Diabetes and coronary artery disease impose similar cardiovascular morbidity and mortality on renal transplant candidates

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Abstract

Background. In renal transplant candidates (RTC), diabetes and coronary artery disease (CAD) are commonly observed. However, whether diabetes imparts a cardiovascular risk equivalent to that of CAD and whether CAD adds to the cardiovascular risk associated with diabetes is unknown.

Methods. To assess the interplay between diabetes and CAD as a determinant of major adverse cardiovascular events (MACE), 288 high-risk RTC (56.4 ± 8.1 years old, 72% males) underwent a comprehensive cardiovascular evaluation including coronary angiography. Patients were divided into four groups based on the diagnoses of diabetes and CAD (> 70% narrowing), and followed up for 1–60 months (median, 17). The primary endpoint was the composite incidence of fatal/non-fatal MACE.

Results. During follow-up, 80 MACE occurred. Patients with diabetes (P = 0.03) or CAD (P < 0.0001) had a worse long-term prognosis. However, only in patients without diabetes was CAD associated with an increased incidence of MACE (10.6% vs 45.9%, P < 0.0001). In patients with diabetes, the endpoints were not different between those with and without CAD. No difference occurred in the long-term prognosis of patients with diabetes (with or without CAD) and patients without diabetes with CAD.

Conclusions. We concluded that in high-risk RTC, diabetes confers a cardiovascular risk comparable to that of CAD in patients without diabetes, independent of coronary obstruction. In patients with diabetes, concomitant CAD does not add to the already very high cardiovascular risk of this population.

Keywords: cardiovascular risk; coronary artery disease; diabetes; end-stage renal failure; renal transplantation

Introduction

Patients with chronic kidney disease (CKD) constitute a very special population regarding the prevalence and consequences of cardiovascular disease, with a large proportion of these patients presenting with diabetes, coronary artery disease (CAD), or both [1]. In the general population, because diabetes is one of the major risk factors for CAD [2], it is reasonable to consider the possibility that the increased cardiovascular risk associated with diabetes may be ascribed, in significant proportion, to the higher prevalence of CAD [3].

Investigations [4–6] regarding the impact of diabetes and CAD alone or together on the prognosis in the general population have shown that persons with diabetes without clinical evidence of CAD have as high a risk of major cardiovascular complications and cardiovascular death as do patients without diabetes but with CAD and that the risk is even higher for those patients with both conditions [4]. A limitation of these works is that subclinical CAD was not ruled out in patients with diabetes without prior clinical cardiovascular disease. Thus, it is possible that some individuals with diabetes who developed coronary events harboured significant asymptomatic CAD, which might help to explain why subsequent studies on the relationship between diabetes and CAD failed to replicate the above-mentioned results [7,8].

Because CKD and diabetes are major risk factors for cardiovascular and coronary diseases, it is not surprising that patients with diabetes with CKD have a high risk of cardiovascular events, in many cases attributed to CAD [9]. In the present work, we investigated the complex relationships among CKD, diabetes and CAD and their impact on the prognosis...
of high-risk haemodialysis patients, by using coronary angiography to establish the diagnosis of CAD. More specifically, we aimed to determine the prognostic effect of diabetic status without CAD; the effect of CAD in the absence of diabetes; and finally, the effect associated with the presence of both on the incidence of major adverse cardiovascular events (MACE) and the cardiovascular mortality in this select population. The main issue addressed was whether the presence of diabetes modifies the effect of CAD (and vice versa) once the main outcomes have been accounted for.

These are important questions, for they will influence therapeutic strategies and the diligence with which the diagnosis of CAD should be pursued in patients who are diabetic with CKD, taking into account the low sensitivity and specificity of non-invasive coronary testing in this population [10,11], a reason for many groups to advocate coronary angiography to be performed directly for all patients with diabetes awaiting renal transplantation [12,13].

**Subjects and methods**

**Patient selection**

The Institutional Ethics Committee approved this prospective cohort study. All patients provided written informed consent. Beginning in January 1998, 288 renal transplant candidates (RTC) were screened for cardiovascular disease before inclusion on the transplantation waiting lists. All patients underwent a comprehensive cardiovascular investigation, including coronary angiography performed regardless of symptoms or results of non-invasive tests. Inclusion criteria were the presence of at least one of the following: (i) diabetes (type 1 or 2); (ii) cardiovascular disease defined by the presence of angina, previous myocardial infarction or stroke, left ventricular dysfunction, or extracardiac atherosclerosis or (iii) age ≥50 years.

**Study protocol**

Patients underwent clinical evaluation (physical/history) with special attention to a history of or overt cardiovascular disease. Laboratory tests, ECG, and echocardiography were performed as described elsewhere [11]. Additionally, coronary angiography was routinely performed in all patients, regardless of the presence of symptoms or signs, or both, suggesting coronary disease. Significant coronary disease was visually defined as lumen reduction ≥70% in one or more of the epicardial arteries by two independent experts. Diabetes was diagnosed according to the American Diabetes Association Guidelines [14]. Glycated haemoglobin was not routinely performed in all patients during follow-up. Patients were divided into four groups based on the diagnoses of diabetes (yes/no) and significant CAD (yes/no). During a mean follow-up of 22 months (1–60 months; median, 17), 67 patients underwent kidney transplantation and, for statistical analysis, were censored at the time of transplant.

The primary endpoint was the composite incidence of fatal/nonfatal MACE defined by the occurrence of myocardial infarction, unstable angina, myocardial revascularization procedures (surgical/percutaneous), sudden death, stroke, peripheral vascular disease, or heart failure, as defined by the World Health Organization [15]. The secondary endpoint was mortality from cardiovascular causes.

**Statistical analysis**

Data analyses were performed with a commercially available statistical program (JMP for Windows—version 6.0.0, SAS Institute Inc., Cary, NC, USA). The results are presented as means ± SD or percentages. The differences among the groups were assessed with Fisher’s exact test (for categorical data), or the two-tailed Student’s t-test (for continuous data) for independent samples, when appropriate. Univariate and multivariate Cox regression models were used to investigate the association of diabetes/coronary disease and cardiovascular events. Kaplan–Meier survival analysis was performed to compare the probability of event-free survival among groups. Statistical significance was set at P < 0.05 and all P-values are two-sided.

**Results**

**Demographic data**

Patients were on haemodialysis for 41.6 ± 38.6 months (median, 34). The mean age was 56.4 ± 8.1 years, 71.9% were men and 68.1% were Caucasians. Classic risk factors for cardiovascular disease included dyslipidaemia (44.5%), smoking (26.7%), diabetes (39.6%), hypertension (93.1%) and overweight/obesity (60.8%). History of or overt cardiovascular disease was found as follows: previous stroke (12.5%), previous myocardial infarction (9.4%), angina (28.5%), symptoms of heart failure (6.9%) and evidence of peripheral arterial disease (29.9%).

Table 1 summarizes clinical characteristics of patients according to the diagnoses of diabetes and significant coronary disease at baseline. In the overall population, diabetes was associated with shorter time on dialysis, greater body mass index and greater prevalence of peripheral vascular disease, lower diastolic pressure and lower serum creatinine. In the overall population, significant coronary disease was associated with ethnicity (Caucasians), shorter time on dialysis, lower serum creatinine, higher fasting glucose level and atherosclerotic disease (peripheral vascular disease and myocardial infarction).

In non-diabetic subjects, those with significant coronary disease were older, and more likely to be Caucasian and have a history of peripheral vascular disease or myocardial infarction. Among subjects with diabetes, a history of myocardial infarction was the only association found with significant coronary disease.
Cardiovascular events

Eighty fatal/nonfatal cardiovascular events (primary endpoint) occurred during the 5-year follow-up, the majority (66%) occurring in subjects with significant coronary disease (Table 2). Table 2 shows the incidence and relative risk of those events in relation to the presence of significant coronary disease at baseline in patients with and without diabetes. In the overall population, those with significant coronary disease at baseline or diabetes had a worse long-term prognosis, with a higher incidence of MACE and a trend towards greater overall and cardiovascular mortality. Interestingly, however, only in subjects without diabetes was significant coronary disease associated with an increased incidence of MACE and an increased mortality (overall and cardiovascular). In subjects with diabetes, both primary and secondary endpoints were not different between those with or without significant coronary disease. Thus, in spite of the close associations between coronary disease and events in the overall population and the higher prevalence of coronary disease in patients with diabetes, the increased incidence of events in this group could not be attributed to concurrent coronary disease. Death from cardiovascular causes (secondary endpoint) was twice as high in non-diabetic patients with significant coronary disease (67 vs 32%, Table 2).

Table 3 shows the results of a Cox proportional-hazards model comparing the incidence of fatal/nonfatal cardiovascular events in subjects with diabetes and non-significant coronary disease with that of non-diabetic patients with significant coronary disease at baseline. The unadjusted hazard ratio was not significantly different from 1.0 (hazard ratio = 1.11; 95% CI = 0.81–1.54), pointing out that these groups have similar cardiovascular event rates. Adjusting for age, sex, race, dialysis duration, creatinine and glucose levels, did not significantly alter the results.
Figure 1 shows the Kaplan–Meier curves for the cumulative survival probability free of cardiovascular events (fatal/nonfatal). Non-diabetic patients without significant coronary disease at baseline had the best prognosis with a 72% cumulative event-free survival in 5 years. Patients with diabetes or coronary disease, or both, had an event-free survival of <25% in the same period. No difference existed in the long-term prognosis of patients with diabetes (with or without significant CAD) and non-diabetic patients with significant CAD.

**Table 2.** Incidence of fatal/non-fatal major adverse cardiovascular events (MACE) during a 5-year follow-up in relation to the presence of significant CAD in subjects with and without diabetes subjects

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>All subjects</th>
<th>Non-diabetic subjects</th>
<th>Diabetic subjects</th>
<th>Hazard ratio for diabetic subjects (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD &lt;70%</td>
<td>10.6</td>
<td>4.59</td>
<td>6.07</td>
<td>1.11 (0.81–1.54)</td>
<td>0.52</td>
</tr>
<tr>
<td>CAD ≥70%</td>
<td>39.7</td>
<td>27.0</td>
<td>66.7</td>
<td>1.35 (0.80–2.28)</td>
<td>0.32</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>29.4</td>
<td>19.5</td>
<td>0.32</td>
<td>1.35 (0.80–2.28)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Discussion**

The purpose of the present investigation was to answer, firstly, whether diabetes, even in the absence of significant CAD, confers a risk of cardiovascular events comparable with that associated with CAD and secondly, whether additional CAD adds to the risk of diabetes in high-risk RTC, using coronary angiography as the ‘gold standard’ for the diagnosis of CAD.

We found that in high-risk RTC, diabetes confers a cardiovascular risk comparable with that of CAD in patients without diabetes, independently of coronary obstruction. Our data give an anatomical basis to the claim, based on clinical grounds, that diabetes mellitus and CAD are equivalent in terms of risk of future cardiovascular events. In patients with diabetes, concomitant CAD does not add to the already very high cardiovascular risk of this population.

The results of our study have important practical implications. Because, contrary to what has been shown in the general population, CAD does not add to the cardiovascular and total mortality risk of patients with diabetes, coronary angiography should be performed in diabetic subjects with CKD only for clinical/therapeutic reasons and not for risk stratification. On the other hand, in non-diabetic patients, coronary disease has an important impact on prognosis independently of clinical evidence of ischaemic heart disease, suggesting that the diagnosis of CAD must be clearly established in non-diabetic patients by using, if needed, coronary angiography to achieve better risk stratification.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio for diabetic subjects (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.11 (0.81–1.54)</td>
<td>0.52</td>
</tr>
<tr>
<td>Adjusted for age, sex</td>
<td>1.09 (0.80–1.51)</td>
<td>0.60</td>
</tr>
<tr>
<td>Adjusted for age, sex, race, dialysis duration, creatinine and glucose level</td>
<td>1.11 (0.74–1.73)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Table 3.** Results of Cox proportional hazards-model comparing the composite incidence of fatal/non-fatal cardiovascular events in 51 subjects with diabetes and non-significant CAD with that in 61 non-diabetic subjects with significant CAD, during a 5-year follow-up of a cohort of patients with end-stage renal disease

DM, diabetes mellitus; CAD, coronary artery disease; CV, cardiovascular; CI, confidence interval.
Others have investigated the relationship between end-stage renal disease, diabetes and cardiovascular mortality [16–18]. However, our study, which used an invasive strategy to rule out coronary disease, is the first to show that diabetes in the absence of significant coronary disease has the same adverse effect on prognosis as significant coronary disease in the absence of diabetes in high-risk patients with CKD.

The finding that CKD patients with diabetes spent a significant shorter time on dialysis at the entry of the study compared to non-diabetics may have led to an underestimation of the true prevalence of CAD and the incidence of cardiovascular events in the former subgroup. It is reasonable to speculate that, to a certain extent, there might have been a ‘natural selection’ process by which patients with diabetes and less-advanced forms of cardiovascular disease were included in this cohort. Their lower mortality was compared with patients with diabetes and more advanced cardiovascular disease, who were more likely to die in the first year after renal replacement therapy starts and then would obviously have been excluded from our cohort. In an article by Chantrel et al. [19], the tremendous cardiovascular burden and high mortality imposed on patients with diabetes entering dialysis was disclosed by the observation that, in their study comprising 84 consecutive patients with type 2 diabetes, 32% were dead (mostly for cardiovascular reasons) after a median follow-up of only 211 days from the start of renal replacement therapy.

The major limitation of our study is that we evaluated a select group of dialysis patients, considered at a particularly high risk of serious events, a precondition to justify the use of coronary angiography in all participants. Therefore, our findings, particularly those related to the incidence of events among diabetic individuals without significant CAD, may reflect the fact that our diabetic patients probably harboured a more advanced degree of systemic and cardiovascular alterations in comparison with diabetic patients in non-selected dialysis populations.

Consequently, our results must be interpreted within the context of our selection criteria. Given this provision, although our data cannot be extrapolated to the overall population starting dialysis, we believe the results are still relevant, because a large proportion of patients on dialysis fulfil the characteristics of the patients studied here. In the last decade, as reported by the USA Renal Data System [9], 78% of CKD patients at the time of onset of renal replacement therapy were ≥50 years of age, while 44% were diabetic patients or had cardiovascular disease (heart failure, 19%; chronic ischaemic heart disease, 15%; previous myocardial infarction, 5%; peripheral vascular disease, 9%; and cerebrovascular disease, 5%). Even so, further studies will be necessary to determine whether our results also apply to unselected patients with CKD on dialysis.

In conclusion, in high-risk RTC, diabetes and CAD confer comparable cardiovascular morbidity and mortality. The effects imposed by coronary disease and diabetes on prognosis appear to be largely independent of each other. In diabetic patients, concurrent coronary disease does not add to the already very high cardiovascular risk in this population. We believe that this message should reach those involved in the care of patients being considered as RTC so that an aggressive risk factor modification strategy, including life-style modifications and

Fig. 1. Kaplan–Meier estimates of the probability of fatal/non-fatal major adverse cardiovascular events (MACE) in patients with end-stage renal disease according to the diagnoses of diabetes (DM = yes/no) or significant CAD (CAD = yes/no) at baseline and during 5-year follow-up.
cardioprotective pharmacological intervention can be implemented, to change the long-term prognosis of high-risk patients with CKD and diabetes, even in the absence of significant CAD.

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Conflict of interest statement. None declared.

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