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Candidate Risk Factors for Cardiovascular Disease in CKD

The list of candidate risk factors in cardiovascular disease is enlarging and homocysteine is coming of age.[1] Homocysteine is a sulfur amino acid. Even small increases in its blood levels are associated with cardiovascular disease in the general population. In fact, many studies, both retrospective and prospective, have shown with few exceptions that hyperhomocysteinemia is an independent risk factor for cardiovascular disease in the general population. In a recent meta-analysis including 30 studies and more than 6,000 events, a 25% lower homocysteine level (a 3-μmol/L decrease) was associated with an 11% lower risk for ischemic heart disease and a 19% lower risk for stroke. Data were adjusted for regression dilution bias and known cardiovascular risk factors. It was concluded that homocysteine is a modest cardiovascular risk factor in healthy people. Nevertheless, the implications of decreasing homocysteine levels still could be substantial if the association is proven to be causal.[2] In fact, the C677T polymorphism example can teach us exactly this. The observed increase in risk for stroke among individuals homozygous for the MTHFR T allele is close to that predicted from the differences in homocysteine concentration conferred by this variant. This concordance is consistent with a causal relation between homocysteine concentration and stroke.[3] chronic kidney disease (CKD) is a pathologic condition with a high prevalence of both hyperhomocysteinemia and cardiovascular disease.

The cause of hyperhomocysteinemia still is unknown. Studies have shown that the most likely possibilities to explain hyperhomocysteinemia in uremia are impaired renal or extrarenal metabolism caused by uremic toxicity.[4,5] Consequences of hyperhomocysteinemia in uremia are, among other mechanisms, protein and DNA hypomethylation, with an accompanying alteration in the allelic expression of genes regulated through methylation.[6] Intervention trials are underway to test if hyperhomocysteinemia is related causally to cardiovascular disease in the general population and in uremia.[7] In the latter, low homocysteine levels can be an expression of malnutrition. Homocysteine levels can be lowered and only in selected cases normalized through B vitamin therapy, either with folates alone or with the addition of vitamin B_6, B_{12}, and possibly riboflavin. All in all, there is a lot that still is unknown about homocysteine, cardiovascular risk, and especially its genetic and epigenetic effects in CKD.

Hyperphosphatemia is one of the most frequent abnormalities in CKD and end-stage renal disease (ESRD) and its treatment has reduced uremic morbidity, however, its role in the pathogenesis of arterial calcification still must be defined. In fact, calcium phosphate, and parathyroid hormone are not related to coronary artery calcification and its progression in longitudinal and cross-sectional studies. However, guidelines recommend strict control of calcium x phosphate product and serum phosphorus to improve survival and quality of life.[8-10]

Treatment of ESRD is a matter of life and death because patients who are not treated with dialysis or a transplant will die. Therefore, it is understandable that a therapy for people who conquer their life everyday is psychologically demanding. However, little has been done for this. The psychologist/psychiatrist is not part of the team caring for the ESRD patient and even the most compassionate renal physicians continue to speak of noncompliant patients with cynical superficiality. They do not ask "why"?[11] There are few exceptions. For example, in Campania, southern Italy, a regional law has been approved in which dialysis units have to establish a stable link with mental health professionals.[12] The law, model in its uniqueness, indicates that we are reaching the critical mass of data, which will lead to the proper appreciation of the association between soul and body and hopefully patients also will receive appropriate help to survive the psychologic burden as well.

Quality of life is the true end point of therapy in CKD. Depression,[13] sleep disorders, and erectile dysfunction[14] affect the life of patients on maintenance dialysis. These patients undergo many losses including the capability to work and to support themselves and their families economically, and the liberty of free eating, drinking, and exercising. They also perceive a reduced level of quality of life, which we know is associated with morbidity and mortality. Unfortunately, the problem of optimal measurement of quality of life has not been solved because there is a need for strategies to be used at

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the individual level. The real challenge remains "to assess it in a meaningful way at the level of the individual patient."[15] This would enable the possibility of devising and using more effective intervention strategies to enhance quality of life and eventually to extend its quantity as well. It is interesting to note that a role for comorbidities has emerged,[16,17] which in turn calls for better assessment methods. Finally, it seems that sleeping disorders may affect CKD patients even at the early stages of their disease.[18]

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