Coronary Artery Disease in End-Stage Renal Disease : Risk Factors and Treatment Strategies

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Dialysis and transplantation have afforded patients with end-stage renal disease effective renal replacement therapy. Advances in the therapies have included a better understanding of adequacy requirements, technological advances, and new pharmacological therapies such as Erythropoietin. Consequently, the number of patients initiating renal replacement therapies has grown around the world.

Cardiovascular events remain the most common cause of death amongst patients with end-stage renal disease. In most registries throughout the world, it is reported that between 35 and 50% of the mortality is attributable to a cardiovascular event^{1~4}). Compared to the general population, dialysis patients have a tenfold increased risk for annual mortality from cardiovascular disease. This increased risk is particularly dramatic for end-stage renal disease patients under the age of 45, but even in those patients over 85 years of age, there is a greater than 4 fold increase in the risk of cardiovascular death for dialysis patients⁵).

The types of cardiovascular disease found in patients with end-stage renal disease include coronary artery disease, left ventricular hypertrophy, hypertension, congestive heart failure, peripheral vascular disease, valvular disease and a variety of others including arrhythmias and infiltrative disease. This paper focuses on risk factors and potential treatment strategies for coronary artery disease (CAD) in patients with chronic renal insufficiency.

Table 1 Risk Factors for Coronary Artery Disease

1. Lipid profile including Lp(a)
2. Elevated homocysteine levels
3. Hyperinsulinemia
4. Abdominal obesity
5. Chronic inflammation
6. Advanced glycosylated end products
7. Oxidant stress
8. Calcium, phosphate and parathyroid hormone abnormalities
9. Adequacy of dialysis
10. Conventional risk factors such as eg. smoking

Amongst the various cardiovascular abnormalities in ESRD patients, coronary artery disease is the most important cause of morbidity and mortality. It is often confounded by the presence of left ventricular hypertrophy and may express itself as congestive heart failure, but as an underlying etiology for cardiac mortality, it is the predominant pathology. Furthermore, it is known that patients who initiate renal replacement therapy with pre-existing ischemic heart disease have a significantly worse prognosis than those without ischemic heart disease⁶). Thus, it is incumbent on the nephrology community to develop strategies for assessing and treating risk factors for ischemic heart disease both in the pre-dialysis phase and the dialysis phase of a patient's course.

Risk for Coronary Artery Disease

Table 1 summarizes known risks for coronary

artery disease in patients with end-stage renal disease.

Lipid Abnormalities in the End-Stage Renal Disease

Dyslipidemia is a well recognized complication of patients with end-stage renal disease. The lipid abnormalities differ for those patients undergoing hemodialysis compared to those on peritoneal dialysis⁷⁻⁹. Specifically, patients on hemodialysis characteristically have low HDL levels, elevated triglycerides, measurable oxidized LDL cholesterol, elevated Lp(a), and normal LDL cholesterol and apolipoprotein B levels. In contrast, patients on peritoneal dialysis usually have an elevated LDL cholesterol and APO B protein, elevated triglycerides, reduced HDL cholesterol, elevated Lp(a) and measurable oxidized LDL. Thus, those patients on peritoneal dialysis have a more atherogenic profile for lipoproteins than patients on hemodialysis.

The evidence is overwhelming that the treatment of lipid abnormalities, particularly the reduction of LDL cholesterol, is effective in improving outcomes with respect to cardiovascular disease in the non-uremic population¹⁰. Equivalent data is not available for the dialysis population. Current recommendations in Canada are that LDL cholesterol be reduced to less than 2.5 mmol/L in patients with known pre-existing coronary artery disease (secondary prevention) and to less than 3.5 mmol/L in others. However patients with 3 known risk factors for coronary artery disease are presumed to have subclinical disease and recommendations thus attribute those patients to a secondary prevention treatment strategy. Given the multiple risks that uremia imposes on our patient population, and given the known high prevalence of the disease, a reasonable argument can be made that all patients with chronic renal insufficiency should be treated for secondary prevention with respect to lipids.

Homocysteine

In the non-uremic population, elevated homocysteine levels have been associated with a higher mortality rate after acute myocardial infarction¹¹.

It is known that patients on dialysis and transplant patients have significantly elevated homocysteine levels and that these high levels are associated with cardiovascular events¹²⁻¹⁶. These elevations of homocysteine cannot be attributed to a difference in the distribution of phenotype for methylenetetrahydrofolate between uremic and non-uremic individuals. Patients on renal replacement therapies are resistant to therapy with folate and B12¹⁷, which in the non-uremic population can usually normalize the plasma levels of homocysteine.

Hyperinsulinemia and Abdominal Obesity

Hyperinsulinemia is an independent risk factor for coronary artery disease¹⁸. Abdominal obesity and insulin resistance with high insulin levels are often associated and is characteristic of patients with type II diabetes. Renal failure is known to lead to insulin resistance and thus hyperinsulinemia is frequent in patients with renal insufficiency¹⁹. Android, or abdominal obesity, with insulin resistance is associated with a number of lipoprotein abnormalities including hypertriglyceridemia, elevated Apolipoprotein B levels and reduced HDL cholesterol which when coupled with insulin resistance constitutes an important risk for the development of coronary artery disease. At least one report has shown that peritoneal dialysis increases abdominal obesity which may further exacerbate the problem²⁰.

Chronic Inflammation

Ridker reported that elevated C-reactive protein was an independent risk for myocardial infarction in the non-uremic population²¹. Dialytic therapy, particularly hemodialysis, induces a state of chronic inflammation in our patient population²². Bergstrom et al reported C-reactive protein as a more powerful predictor of mortality than albumin. There is also an association between C-reactive protein and elevated Lp(a) levels which may be important in the evolution of coronary artery disease²³.

Advanced Glycosolution End Products (AGE's)

Advanced glycosolution end products deposit in the vessels of patients with diabetes and in the peritoneum of patients on peritoneal dialysis. The excretion of AGE's are impaired as the renal function deteriorates. It may be important in contributing to oxidant stress, although the direct deposition into vessels in uremia unrelated to diabetes remains an uncertain, but potential risk for the development of atherosclerosis.

Oxidant stress

The ingestion of a high anti-oxidant diet is associated with less atherosclerotic disease in the general population²⁴). Uremia is associated with a high rate of formation of oxidants and may be another risk factor for the development of atherosclerosis²⁵). Oxidation of LDL is increased in uremia and is important in the formation of foam streaks.

Calcium, Phosphate and Parathyroid Hormone

Hemodialysis patients have been found to have markedly elevated cardiac calcification when measured using an electron beam CT technique²⁶). Furthermore, the coronary calcium score for patients on hemodialysis is dramatically higher than those levels found in patients with coronary artery disease. These high levels of cardiac and coronary calcium increases substantially with age and correlates with a long known phenomenon of dense calcifications seen in coronary as well as peripheral vessels of patients with uremia. More recently in the USRDS, hyperphosphatemia has been found to be associated with a higher general mortality in patients on hemodialysis²⁷). Specifically cardiac mortality is significantly increased in patients with phosphate levels greater than 6.5 mg/dl²⁸). This implicates the importance of abnormalities of calcium and phosphate in the evolution of calcific atherosclerosis. Foley et al have reported that patients with hypocalcemia and elevated alkaline phosphatase (and therefore presumably have ele-

vated parathyroid hormone levels) have a significant increase risk for de novo ischemic heart disease²⁹).

Adequacy

Patients with improved adequacy of dialysis have a reduction in their overall mortalities and this includes a significant reduction in cardiovascular mortality.

Conventional Risk Factors

Conventional risk factors such as diabetes, hypertension, positive family history and smoking have all been demonstrated to be relevant to increased risks of CAD in patients with chronic renal insufficiency. The cessation of smoking is particularly noteworthy since it is a modifiable risk factor for these patients³⁰).

Risk Factors : Summary

In summary, patients with chronic renal insufficiency have multiple risk factors for the development of coronary artery disease. Although the exact prevalence of coronary artery disease is not known, the US CASE MIX study reported that 40% of hemodialysis and peritoneal dialysis patients have clinical coronary artery disease³¹). In the 1998 Canadian Registry, coronary artery disease was present in 23.1% of the diabetic and 5.2% of the non-diabetic patients under the age of 45. In those over the age of 45, this increased to 56.6% of the diabetics and 45.8% of the non-diabetics³). In a detailed study of 400 dialysis and transplant patients followed at the Royal Victoria Hospital at McGill University, in May 1998, there was a prevalence of coronary artery disease of 60% in the dialysis population and 18% in the transplant population. When one combines the high risk profile of patients with chronic renal insufficiency together with a known high prevalence of the disease, it seems reasonable to adopt a treatment strategy for secondary prevention.

Current Treatment Practices for Ischemic Heart Disease

Data on current treatment practices for ischemic heart disease are sketchy in the literature. Based on the USRDS report in 1998, approximately 15% of patients on peritoneal dialysis and 8% of patients on hemodialysis were receiving anti-lipid therapy. In this same population, at least 40% of the patients had known coronary artery disease and the vast majority would have significant dyslipidemia. Thus, the current rate of treatment for dyslipidemia in the United States would appear to be less than that which would be recommended if secondary prevention strategies were used.

In a single centre study at the Royal Victoria Hospital, McGill University, Canada, prevalent patients on May 15th, 1998 were reviewed with regard to their coronary artery disease status and current treatments. Results are shown in Table 2. A total of 400 patients were reviewed which constituted the entire ESRD population at that institution. Patients who had died between May 15th and the date of chart review, new transplants and those with prolonged hospital courses were excluded. The latter two groups were excluded because their treatment on May 15, 1998 would likely not represent their usual treatments. Of those 400 patients, 147 were dialysis patients and 88 or 60% had ischemic heart disease documented in the chart. Forty-five of 208 transplant patients, or 18%, had coronary artery disease.

A review of their current medications revealed that 18% of the dialysis patients with ischemic heart disease were receiving an HMG CoA reductase inhibitor, 38% were receiving aspirin and 1% were receiving folic acid in excess of 1 mg/day. Amongst the transplant population, 38% of those with ischemic coronary artery disease were receiving an HMG CoA reductase inhibitor, 42% were receiving aspirin and none were receiving folic acid in excess of 1 mg/day. Therefore, consistent with the USRDS data, it would appear that the dialysis and transplant population in this centre were not receiving treatments which one would consider to be appropriate in the non-uremic population. No explana-

Table 2 Treatment of Coronary Artery Disease
Royal Victoria Hospital, Montreal, Canada

	Dialysis*	Transplant*
Number of patients	147	253
Number of patients with CAD	88	45
% of patients with CAD	60%	18%
% of patient with CAD on :		
• Antilipid therapy	18%	38%
• ASA	38%	42%
• Folic Acid > /mg/dl	1%	0%

* Prevalent patients on May 15, 1998

tion for these findings could be ascertained from the current study.

Conclusion

Patients with chronic renal insufficiency and end-stage renal disease have a high incidence of coronary artery disease and have many risk factors which predispose them to the disease. Treatment strategies need to be developed which will reduce this risk profile for these patients. Based on data from the USRDS and from a single centre study in Canada, it appears that nephrologists have not embraced the concept of treatment strategies for secondary prevention of coronary artery disease. There is no evidence to indicate that such strategies are effective in reducing coronary artery disease in this patient population, but until such time as the evidence is forthcoming, it would seem reasonable to give renal insufficiency patients the benefit of treatments known to be efficacious in the non-uremic population. Further studies are needed in the uremic population to assess the efficacy of such treatment strategies.

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