Novel Cardiovascular Risk Factors in End-Stage Renal Disease

CARMINE ZOCCALI, FRANCESCA MALLAMACI, and GIOVANNI TRIPEPI
CNR-IBIM, Epidemiologia Clinica e Fisiopatologia delle malattie Renali e dell’Ipertensione Arteriosa, Reggio Calabria, Italy

Abstract. Traditional risk factors only in part explain the risk differential between the general population and the population of patients with chronic nephropathies. Uncontrolled hyperphosphatemia and high calcium phosphate product constitute risk factors for cardiovascular calcifications, cardiac ischemia, and adverse cardiovascular outcomes, yet inflammation may be an even more important trigger of vascular calcification than these metabolic derangements. Homocysteine predicts cardiovascular events in ESRD, but evidence that this sulfur amino acid is directly implicated in the high cardiovascular mortality of uremic patients is still lacking. It seems unlikely that Chlamydia pneumoniae is a major risk factor in dialysis patients because the association between anti-Chlamydia antibodies and incident cardiovascular events seems to depend largely on the confounding effect of some traditional risk factors. Oxidative stress and raised plasma concentration of asymmetric dimethylarginine (ADMA) are pervasive in ESRD, and high ADMA in these patients may be at least in part the expression of the high rate of generation of oxidants. ADMA per se seems responsible for a 52% increase in the risk of death and for a 34% increase in the risk of cardiovascular events in dialysis patients.

Cardiovascular risk in patients with ESRD has now gained center stage in clinical research. The interest on this issue is motivated by the striking risk differential for coronary heart disease between the dialysis population and the general population. The problem may be seen as the final, catastrophic consequence of a process that starts very early in renal diseases (1). Cardiovascular risk in renal insufficiency is perceived as an important public health problem, and preventing and curing cardiovascular complications in patients with renal dysfunction is considered a true priority (2). Prevention and treatment strategies demand precise knowledge of risk factors and of the possibility of modifying them with appropriate treatments.

This review focuses on the end-stage phase of chronic renal failure, i.e., the stage in which only secondary or tertiary prevention measures can be taken. The issue has been investigated intensively in the past 10 yr, and emerging evidence indicates that novel rather than traditional risk factors dominate the scene in this clinical condition. Here I only briefly touch on traditional risk factors and circumscribe the discussion to their relationship with inflammatory mechanisms. I then move the focus on vascular calcifications and alterations in calcium phosphate metabolism (i.e., on a risk factor peculiar to chronic renal failure) to end with emerging risk factors.

Atherosclerosis as an Inflammatory Disease: C Reactive Protein in Dialysis Patients

According to Ross’ theory (3), endothelial dysfunction is the initial event of atherosclerosis. Insults may be of various nature (e.g., metabolic, physical, infectious). As an expression of such dysfunction, the endothelium synthesizes and releases vasoactive and adhesion molecules, cytokines, and growth factors. Macrophages adhere to dysfunctional endothelium and then migrate into the arterial wall to become the key element in the formation and in the evolution of the atherosclerotic plaque.

In the general population, substantial evidence has been accrued that atherosclerosis underlies a systemic microinflammatory process and that serum C reactive protein (CRP) is a reliable risk marker of atherosclerotic complications. In patients with ESRD, serum CRP represents a strong predictor of death (4) and adverse cardiovascular events. As discussed in detail elsewhere (5), inflammation in ESRD is a multifactorial process, and it seems likely that this process, at least in part, mediates the effect of most traditional and nontraditional risk factors.

Inflammation, the Endothelium, and Hypertension Triggers

Hypertension is a complex phenotype because causative factors implicated in hypertension, such as angiotensin II, sympathetic activity, and chronic volume overload, besides triggering hypertension, exert inflammatory and growth-promoting effects on the cardiovascular system. Angiotensin II is a potent vasoconstrictor as well as a proinflammatory substance and a recognized growth promoter. Double transgenic rats that overexpress the angiotensinogen and renin gene display marked left ventricular hypertrophy. A similar process may be operative in ESRD disease because it has been shown
that left ventricular mass in these patients is directly related to plasma renin activity (6). Likewise, the sympathetic system is not only a major regulator of cardiovascular function but also an important control mechanism of the immune response and of inflammation (7). The interference of the sympathetic system with inflammation in cardiovascular diseases is exemplified by the observations that in a syndrome characterized by high sympathetic tone such as dilated cardiomyopathy, the plasma concentration of the inflammatory cytokine TNF-α is markedly raised and that β-blockers cause a substantial decrease in plasma TNF-α (8). Furthermore, very recent findings suggest that in patients with high CRP and stable coronary heart diseases, β-blockers reduce exercise-inducible myocardial ischemia (9). Norepinephrine is also a recognized growth promoter for myocardial cells. In this regard, it is interesting to note that in patients with ESRD, independent of BP, circulating norepinephrine is directly related to the muscular component of the left ventricle (the mean ventricular wall) (10) (Figure 1) and that it is a strong and independent predictor of cardiovascular death (11).

Chronic volume overload is a major cardiovascular stressor. In the long term, the deleterious effects of volume overload depend to an important extent on the fact that the hemodynamic burden activates a series of adaptive processes that modify profoundly the structure of the myocardium. An increased amount of fibroblasts and macrophages is commonly observed in the volume-overloaded, failing heart. Monocyte chemoattractant protein, an inflammatory protein, is overexpressed in cardiomyocytes of rats with volume-overload congestive heart failure (12). Overexpression of this protein does not represent a late event in this process because it is evident also in rats with compensated heart failure. Of note, stress-activated cytokines play a well-defined role in the functional and anatomical (left ventricular remodeling) adaptations to volume overload, and it is well demonstrated that TNF and IL-6 are overexpressed in the volume-overloaded, failing human myocardium (13). Fibrinogen is an acute-phase reactant of particular interest in relation to volume overload because evidence is emerging that this pro-coagulant protein is responsive to volume stimuli. Indeed, in hemodialysis patients who do not have systemic evidence of inflammation and display raised plasma volume, the synthesis rate and the plasma concentration of fibrinogen is increased (14). This increase has been interpreted as a physiologic response aimed at countering hemodilution and at restoring the plasma concentration of this protein (15). Because the plasma concentration of fibrinogen reflects two powerful cardiovascular-event triggers (inflammation and volume overload), it is expected that this factor is a strong predictor of adverse outcomes. In keeping with this hypothesis, in a recent analysis adjusting for other risk factors, a 200-mg/dl increase in plasma fibrinogen (the average difference in plasma fibrinogen between healthy subjects and dialysis patients) was associated with a 50% increase in cardiovascular risk (16).

Phosphate, Vascular Calcifications, and Inhibitors of Calcification

Uncontrolled hyperphosphatemia and high calcium phosphate product constitute risk factors for cardiovascular calcifications, cardiac ischemia, and adverse cardiovascular outcomes (17), yet alterations in phosphate and in calcium metabolism do not represent the sole cause of vascular calcifications in ESRD patients. Osteoclast-like cells are normally demonstrable in heart valves and in arterial vessels, and it is interesting to note that alkaline phosphatase activity in these cells is much enhanced when they are co-cultured with macrophages (18). This in vitro observation seems to be of importance because it provides a rational link between inflammation, derangements in calcium-phosphate metabolism, and vascular calcification. Osteoclast-like cells seem to be incorporated into bone-like lamellae in calcified lesions. Because this process is a true “ossification” of the vascular wall, it may involve an alteration in the balance between factors that promote calcification and those that inhibit the deposition of calcium salts. A relative lack of protective factors seems to be of relevance because vascular calcifications in ESRD have been linked to low levels of the calcification-inhibitor fetuin (19). Fetuin is an intriguing glycoprotein because it is a calcification inhibitor as well as an inverse acute-phase reactant (like serum albumin), i.e., it is markedly reduced during inflammatory processes. Of note, a low plasma concentration of this substance has been recently associated with a high rate of incident cardiovascular events in dialysis patients.

Hyperhomocysteinemia and Infections

Hyperhomocysteinemia and infections, particularly Chlamydia pneumoniae infections, have been implicated as potential triggers of atherosclerotic complications in patients with chronic renal diseases. Hyperhomocysteinemia was associated with high cardiovascular morbidity in two cohort studies in dialysis patients (20,21), and ongoing intervention trials will establish whether reducing the plasma concentration of this substance may improve cardiovascular outcomes in ESRD. In contrast, the role of Chlamydia pneumoniae in the high cardiovascular mortality in these patients remains uncertain because the association between anti-Chlamydia antibodies and incident cardiovascular events seems to depend largely on the confounding effect of some traditional risk factors (22).
Oxidative Stress and Asymmetric Dimethyl-Arginine

In this and another review (5), we examined in some detail the hypothesis that in patients with ESRD, several traditional and emerging risk factors may damage the cardiovascular system by inflammatory mechanisms. However, the high cardiovascular risk of ESRD may depend not only on a high burden of emerging risk factors such as homocysteine or high sympathetic activity but also on a relative lack of vasculoprotective factors.

Under normal conditions, nitric oxide (NO) is continuously generated in the endothelium by the enzyme NO synthase (NOS), which transforms L-arginine into NO and citrulline (Figure 2). NO has a protective role for the cardiovascular system because it inhibits vascular muscle cell proliferation, platelet aggregability, and the adhesion of monocytes to the endothelium. NOS can be inhibited by endogenous methylarginines, and asymmetric dimethylarginine (ADMA) seems to be the most important of these endogenous NOS inhibitors. ADMA is in part excreted by the kidney, but this compound is mainly disposed by transformation into citrulline, a reaction driven by the enzyme diethyl-diamino-hydrolase. Diethyl-diamino-hydrolase is present within the endothelial cells and is very sensitive to oxidative stress (23) (Figure 2). Oxidative stress is pervasive in ESRD (24); therefore, high ADMA in this condition may be the expression of the high rate of generation of oxidants. ADMA per se seems responsible for a 52% higher risk of death and for a 34% higher risk of cardiovascular events in dialysis patients (25). Besides predicting incident cardiovascular events, high ADMA is strongly associated with well-established risk markers such as increased intima-media thickness in the carotid arteries (26) and concentric left ventricular hypertrophy (27).

ADMA is a potentially modifiable risk factor. Treatments aimed at reducing oxidative stress or high doses of the NO precursor L-arginine constitute interesting opportunities for intervention on this putative risk factor. Perhaps further information on the role of ADMA in cardiovascular complications in ESRD will be gained as spin-off of trials aimed at reducing hypercholesterolemia, inflammation, and oxidative stress in uremics on chronic dialysis treatment like the 4D study (28).

References

15. Kayser GA, Dubin JA, Muller HG, Mitch WE, Rosales L, Levin NW; The HEMO Group: Impact of albumin synthesis rate and the acute phase response in the dual regulation of

Figure 2. Basic biochemical steps regulating nitric oxide synthesis.