Reassessing the Cardiac Risk Profile in Chronic Hemodialysis Patients: A Hypothesis on the Role of Oxidant Stress and Other Non-Traditional Cardiac Risk Factors

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Cardiovascular disease is the single largest cause of mortality in the general population (1) and, as such, it is not surprising that it is also the leading cause of mortality in chronic hemodialysis patients, accounting for nearly half of all deaths in this population in the United States (2). Numerous studies have described the high prevalence of atherosclerotic cardiovascular disease (2,3) and congestive heart failure in the ESRD population (4,5), with these entities accounting for a great majority of cardiovascular mortality in the chronic hemodialysis population.

The prevalence of cardiovascular-related deaths in the ESRD population is highest in the 65-year-and-older age group (approximately 150 cardiovascular-related deaths per 1000 patient-years at risk) (2), whereas, in the younger hemodialysis patient population (ages 20 to 44), the prevalence of cardiovascular-related death is less, but still substantial (40 cardiovascular deaths per 1000 patient-years at risk) (2). What is perhaps surprising is that as a percentage of total deaths, cardiovascular deaths are approximately equivalent across all age groups (Figure 1). Thus, although for older hemodialysis patients (≥65 years of age), cardiovascular-related death contributes to 45% of overall mortality, in the younger age bracket (20 to 44 years of age), cardiovascular death still contributes to 40% of all deaths in this group (2).

It is also important to note that whereas hemodialysis patients in general have a high prevalence of diffuse atherosclerosis, independent of age (6), autopsy studies in ESRD patients maintained on hemodialysis describe not only coronary and aortic atherosclerosis but also an 80 to 90% prevalence of left ventricular hypertrophy (LVH) (7,8). The factors contributing to LVH and atherosclerosis in these patients underlie cardiovascular pathology and cardiovascular-related death in this population. Therefore, understanding these factors and developing a strategy for limiting their effects may impact on the epidemic of cardiovascular disease among hemodialysis patients. Furthermore, it is clear that to achieve significant improvement in the high mortality rate so prevalent in ESRD, progress must be made in the prevention and treatment of atherosclerotic cardiovascular disease in this patient group.

Risk Factors for Cardiovascular Disease in the General Population

Epidemiologic studies in the general population have identified several factors that significantly influence the development of cardiovascular disease and atherosclerosis. These include hypertension, smoking, and hypercholesterolemia (9), all of which have a modulating influence on cardiovascular mortality, and are treatable. Other potential cardiac risk factors that have been identified in the general population include a positive family history for cardiovascular disease (9), LVH (10), elevated lipoprotein (a) [Lp(a)] (11), and, more recently, elevated serum homocysteine levels (12).

A number of recent advances delineating aspects of the pathogenesis of atherosclerosis have spurred a reassessment of these classical cardiac risk factors. In particular, studies have examined how altered endothelial (13) and vascular smooth muscle cell function (14) and circulating inflammatory leukocytes and platelets (15) affect the development of atherosclerosis. Increasing evidence also links the oxidative modification of lipids to the development of atherosclerotic plaques (16). Additional investigations suggest that Lp(a) and apolipoprotein(a) (17) act as independent risk factors in the development of atherosclerosis. Other works have focused on the potential role of homocysteine as an independent risk factor for atherosclerotic vascular disease (18). As we detail below, our advancing knowledge of the mechanisms underlying atherosclerosis may have particular relevance in understanding the accelerated atherogenesis associated with uremia and hemodialysis.

Risk Factors for Cardiovascular Disease in the ESRD Population

Although hypercholesterolemia is clearly associated with a significantly increased risk of cardiovascular-related disease and mortality in the general population, in hemodialysis pa-
patients, it is a low serum cholesterol that is associated with an increased relative risk of mortality (a 4.2-fold increase for cholesterol <100 mg/dL) (19). Very high serum cholesterol levels carry only a moderately increased mortality risk in ESRD patients (a 1.3-fold increased relative risk of death for cholesterol >350 mg/dL) (19). This suggests that the relative significance of cholesterol may be altered in the cardiac risk profile for ESRD patients.

A similar finding was noted when the association between hypertension and relative mortality risk was examined in ESRD patients. High blood pressure does not seem to increase the relative risk for cardiovascular-related mortality in hemodialysis patients, as suggested by Figure 2. Rather, low systolic blood pressure was associated with a significantly increased relative risk of mortality in ESRD (4,19) (Figure 2). This risk has been estimated to be increased 1.43 times for every 10-mm Hg decrease in mean arterial pressure (20) and appears to be as significant, if not more significant, than the association between elevated mean arterial blood pressure and increased rate of death in ESRD patients noted by Charra and others (21,22).

However, these two ends of the blood pressure spectrum may actually represent a graded relative risk for cardiovascular mortality risk in hemodialysis patients. Foley et al. (23) suggested that hypertension in dialysis-dependent patients has detrimental effects on the development of de novo ischemic heart disease and myocardial function. This results in cardiac failure, hypotension, and death. Such data raise important questions as to the continuum between optimal blood pressure control and long-term myocardial performance in hemodialysis patients.

**Oxidized Low-Density Lipoproteins (LDL)**

Dyslipidemia remains a prominent feature of ESRD. Lipid abnormalities—including hypertriglyceridemia (24), increased levels of very-low-density lipoproteins (VLDL) (25), intermediate-density lipoproteins (IDL) (26), triglyceride-enriched LDL (27), and low levels of high-density lipoproteins (HDL) (26)—have been described in chronic hemodialysis patients. However, recent data suggest that the oxidative modification of LDL may be an integral and necessary step for the development of atherosclerosis (28) (Figure 3).

![Figure 3](image-url)

*Low-density lipoprotein (LDL) can enter the arterial intima and be converted into mildly oxidized LDL by free radicals or oxidized lipids released from endothelium and smooth muscle. This form of oxidatively modified LDL may stimulate platelet-derived growth factor (PDGF) secretion and secretion of other chemotactic factors for monocytes (reprinted with permission from Leake DS: Effects of mildly oxidized low-density lipoprotein in endothelial cell function. *Curr Opin Lipidol* 2: 301–305, 1991).*
alterations in LDL induced by carbamylation may act akin to oxidized LDL and initiate or participate in atherosclerotic plaque formation (42).

The observations linking carbamylated or oxidized LDL to atherosclerosis in the general population may have direct relevance to hemodialysis-dependent patients. Several studies have documented the presence of oxidized LDL in chronic hemodialysis patients (43–46). Notably, Maggi et al. used in vitro copper oxidation to demonstrate a mild decrease in the lag phase and increase in the propagation rate of LDL in uremic and dialysis patients compared with normal control subjects (43). Other investigations have demonstrated an increase in products of lipid peroxidation in plasma and in lipoprotein fractions of ESRD patients on hemodialysis compared with normal control subjects (44–46).

These data have been questioned in studies from Sutherland et al. (47) and Schultz et al. (48), who found a different pattern for the LDL lag phase during copper ion-catalyzed oxidation and preserved antioxidant lipoprotein defense during hemodialysis, respectively. However, recent evidence suggests that there may not be a good correlation between LDL resistance to oxidative changes that promote atherogenicity (49). Thus, direct measurements of uremia-related oxidative changes to LDL in vivo are difficult to interpret. Conjugated dienes and malondialdehyde (MDA), products of lipid peroxidation, can diminish during the later stages of the peroxidation reaction, limiting their usefulness in evaluating oxidation products at any single point in time. Furthermore, lipid peroxidation products are commonly assayed in plasma samples, yet lipoprotein oxidation likely occurs in the milieu of an arterial wall or an atherosclerotic plaque rather than in the circulation, and scavenger receptors may clear oxidized lipoproteins from the circulation limiting their plasma half-life and, hence, their measurement.

To overcome some of these difficulties, an alternate approach using a murine monoclonal antibody that recognizes oxidized products of phosphatidylcholine has been examined (50). Using this technique, Itabe et al. (50) determined that oxidized LDL was increased more than eightfold in chronic hemodialysis patients compared with normal control subjects. Another method of assaying oxidatively modified LDL, measuring autoantibodies directed against MDA-modified LDL, takes advantage of the fact that significant titers of these autoantibodies are an independent predictor of progressive atherosclerosis (37). Chronic hemodialysis patients develop increased titers of autoantibodies against oxidized LDL in comparison to normal age-matched control subjects (51). Furthermore, hemodialysis patients develop autoantibodies with greater specificity for oxidized LDL than patients maintained on peritoneal dialysis. These data support the hypothesis that chronic hemodialysis patients display increased levels of oxidized LDL and that these modified lipids may play a significant role in accelerated atherosclerosis in these patients.

**Lipoprotein (a)**

The high cardiovascular mortality in ESRD patients emphasizes that patients with low serum cholesterol values actually
have an increased relative risk for cardiovascular-related mortality. Therefore, it is logical to conclude that other factors, in concert with lipid peroxidation, potentiate atherosclerotic cardiovascular disease in hemodialysis patients.

Selective alterations in lipid subsets may influence the development of atherosclerotic cardiovascular disease in chronic hemodialysis patients. A candidate lipoprotein, linked to atherogenesis in the general population, that may also play a role in cardiovascular disease in ESRD patients is Lp(a). Lp(a), a lipoprotein particle similar to LDL, contains an additional glycosylated protein, apolipoprotein (a) [apo(a)]. The atherogenicity of Lp(a) may be related to its ability to bind apolipoprotein B (apo B)-containing biproteins and be taken up by macrophages into early foam cells (52). Lp(a) accumulates in atherosclerotic plaque and can undergo further modifications, including oxidation. In fact, data suggest that Lp(a) is readily oxidized (53), which may contribute significantly to its atherogenicity. In addition, because apo(a) is structurally similar to plasminogen, it has been postulated that Lp(a) displays anti-fibrinolytic characteristics by interfering with the physiologic functions of plasminogen (54) (Figure 5). Lp(a)-induced inhibition of plasminogen activation can also stimulate vascular smooth muscle proliferation, thereby enhancing atherosclerotic plaque formation (55).

Multiple studies have examined the presumed link between increased serum Lp(a) levels and atherosclerotic cardiovascular disease in the general population (56). Studies in chronic hemodialysis patients have also described elevated Lp(a) levels, ranging from two- to threefold greater than in healthy control subjects (57). The physiologic basis for this increase may be a consequence of hepatic overproduction or diminished renal catabolism. Nevertheless, there appears to be a significant association between elevated Lp(a) levels and cardiovascular mortality in hemodialysis patients (53). Furthermore, hemodialysis patients with low-molecular-weight Lp(a) phenotypes may be even more susceptible to atherosclerosis (58). These data support the possibility that increased Lp(a) concentrations or alterations in Lp(a) phenotypes may be associated with increased cardiovascular mortality in hemodialysis patients. However, the role of Lp(a) subtypes and the mechanism linking Lp(a) to cardiovascular-related death remain important areas for further investigation.

Antioxidants in Uremia and Dialysis
Abnormal chronic oxidant stress and/or low antioxidant levels may also contribute to the high prevalence of atherosclerosis in the hemodialysis population. Large-scale studies in the general population have reported a decreased relative risk for fatal myocardial infarction in patients with the greatest beta-carotene or vitamin E dietary consumption (59,60). Large prospective randomized trials examining antioxidant dietary supplementation have been less conclusive, however, in establishing a reduction in the incidence of fatal myocardial events (61). Nevertheless, recent data suggest that vitamin E dietary supplementation may confer time-dependent benefits in reducing the progression of coronary artery atherosclerosis and the risks of major vascular events (62). In addition, prospective randomized trials have shown that patients receiving antioxidants or antioxidants plus lipid-lowering therapy demonstrated improvements in endothelium-dependent vasoreactivity (63,64). Such evidence suggests that antioxidant therapy may have direct effects in reducing the incidence of ischemic heart disease-related myocardial infarction and acute coronary syndromes.

Increased oxidant stress in uremia may simply be related to endogenous oxidant generation overwhelming reduced antioxidant levels. Oxidant activity is present in uremia, as evidenced by endogenous dialyzable oxidant activity (65) and advanced oxidation protein products in uremic plasma (66). Endogenous oxidant activity likely arises as a byproduct of acidosis and altered metabolism inherent in uremia (67). Moreover, in dialysis patients, reduced concentrations of endogenous antioxidants, e.g., vitamin C (ascorbate) and vitamin E (alpha-tocopherol) (68,69) may be inadequate to counter oxidant activity, thus favoring pathogenic oxidative stress. Endogenous antioxidants may be low in dialysis patients because of diminished oral intake, dietary restrictions, dialytic clearance, or as a result of increased degradation. In addition, the concentration of other antioxidants, erythrocyte superoxide dismutase and selenium, is decreased in patients receiving hemodialysis (70,71). Clearly, the balance between oxidizing activity and antioxidants is crucial for limiting oxidative stress and, in uremia, that balance appears to favor oxidative stress.

Role of Malnutrition in Cardiovascular Disease
A factor that may contribute to oxidant stress in dialysis patients is malnutrition. It is well established that malnutrition is highly predictive of death on dialysis (72,73). One potential...
link between malnutrition and dialysis-related cardiovascular death is the inverse relationship between low serum albumin levels and elevated Lp(a) levels in chronic hemodialysis patients (74). Although malnutrition could also result in inadequate levels of antioxidants, Ritz et al. (75) proposed that poor nutrition may increase the risk of dialysis-related cardiovascular mortality by altering the balance between endogenous vasodilatory and vasoconstrictive compounds, e.g., nitric oxide and asymmetric dimethyl-L-arginine (ADLA). ADLA, a low-molecular-weight, water-soluble, endogenous inhibitor of nitric oxide, accumulates in renal failure (76). Ritz et al. hypothesized that ADLA accumulation diminishes endogenous nitric oxide activity, predisposing to vasoconstriction and increasing the likelihood of myocardial ischemia (75). Furthermore, nitric oxide inhibition could potentiate vascular smooth muscle proliferation and enhance plaque formation as well (77). These ideas, although attractive in their simplicity, require further investigation before they can be accepted as a true mechanism for cardiovascular disease in the hemodialysis population.

Hypoalbuminemia, often cited as a manifestation of malnutrition in the ESRD population, also is associated with an increased risk for cardiovascular death in chronic hemodialysis patients. Foley et al., examining 432 ESRD patients, determined that hypoalbuminemia was associated with an increased risk of developing de novo ischemic heart disease (23) and a trend toward developing left ventricular dilation (78). The mechanisms underlying this association are still unclear and may relate to hypercoagulability in the setting of low serum albumin levels (79), alterations in lipid states (74), and a reflection of profound nutritional deficits in antioxidant levels. Additionally, it may relate to the ability of albumin to act as a scavenger for oxidative products. Thus, poor nutrition and/or low serum albumin levels by mechanisms as yet undetermined adversely affect cardiovascular-related mortality in chronic hemodialysis patients.

Role of the Dialysis Membrane in the Production of Reactive Oxygen Species

Why should hemodialysis predispose to changes in antioxidant activity? The simplest answer is biocompatibility. Biocompatibility can be defined as the sum of the interactions between blood and the hemodialysis circuit. When blood encounters the artificial components of the dialysis circuit, it initiates an "inflammatory response." Bioincompatibility occurs when these reactions are excessive and severe. The importance of this concept for hemodialysis patients lies in their repetitive exposure to the "non-self" structures of the dialysis circuit.

The close approximation between granulocytes and endothelial cell that occurs during the early phase of dialysis with cellulosic (bioincompatible) membranes dramatically increases H$_2$O$_2$ release from activated granulocytes (80). This setting of high ROS production and activated neutrophils in proximity to endothelial cells is a prototypical model for endothelial cell injury.

Oxidative stress during hemodialysis with cellulosic membranes has been correlated with increased levels of MDA and inversely correlated with glutathione peroxidase and erythrocyte superoxide dismutase activity (81–83). Enhanced antioxidant degradation or utilization may deplete antioxidant defenses in response to the oxidative stimulus generated by exposure to cellulosic membranes. Unfortunately, simultaneous measurements of oxidative stress (lipid peroxidation by-products) in conjunction with antioxidant levels are lacking in the majority of these studies, and few studies have measured the plasma concentration of oxidized LDL in hemodialysis patients. Two recent reports, however, demonstrated increased concentrations of lipid peroxidation byproducts in hemodialysis patients, compared with control patients (81,82). Exposure to cellulosic membranes in these studies appeared to augment the increase in lipid peroxidation byproducts.

Cellulosic membranes lead to increased ROS production via complement-dependent and complement-independent processes (80,84). Increased intracellular ROS production is evident in isolated phagocytes harvested during cellulosic dialysis (80). However, detailed analyses of ROS production during dialysis have been limited by available methodologies. The time necessary to isolate polymorphonuclear leukocytes (PMN) and the isolation techniques themselves may have affected the actual degree of leukocyte activation.

Improved methodologies have eliminated artifactual leukocyte activation and allowed for accurate measurement of intracellular granulocyte ROS production in whole-blood. ROS production, determined by these methods, increased maximally by 650% during dialysis with cellulosic membranes, coincident with the peak of complement activation. In contrast, non-complement-activating membranes (PMMA) displayed minimal ROS production. These studies support previous data suggesting that cellulosic membranes cause increased ROS in vivo (85,86), in contrast to biocompatible dialysis membranes (87).

Complement Activation and its Potential Effects on other Cellular Systems

Complement activation induced by exposure to cellulosic membranes has additional effects that may participate in the progression of atherosclerosis (Figure 6). Complement activation leads to the deposition of the membrane attack complex, C$_{5b-9}$, on platelet surfaces, exocytosis of $\alpha$-granule contents, and PDGF release (88,89). C$_{5b-9}$ also induces the expression of an activation-dependent epitope in GpIIb-IIIa on platelet surfaces and increases calcium entry into affected cells (90). C$_{5b-9}$ deposition on PMN stimulates the generation of leukotriene B$_4$ (LTB$_4$) and platelet-activating factor (PAF), which mediate platelet aggregation and activation (90,91). Furthermore, C$_{5b-9}$ augments endothelial cell secretion of high-molecular-weight multimers of von Willebrand's factor (vWF) and exposes their catalytic surfaces to the prothrombinase enzyme complex (92). Many of these events could occur concomitantly with acute coronary thrombosis (93) or, more likely, as a component of the long-term growth of an atherogenic plaque.

Gris et al. examined markers of endothelial function to determine the extent of endothelial activation in 22 patients undergoing chronic hemodialysis with cellulosic membranes (94). These patients had decreased levels of desmopressin-
induced release of tissue-type plasminogen activator, vWF, and serum albumin and increased concentrations of Type 1 plasminogen activator, fibrinogen, and thrombomodulin, in comparison with normal control subjects. These data suggest that endothelial activation and injury induced a state of endothelial hyperreactivity and potential hypercoagulability in these patients. As a result, abnormal endothelial vasoreactivity could exacerbate pre-existing ischemic heart disease in hemodialysis patients.

Figure 6. The spectrum of pathways activated by blood-membrane interactions mediated by cellulosic dialysis membranes (adapted from Hakim RM: Clinical implications of hemodialysis membrane biocompatibility. Kidney Int 44: 484–494, 1993).
patients, as it does in non-ESRD patients (95). In this regard, it is notable that antioxidant therapy alone (64) or in combination with lipid-lowering therapy improved aberrant arterial vasoreactivity in patients with coronary artery disease (65). This suggests that factors other than lipid reduction may be important for maintaining or improving normal endothelial vasoreactivity.

**Acute Phase Reactants**

The data from Gris et al. suggest that repeated “inflammatory” or acute phase reactions, evidenced by high levels of fibrinogen and low serum albumin levels, could play an additional role in endothelial dysfunction, or in atherogenesis. The premise that hemodialysis induces acute phase reactants has been examined in numerous studies (96, 97). An intriguing aspect of these studies is that C-reactive protein (CRP) levels are elevated in hemodialysis patients compared with control patients, and levels directly correlate with the duration of hemodialysis (98). Moreover, elevated CRP levels also correlate with an increased relative risk of mortality in hemodialysis patients (99).

CRP may serve as a marker of atherosclerosis. Heinrich et al. evaluated 929 male patients and demonstrated a significant increase in CRP concomitant with increasing severity of coronary artery atherosclerosis (100). They also noted a positive correlation between plasma fibrinogen, plasminogen, and d-dimer levels and the extent of coronary artery disease. Furthermore, CRP levels can be of prognostic value in non-ESRD patients with unstable angina, predicting progression to myocardial infarction (101).

These observations suggest that the concept of elevated CRP levels in dialysis patients as reflecting merely decreased renal clearance may need revision. CRP levels may represent the cumulative effect of repetitive low-grade, dialysis-related inflammatory “reactions,” as well as coronary artery inflammatory cell infiltrate (102), arterial wall mononuclear cell foci (103), or T cells expressing late-activation antigens (104). In addition, it is possible that elevated CRP levels could actually be atherogenic by enhancing ROS generation in IgG-stimulated monocytes and neutrophils (105). Despite these intriguing possibilities, CRP remains a non-specific acute phase reactant, and further studies will be necessary to determine whether elevated levels in hemodialysis patients accurately predict atherosclerotic vascular disease.

**Reperfusion Injury**

Additional mechanisms related to myocardial remodeling may play a role in cardiovascular-related mortality in hemodialysis patients. The progression of LVH in dialysis-dependent patients places them at risk for arrhythmias (106) and ischemia-related reduced coronary reserve (107). The latter may result from changes in myocardial microvasculature. Amann et al. reported that the left ventricular capillary density was diminished in uremic rats (108). Moreover, Amann and Ritz correlated this observation in humans by noting a reduction in left ventricular capillary volume in uremic patients (107). It is therefore possible that small regions of myocardium in dialysis patients are relatively underperfused because of a reduction in capillary reserve, and that these areas become ischemic during dialysis. The return of blood supply to its normal predialysis state would thus potentially trigger reperfusion injury and free-radical generation in this microenvironment. Such events may have deleterious effects on myocardial contractility and function (109), and repetition of these events could be another model for pathologic cardiovascular changes related to ROS. In this regard, it is also interesting to note that studies examining ischemic injury in spontaneously hypertensive (SHR) rats demonstrated that chemotactic products of lipid peroxidation were markedly increased in reperfused hypertrophic myocardium in comparison with normal control animals (110).

**Potential Role of F2-Isoprostanes**

Prostaglandin F2 (PGF2)–like compounds, F2-isoprostanes, generated as fatty acid oxidation byproducts during lipid peroxidation, also may potentiate atherogenesis. F2-isoprostane formation can occur in vivo by cyclooxygenase-independent free-radical–mediated processes (111). Thus, plasma assays for F2-isoprostanes could provide a sensitive and specific assessment of in vivo lipid oxidative damage. The biological consequences of isoprostane formation are not yet fully understood; however, the F2-isoprostane, 8-epi-PGF2α, has potent vasoconstrictive and platelet-aggregating properties (112). Previously, Morrow et al. demonstrated that circulating F2-isoprostane levels correlated with lipid peroxidation in vivo (113). Therefore, F2-isoprostane formation could be an important agent of oxidant-mediated lipid damage as well as an important gauge of in vivo lipid modifications.

In a small crossover study involving three hemodialysis patients, F2-isoprostane levels were almost fivefold higher when the patients were dialyzed with cellulosic membranes, in comparison with dialysis with polysulfone membranes. These data again suggest that dialysis membranes that stimulate ROS generation may differentially affect lipid modifications that could potentiate atherogenesis.

**Advanced Glycosylation End-Products**

Advanced glycosylation end-products (AGE) form from covalent non-enzymatic interactions between aldose sugars and lipids or proteins (114). AGE accumulate in renal failure, and conventional hemodialysis ineffectively removes them from the circulation (115). Moreover, AGE reaccumulate readily in the circulation even after high-flux dialysis (115).

AGE may be a contributing factor to oxidant stress and cardiovascular disease in hemodialysis patients. Non-enzymatically glycated proteins, such as AGE, can generate ROS (116,117), thereby exacerbating oxidant stress. Moreover, the presence of non-enzymatically glycated proteins and ROS in the extracellular environment can quench nitric oxide, potentially affecting immediate vasoreactive responses and chronic vascular smooth muscle proliferation (118).

It has been suggested that lipid peroxidation may enhance AGE formation, thus accelerating atherogenesis (116). Data from Palinski et al. (119) examining AGE immunolocalization in euglycemic LDL receptor-deficient rabbits suggest that
AGE are present in atherosclerotic lesions, lending support for this hypothesis. Although it is possible that AGE potentiate atherosclerotic cardiovascular disease in hemodialysis patients, further studies will be necessary to correlate their deposition, their activity, and their ultimate effect on cardiac disease in this population.

**Hyperhomocysteinemia**

Homocysteine is a sulfur-containing amino acid that results from the demethylation of methionine. Homocysteine can be oxidized to the disulfide homocysteine or the mixed disulfide, homocystine-homocystine. More than 25 yr ago, McCully concluded that hyperhomocysteinemia was associated with occlusive vascular disease (120), yet only in recent years has this hypothesis been examined in-depth. Recent studies have demonstrated a significant correlation between hyperhomocysteinemia and atherosclerotic vascular disease (121,122). A 5-yr prospective study analyzing 14,916 male physicians demonstrated a 3.4-fold greater risk for myocardial infarction in men with elevated baseline homocysteine levels (123). The increased risk for myocardial infarction conferred by hyperhomocysteinemia was independent of other known cardiac risk factors. Meta-analysis of studies examining the relationship between homocysteine and arteriosclerotic vascular disease also supports the idea that hyperhomocysteinemia is a risk factor for occlusive vascular disease (124). Reanalysis of the Framingham study cohort noted a strong positive correlation between plasma homocysteine concentrations and degrees of carotid artery stenosis (125). However, despite such epidemiologic evidence, the mechanisms underlying the relationship between hyperhomocysteinemia and occlusive vascular disease are not clearly defined at present.

Several reports have now demonstrated that hyperhomocysteinemia is frequently evident in chronic renal failure patients (126–128). In addition, patients with vascular disease who were enrolled in these studies tended to have homocysteine levels greater than patients free of known vascular disease (129). Renal failure may enhance the oxidation of homocysteine, which could alter its atherogenicity. Hultberg demonstrated that, despite elevations in total plasma homocysteine, reduced homocysteine levels were decreased in some patients with reduced renal function, suggesting that homocysteine could be oxidized in vivo in patients with renal failure (130).

A better understanding of the pathogenetic processes linking hyperhomocysteinemia and atherosclerosis is required before any definitive clinical recommendations can be made. Several studies have identified potential mechanisms of vascular injury associated with hyperhomocysteinemia that may be relevant in hemodialysis patients. Harpel et al. documented that homocysteine can enhance the binding of Lp(a) to fibrin (131), increasing the potential for Lp(a) to promote thrombosis and atherogenesis by anti-fibrinolytic activity. Homocysteine in vitro also enhances the auto-oxidation of LDL cholesterol (132). Thus, many of the potential mechanisms of atherogenesis discussed earlier in this article may be synergistically interactive leading to accelerated atherogenesis (Figure 7).

Whether treatment for hyperhomocysteinemia is effective in reducing the incidence of cardiovascular-related deaths in ESRD, or even necessary, remains to be determined. Janssen et al. suggested that folate supplementation for 6 wk in hyperhomocysteinemic dialysis patients significantly lowered plasma homocysteine levels (128). Moreover, when folate supplementation was discontinued, plasma homocysteine increased in parallel with decreasing folic acid levels. Thus, hyperhomocysteinemia may be a treatable risk factor for accelerated atherosclerosis in dialysis patients.

**Summary**

ESRD patients also come to dialysis with conditions known to predispose to atherosclerosis, e.g., diabetes mellitus (133,134). It would be inappropriate to discount these conditions in the overall analysis of cardiovascular-related mortality in the hemodialysis population. Parfrey et al. reported that diabetes mellitus, older age, hypertension on dialysis, and hypoalbuminemia were all significant predictors of de novo ischemic heart disease in patients receiving dialytic therapy (135). LVH was also independently associated with the development of de novo ischemic heart disease in ESRD patients (134). Furthermore, LVH, whether concentric or dilated, was associated with a significantly increased relative risk of late mortality (>2 yr after initiation of dialysis therapy) in ESRD patients (2.5- to 17.14-fold increase) (136). Therefore, these factors alone potentiate the risk of cardiovascular mortality in ESRD patients and thus merit consideration when the risk profile for cardiovascular disease in the dialysis population is evaluated.

However, attributing classic cardiac risk factors as defined for the general population to hemodialysis patients does not appear to be sufficient to explain the prevalence of cardiovascular disease and cardiovascular-related death in this population. It is possible that a number of other etiologies also contribute to cardiovascular complications in hemodialysis patients. The hypothesis presented herein that oxidized LDL, oxidant stress, cytoactive products of complement activation, endothelial dysfunction, and hyperhomocysteinemia may play
a role in the genesis of cardiovascular disease in dialysis-dependent patients is still that—a hypothesis. Nonetheless, in vivo and in vitro data are consistent with the concept that each may influence atherogenesis or vascular function, either individually or in combination with other factors. A caveat for analyzing some of these data is the absence of a true cause-and-effect relationship: that is, antioxidants and atherogenesis or a defined pathophysiological mechanism, e.g., homocysteine and vascular disease. However, such a caveat also provides the justification for constructing clinical trials to study how these factors might directly mitigate cardiovascular disease in the dialysis population. Moreover, the potential for repetitive dialysis-related low-grade inflammatory responses, ROS-mediated LDL oxidation, and the metabolic milieu that appears to allow for increased Lp(a) and homocysteine levels suggests that the dialysis population would be a logical choice for investigation of the possible links between these factors and the development of cardiovascular disease. Clinical trials designed to minimize dialysis-related ROS generation, to determine specific markers of endothelial dysfunction and acute phase reactants in setting of ESRD, and to further define the link between nutrition and cardiovascular disease may be appropriate studies for establishing whether alternative cardiac risk factors are important enough to be targeted therapeutically in much the same way that traditional cardiac risk factors are addressed in the general population.

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