years determined by the Framingham score in male candidates for renal transplantation and with primary hypertension

Age group (years)	Candidates for renal transplantation (n= 85)			Individuals with primary hypertension (n= 113)			Low Framingham risk
	n	Absolute risk	Relative risk	N	Absolute risk	Relative risk	Absolute risk
50 – 54	28	13%	2.6	25	12%	2.4	5%
55 – 59	24	15%	2.1	30	18%	2.6	7%
60 – 64	22	16%	2.0	26	19%	2.4	8%
65 – 69	9	20%	2.0	23	21%	2.1	10%
70 – 74	2	21%	1.6	9	22%	1.7	13%

Table IV - Estimates of absolute (%) and relative coronary risk in 10 years determined by the Framingham score in female candidates for renal transplantation and with primary hypertension

Age group (years)	Candidates for renal transplantation (n= 37)			Individuals with primary hypertension (n= 221)			Low Framingham risk
	n	Absolute risk	Relative risk	n	Absolute risk	Relative risk	Absolute risk
50 – 54	13	5%	1.0	58	5%	1.0	5%
55 – 59	6	9%	1.3	71	9%	1.3	7%
60 – 64	7	7%	0.9	44	10%	1.2	8%
65 – 69	9	21%	2.6	34	13%	1.6	8%
70 – 74	2	30%	3.8	14	16%	2.0	8%

tion of cardiovascular disease specific to the population with chronic renal failure, we understand that they constitute a high-risk population and that the current guidelines about modification in the risk factors should be used with the same strictness [1,12].

In regard to the "classical" risk factors in our case series of chronic renal failure patients with no evidence of cardiovascular disease, as compared with the hypertensive group, we found a greater predominance of the male sex, a greater prevalence of smoking, and a greater concentration of diabetic patients. These clinico-epidemiological characteristics *per se* already define a group of cardiovascular high-risk individuals, independently of the presence of uremia. The proportion of diabetic individuals in our case series was approximately 4 times greater than that found in the general Brazilian population [15], illustrating the importance of diabetes as a cause of or as a factor associated with chronic renal failure.

From the laboratory test point of view, the lower level of total cholesterol found in patients with chronic renal failure compared to the group of patients with primary hypertension is noteworthy. This is a frequent finding in the so-called uremic dyslipidemia, which is characterized by normal or reduced levels of total cholesterol and LDL-cholesterol, a reduction in the levels of HDL-cholesterol, and an increase in the level of triglycerides[16]. De Lima et al [17], studying the lipid profile of 75 patients undergoing hemodialysis, reported total cholesterol levels lower than those found in the control group of healthy volunteers paired for sex and age.

In regard to the cardiovascular risk, the greater prevalence of left ventricular hypertrophy and approximately 30% greater left ventricular mass index in patients with chronic renal failure compared with those in hypertensive patients are worth noting, despite the lower systolic and diastolic blood pressure levels. In addition to the pressure overload imposed on the left ventricle, the increase in arterial wall stiffness, the volume overload, and humoral factors contribute to the greater degree of left ventricular hypertrophy [18]. Its presence is known to be associated with ischemic heart disease and complex ventricular arrhythmias, and, consequently, with a greater rate of cardiovascular events [19,20]. This corroborates the notion that the group with chronic renal insufficiency is already exposed to a greater risk of future events when renal transplantation is indicated.

The relative risk, calculated by using the Framingham equation, was elevated in both groups and was always greater than 1.5 and 0.8 in men and women, respectively, in the 5 age groups. Several cross-sectional studies have suggested that the Framingham risk equations are not sufficiently powerful for quantifying the real cardiovascular risk in patients with chronic renal failure [21]. Our data indirectly confirm this impression because they show similar absolute and relative risks in both groups, independently of sex. Knowing that cardiac mortality is much greater in chronic renal individuals than in hypertensive individuals, we expected that that behavior would be reflected in greater risk rates in patients with chronic renal failure. This was not observed, despite the greater prevalence of smoking and diabetes among candidates for renal transplantation, suggesting that other factors present in uremia and not considered in the Framingham equations, such as left ventricular hypertrophy, may play a more significant role in determining the risk in chronic renal patients as compared with that in the general population.

In contrast with the above observation, which demonstrates that uremic status does not alter the Framingham risk compared with that in hypertensive individuals, the cardiac risk was clearly influenced by sex, as seen in the general population. Relative risk in women increased with age, while the inverse occurred in men. This phenomenon occurs because cardiovascular risk does not proportionally vary with age in both sexes, as can be confirmed by comparing the risks of men and women in the Framingham control population. However, one cannot forget that the small number of individuals with chronic renal failure limits the power of data analysis.

One limitation to be considered in calculating the absolute and relative risks in this study was not including the measurement of HDL-cholesterol levels, which was not routinely performed in the population studied. Knowing that patients with chronic renal failure usually have a decreased HDL-cholesterol fraction, one may assume that the cardiovascular risk determined by the Framingham equations may have been underestimated.

In conclusion, the prevalence of cardiovascular disease in patients with chronic renal failure who are candidates for renal transplantation is high. In addition, even after excluding patients with cardiovascular disease, the prevalence of classical risk factors is significant, as is that of others that may more adequately explain the real risk of future events in that population, a risk recognized as high.

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