The role of cardiovascular risk factors in uremia and hemodialysis patients

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Introduction

Despite great improvement in the clinical management of patients requiring chronic dialysis and the use of more sophisticated technology, morbidity and mortality secondary to cardiovascular disease continue to be high in the dialysis population [1]. Early studies suggested that accelerated atherosclerosis occurs in hemodialysis patients, however subsequent studies have questioned the validity of the conclusions drawn by these previous studies [2-6]. In this limited review we will attempt to suggest that those cardiovascular risk factors which are known to be adverse in the general population are present in those patients with progressive renal insufficiency and that they in fact precede the onset of frank uremia and the institution of dialysis. Multiple cardiovascular risk factors have been documented in uremic and in regularly dialyzed patients. In these populations the incidence of hypertension, hyperlipidemia, diabetes, and glucose intolerance is significantly increased [1, 7-9]. In patients without renal failure interventional trials designed to reduce cardiovascular risk factors have shown a clear benefit, by decreasing the incidence of morbid and mortal cardiovascular events [10]. In particular reduction of blood pressure, and of serum cholesterol, and smoking cessation are of significant benefit in reducing the morbidity and mortality from cardiovascular disease. Future observations in hemodialysis patients subjected to regimens to reduce cardiovascular risk factors should allow physicians to determine the likelihood of abating the high mortality and morbidity from cardiovascular disease in this patient population. Advances have occurred in nutrition, pharmacotherapeutics and psycho-behavioral programs, all of which will enhance our abilities to decrease the cardiovascular risk factor profile in the hemodialysis patient population. Further understanding of the basic pathogenesis of atherosclerosis should also contribute to reduce cardiovascular disease in the uremic and hemodialysis patient population.

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Hypertension as a cardiovascular risk factor

Epidemiologic studies have clearly established that hypertension, dyslipidemia, glucose intolerance and left ventricular hypertrophy (LVH) are major risk factors for cardiovascular disease in the population at large [11]. Again all of them frequently complicate the course of chronic renal disease [2, 7, 8]. In fact hypertension is very common in chronic renal disease and has been shown to accelerate the progression to end-stage renal failure. The etiology of hypertension in renal failure is probably multi-factorial [8]. Sodium and water retention secondary to a reduced glomerular filtration rate complemented by an increase in total peripheral resistance (TPR) appear to be pathogenetically important. The increased TPR is functional initially but with time becomes structural due to changes in the vascular architecture. These vascular changes are accentuated in patients who smoke and also in the chronic renal failure patients who have diabetes as the etiology of their renal disease. Evidence supporting the contribution of the renin-angiotensin system to the increased TPR of chronic renal failure has been variable particularly because plasma renin is often low or normal. However, it should be noted that a normal plasma renin may in fact be abnormally elevated in patients in whom an expanded plasma volume should result in a maximally suppressed renin-angiotensin system. The exact role that the renin angiotensin system (either humoral or vascular) plays in the hypertension of chronic renal disease and in vascular pathology remains to be elucidated.

Alterations in baro-receptor function and in the sympathetic nervous system may also contribuye to the hypertension of chronic renal failure [8]. These alterations often worsen in regularly dialyzed patients and contribute to their deficient hemodynamic adaptation to changes in blood volume during dialysis.

Ibels and others reviewed data from 574 patient years in renal transplant recipients. This group reported 100 deaths, 10 % of which were attributable directly to cardiovascular disease. Of particular note in this study was that the excessive number of cardiovascular deaths occurred in patients with hypertension. Five of 23 patients with chronic renal failure secondary to hypertension died of myocardial infarction compared with only six of 302 patients with chronic renal failure

due to other causes [12]. Subsequent studies have shown a similar trend; i.e. increased mortality in uremic patients on hemodialysis who are hypertensive [13].

Ikrum et al. in 1983 [4] studied 32 hemodialysis patients with coronary angiography and left ventriculography. The patients were being evaluated for renal transplantation. Interestingly in patients without evidence of cardiovascular disease by angiography there were no cardiovascular deaths in a seven year period. The patients with coronary artery disease, however, had higher blood pressures and left ventricular hypertrophy as has been previously reported.

Multiple clinical trials evaluating the intervention and therapy of hypertension have been completed [14].

Taken together the available evidence from most of the studies that have been performed shows clearly that antihypertensive treatment reduces the risk of stroke in patients even among those with mild hypertension, i.e. diastolic pressure of 90-105 mmHg. There is also evidence that cardioselective beta-blockers may offer some significant advantage over diuretic therapy and might actually lead to coronary artery disease prevention particularly at higher levels of blood pressure [14]. Currently there is no long term data reporting the effects of calcium channel blockers and angiotensin converting enzyme inhibitors effects of calcium channel blockers and angiotensin converting enzyme inhibitors on cardiovascular risk factors although it is expected in the future that major studies involving these drugs will show significant benefit.

It is also clear that the major benefit from blood pressure reduction is observed in those subgroups of patients at highest risk such as Blacks, and those with diastolic blood pressures above 100 mmHg, as well as in those patients with other cardiovascular risk factors i.e. diabetes, glucose intolerance, heritable factors and patients who are male. It should be noted however that, although lowering of blood pressure clearly results in significant reduction in cardiovascular events there could be some adverse effect of lowering the blood pressure too much, particularly in the elderly with coronary artery disease [14, 14a].

Abnormal glucose tolerance in cardiovascular events in the uremic hemodialyzed population

Abnormal glucose tolerance is associated with increased cardiovascular events in the general population [15]. Moreover, in recent years an association has been established between hyperinsulinemia, insulin resistance and hypertension [16]. In chronic renal failure peripheral insulin resistance frequently coexists with relatively impaired insulin secretion and abnormal glucose tolerance [7]. Epidemiologic studies have established that abnormal glucose tolerance significantly increases the risk for cardiovascular complications [15]. Patients with chronic renal failure have abnormal glucose tolerance. Mechanisms contributing to the glucose intolerance in these patients include insulin resistance, impaired insulin secretion, enhanced gluconeogenesis, reduced degradation of insulin and of glucagon [7]. Impaired insulin release occurs in patients with chronic renal failure and particularly in those on chronic hemodialysis.

The cause is unclear although an association with high levels of PTH resulting in accumulation of calcium in the pancreas has been proposed to be responsible for the impaired insulin release [17].

Hyperlipidemia as a coronary risk factor in chronic renal failure and hemodialysis patients

Uremic patients, nephrotic patients and renal transplant patients receiving chronic corticosteroid therapy have alterations in serum lipids [9]. Studies of uremic patients show hypertriglyceridemia in 32 to 51 %, decreased HDL levels in 50 to 70 % and increase in total cholesterolemia in 20 % of patients. There is evidence for abnormal apoprotein patterns and decreased lipoprotein lipase activity as the cause for low HDL production in these patients [9, 20, 21]. Attempting early intervention to reduce formation of the atheromata with lipid lowering agents may prove to be of some benefit. However this has not been tested at this time. Castelli et al. showed that decreased levels of HDL and increased levels of LDL are significant cardiovascular risk factors in the general population [10a]. Given that these changes are exacerbated in the hemodialysis population it is likely that they may contribute to the development of atherosclerosis in these patients [9, 22]. The reasons for these lipid changes in chronic renal failure are unclear although there have been suggestions that alterations in the endothelial and hepatic lipoprotein lipase and L-CAT production are important [9]. In patients with chronic renal failure the alterations in blood lipids are present early before uremia. Indeed, patients with creatinine clearances that are approximately 30 cc/min may already have altered lipoprotein patterns. A recent study showed that protein restriction decreases the rate of progression of renal failure in patients. However the salutory effect of this diet was not accompanied by changes in the serum lipids thus suggesting that arrest of progression of renal failure can be accomplished without significant changes in serum lipids. Thus, patients on low protein diets might continue to be at risk for cardiovascular morbidity and mortality due to vascular disease related to abnormal lipid profiles [20a].

Cigarette smoking in cardiovascular disease and in chronic hemodialysis patients

Many pathologic studies have shown that cigarette smokers have considerably more atherosclerotic disease than non-smokers. The effects on the heart and coronary arteries are also important examples of the cardiovascular pathophysiology of cigarette smoking[23]. It is also reported that smoking causes abnormal glucose metabolism in both animals and humans, however, there is no evidence that smokers are more likely to develop diabetes mellitus[24]. Cessation of smoking significantly reduces the excessive cardiovascular risks attributed to cigarette smoking. There has been some disagreement about how substantial this actually is and whether a reduction extends to all individuals and all of the related problems. Most investigators do agree however, that all physicians should encourage their patients to discontinue smoking cigarettes.

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