# Cardiovascular Risk in Chronic Renal Failure : Special Focus on Association with Calcium-phosphate Metabolism and Oxidative Stress

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Chronic renal failure (CRF) is characterized by a high prevalence of cardiovascular morbidity and mortality, compared with general population. Part of this high prevalence is explained by accelerated atherosclerosis. This topic will be the focus of my presentation. Atheromatous plaques of patients with chronic kidney disease (CKD) are generally calcified to a much higher degree than those of patients without CKD. The majority of studies aimed at reducing the progression of atherosclerosis used lipid-lowering therapeutic approaches designed to reduce serum total cholesterol and LDL-cholesterol and/or to increase serum HDL-cholesterol. Several clinical trials done in general population have demonstrated that it is possible to obtain a significant reduction of atheroma progression and cardiovascular events, in particular with the use of statins. Similarly, the progression of coronary calcification can be considerably reduced by statins[1]. However, the only prospective, randomised clinical trial aimed at examining the effect of statins on cardiovascular morbidity and mortality in CKD patients, namely the effect of atorvastatin in diabetic hemodialysis patients, failed to show a difference in cardiovascular outcome in the active treatment group, as compared to placebo group[2]. Several explanations have been given for this treatment failure, including too late an intervention in subjets with extensive cardiovascular lesions and the possible predominance of non-atheromatous cardiovascular lesions in dialysis patients.

It is probable that the pathogenesis of the particular type of atherosclerosis associated with CKD is more complex than in patients with no renal disease. It could mainly depend on factors other than cholesterol, as for instance inflammation, oxidative stress et disturbances of calcium and phosphorus metabolism. Since statins also exert a powerful anti-inflammatory action, in addition to their lipid-lowering effects, the implication of inflammation per se in the accelerated atherosclerosis of CRF does not appear to be the most important factor either. In recent years, several studies have suggested that oxidative stress and calcium and phosphorus abnormalities play a predominant role.

Potential involvement of oxidative stress. Boaz et al showed that vitamin E supplementation of chronic hemodialysis patients for nearly 2 years resulted in a significant reduction of composite cardiovacular events, compared with the administration of placebo[3]. Subsequently, Tepel et al showed that the supplementation of N-acetyl cysteine (NAC), compared with placebo, to chronic hemodialysis patients for 15 months also led to a significant reduction of composite cardiovacular events[4]. These two studies have been criticized because of small sample size and short duration. We have added experimental evidence to the findings by Tepel et al, using the apoE-/- mouse

model with superimposed CRF[5].

We gave NAC to these mice for 8 weeks and observed a significant decrease in atherosclerosis progression in the aorta. This effect was associated with a concomitant reduction of nitrotyrosine expression within the atheromatous plaques, demonstrating a decrease in oxidative stress.

Potential role of hyperphosphatemia. Epidemiological studies have suggested an association between hyperphosphatemia and cardiovascular mortality in chronic dialysis patients. Chertow et al[6] et Asmus et al[7] subsequently showed, in a prospective randmized trial, that the administration of the non-calcium containing phosphate binder sevelamer for one year and two years, respectively, was able to retard the progression of coronary and aortic calcifications in such patients, in comparison with calcium-containing phosphate binders. This study has been criticized because sevelamer lowers serum cholesterol at the same time it lowers serum phosphorus. We have subsequently shown, using the apoE-/- mouse model with superimposed CRF, that sevelamer's lipid-lowering action probably did not play a major role in preventing the progression of vascular calcifications in these animals[8]. We were further able to show that the administration of sevelamer to uremic apoE-/- mice led to a decrease in the occurrence of atheromatous lesions, in association with a reduction of aortic nitrotyrosine expression, similar to the observation with NAC.

In conclusion, recent studies suggest that oxidative stress and disturbances of calcium and phosphorus metabolism play an important role in the progression of atherosclerosis in CKD. The correction of these abnormalities may help to reduce the incidence and progression of atherosclerosis and vascular calcification.

## References


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