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Cardiovascular risk factors in predialysis patients: Baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study

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Cardiovascular risk factors in pre-dialysis patients: Baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study.

Background. Patients with end-stage kidney failure have a greatly increased risk of developing premature cardiac and vascular disease. However, little is known about the evolution of cardiovascular diseases in individuals with less severely impaired kidney function.

Methods. The prevalence of cardiovascular diseases and of suspected cardiovascular risk factors was studied in a group of 369 individuals (median age, 63 years, 67% male) with various degrees of impaired kidney function (calculated creatinine clearances 6 to 105 mL/min), in 103 patients with angiographically proven coronary artery disease, and in 103 apparently healthy individuals. These patients are being followed prospectively.

Results. Of those patients with kidney disease, 34% had a history of vascular disease and 21% had left ventricular hypertrophy on electrocardiogram at baseline. Traditional risk factors were prevalent, with a history of hypertension in 76% of kidney disease patients, diabetes in 15%, and dyslipidemia with reduced low-density lipoprotein (LDL) cholesterol, elevated serum triglycerides, and decreased high-density lipoprotein (HDL) levels. Other possible cardiovascular risk factors include elevated concentrations of plasma homocysteine, as well as low serum albumin and hemoglobin levels. Patients with more severely impaired renal function had lower diastolic blood pressures, lower LDL and HDL cholesterol levels, were more anemic, and had higher plasma homocysteine concentrations.

Conclusions. Vascular disease and left ventricular hypertrophy are prevalent among patients with chronic kidney disease not requiring dialysis. In addition to traditional risk factors, other features of the uremic syndrome such as anemia, hyperhomocysteinemia, and inflammation (suggested by hypoalbuminemia) may contribute.

With the widespread availability of renal replacement therapies, cardiovascular disease has emerged as the leading cause of premature death among individuals with chronic kidney disease [1]. Even at the onset of dialysis, about one third of patients have clinical manifestations of congestive heart failure, one quarter have angina, and about 10% have a history of myocardial infarction [2]. These observations suggest that such conditions become established early in the course of chronic kidney failure. The Chronic Renal Impairment in Birmingham (CRIB) study set out to investigate the relationship between kidney function and cardiovascular risk factors in a cohort of patients with chronic kidney failure not requiring renal replacement therapy (CKD group). For comparison purposes, two control groups, unselected for renal function, were also studied; one comprised overtly healthy individuals with minor medical complaints (HI group), and the other, patients with angiographically-proven coronary artery disease (CAD group) [3].

Key words: anemia, cardiovascular disease, chronic kidney disease, hyperhomocysteinemia, inflammation, left ventricular hypertrophy.

METHODS

Chronic kidney disease patients with a serum creatinine greater than 1.47 mg/dL (130 μmol/L) and the two age- and sex-matched control groups were recruited [3]. Medical history, medications, height, weight, and blood pressure were documented, venous blood samples were collected, a 12-lead electrocardiogram was recorded, and evidence of left ventricular hypertrophy (LVH) sought using the Sokolow-Lyon criteria. Total cholesterol and triglyceride were assessed using standard techniques, high-density lipoprotein was measured directly, and low-density lipoprotein calculated using the Friedewald equation. Plasma homocysteine was analyzed by reverse-phase high performance liquid chromatography with coulometric detection. Discrete and continuous variables were compared using Chi-squared and unpaired *t* tests, respectively. Relationships between correlated parameters were assessed using regression methods. Differences and trends in variables with respect to level of kidney function were assessed by analysis of variance and rank correlation among quintiles of serum creatinine.

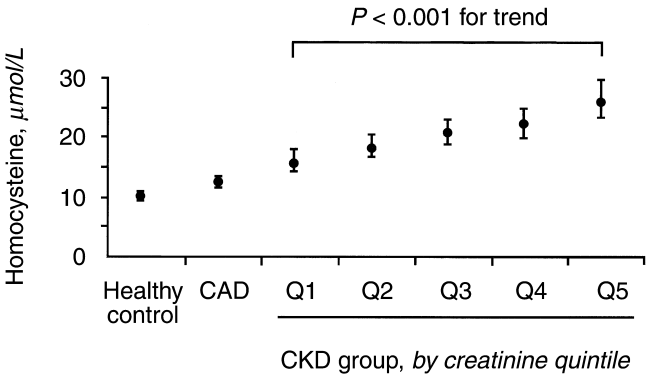

Fig. 1. Homocysteine concentrations (mean ± 95% CI) in healthy controls, coronary artery disease (CAD), and chronic kidney disease (CKD) patients. Concentrations are stratified by quintile of serum creatinine (median Q1 = 1.92 mg/dL, Q2 = 2.31 mg/dL, Q3 = 2.98 mg/dL, Q4 = 3.79 mg/dL, and Q5 = 6.32 mg/dL).

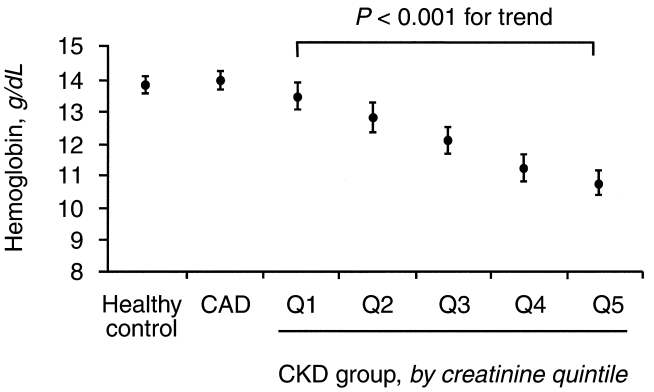

Fig. 2. Hemoglobin concentrations (mean ± 95% CI) in healthy controls, coronary artery disease (CAD) patients and chronic kidney disease (CKD) patients stratified by quintile of serum creatinine.

RESULTS

Of the CKD group, 34% had vascular disease and, while the prevalence increased with age, the proportion was similar across all five quintiles of kidney function. Left ventricular hypertrophy was identified on electrocardiogram in 21% of these patients as compared to 9% in the CAD group ($P < 0.01$) and 4% in the HI group ($P < 0.001$), with a higher prevalence among those individuals with more advanced renal impairment (test for trend $P = 0.01$). Among the CKD patients, prevalent traditional risk factors included diabetes mellitus in 15% (CAD 10%, P = NS, HI 6%, $P < 0.05$) and hypertension in 76% (CAD 49%, P = NS, HI 30%, $P < 0.001$). A similar proportion of patients in all three groups were past or present smokers (CKD 61%, CAD 70%, HI 56%). Body mass index was lower in the patients with kidney disease than in the CAD group ($P < 0.05$), and 76% of the CKD patients were hypertensive compared with 49% in the CAD group (P = NS) and 30% of overtly healthy individuals ($P < 0.001$). While systolic pressure was similar at all levels of kidney function, diastolic pressure was lower in CKD patients with more severe renal impairment (test for trend $P = 0.001$) and was associated with a wider pulse pressure (test for trend $P = 0.05$). These results are likely to be confounded by the use of antihypertensive medications since a larger number of drugs were prescribed to patients with more advanced kidney failure (test for trend $P < 0.001$). In contrast, lipid-lowering therapies were prescribed equally across the quintiles of kidney function (mean 18%, test for trend $P = 0.37$), and are unlikely to explain trends in dyslipidemia. Patients with kidney disease had lower LDL cholesterol levels than the HC group (130 mg/dL vs. 140 mg/dL; $P < 0.01$), lower levels of HDL cholesterol (46 mg/dL vs. 53 mg/dL; $P < 0.001$), and higher triglyceride concentrations (179 mg/dL vs. 113 mg/dL; $P < 0.001$). Increasing severity of kidney failure was associated with lower total cholesterol (test for trend $P < 0.001$), lower LDL cholesterol ($P < 0.001$), and lower HDL cholesterol ($P = 0.01$), but no difference in triglyceride concentrations ($P = 0.22$).

In addition to these traditional risk factors, we investigated the prevalence of other metabolic abnormalities implicated in the pathogenesis of cardiovascular disease in the context of chronic kidney failure. Plasma homocysteine levels were higher in CKD (mean 20.6 μmol/L) as compared to the CAD (12.3 μmol/L; $P < 0.001$) and HI (10.0 μmol/L; $P < 0.001$) groups. Patients with more severe kidney impairment had higher plasma homocysteine levels (test for trend $P < 0.001$; Fig. 1), despite more frequent use of folic acid and vitamin B preparations among the highest quintile of serum creatinine (22% vs. 10% in the other 4 quintiles; $P < 0.01$). Hemoglobin concentrations were lower among patients with kidney disease as expected (12.1 g/dL vs. 14.0 g/dL in CAD group and 13.8 g/dL in HI, both $P < 0.001$). Although the use of erythropoietin and iron were higher in the quintile with the most severe renal impairment, advanced renal failure was associated with a lower hemoglobin (test for trend $P < 0.001$; Fig. 2). In the CKD group, LVH was associated with more severe anemia, as well as a higher systolic blood pressure (Fig. 3). Finally, serum albumin concentrations were lower in patients with renal impairment (41.8 g/dL vs. 43.6 g/dL in CAD group and 44.1 g/dL in HI group, both $P < 0.001$), particularly in those with more severe renal impairment (test for trend $P < 0.001$).

DISCUSSION

These results confirm the high prevalence of cardiovascular diseases in patients with chronic kidney disease not requiring renal replacement therapy, and emphasize the potential for early therapeutic intervention to reduce morbidity and mortality in these individuals. Our findings are in keeping with other studies of cardiac and vascular disease among similar populations, even when

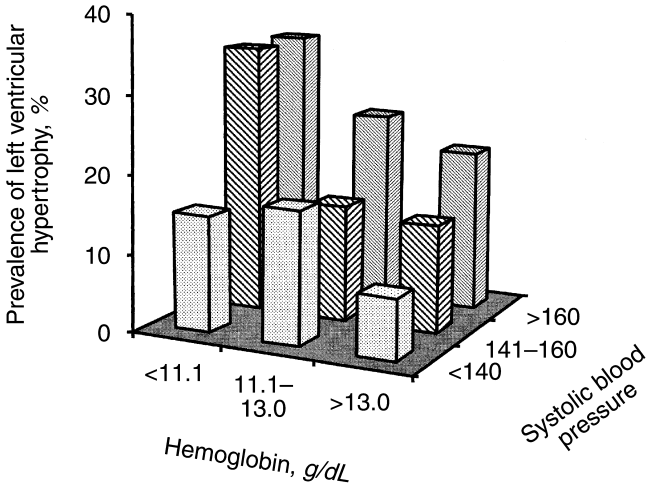

Fig. 3. Prevalence of left ventricular hypertrophy on electrocardiogram by Sokolow-Lyon criteria stratified by hemoglobin and systolic blood pressure.

LVH has been assessed by echocardiogram [2, 4]. While cardiovascular diseases may develop early in the course of chronic kidney failure, we cannot reliably determine the etiological importance of declining renal function to this process in this cross-sectional analysis. However, we are able to establish that these patients are exposed to a range of cardiovascular risk factors recognized to contribute to cardiovascular disease in the general population. As compared to age- and sex-matched controls without overt cardiovascular or renal disease, CKD patients were more likely to have diabetes, hypertension, and dyslipidemia. However, these patients were no more likely to smoke (or have a smoking history), had similar diastolic blood pressures, and lower LDL cholesterol concentrations when compared to the apparently healthy controls.

Whether or not these traditional risk factors explain the increased burden of cardiovascular disease in patients with impaired kidney function [5], our results demonstrate that patients are also exposed to other metabolic abnormalities that may contribute to both cardiac and vascular injury. These include hyperhomocysteinemia, an abnormality which correlates strongly with renal function and which other investigators have found to be associated with increased cardiovascular risk in populations with chronic kidney disease [6]. In addition, anemia is a recognized risk factor for the development of uremic cardiomyopathy [7] and was associated with the presence of LVH in this cross-sectional analysis. Finally, low serum albumin concentrations in these patients are likely to reflect activation of the inflammatory response. Reduced serum albumin and other markers of inflammation (such as elevated C-reactive protein) are associated with an increased risk of cardiovascular events, both in the general population [8], and in patients with chronic kidney disease on dialysis [9].

Although none of these risk factors have been proven to contribute to cardiovascular disease in patients with renal impairment, prospective follow-up of the CRIB cohort will help to identify those factors with a substantial impact on the development of cardiovascular events, although much larger studies will be required to identify more moderate associations. However, this cross-sectional analysis does demonstrate that, even in patients with relatively mild renal impairment, there is a substantial burden of cardiovascular disease along with changes in a number of traditional and putative cardiovascular risk factors. Since even minor degrees of renal impairment are associated with increased relative risk of cardiovascular disease and are relatively common [10], these observations raise the possibility that mechanisms responsible for the pathogenesis of aggressive cardiovascular disease in dialysis patients may be relevant to a much broader population.

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