MAJOR AND MINOR RISK FACTORS FOR CARDIOVASCULAR DISEASE IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS

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Cardiovascular disease remains the most common cause of mortality for patients with end-stage renal disease (ESRD), accounting for up to 50% of deaths in this patient population. Furthermore, ESRD patients have a rate of coronary artery disease (CAD) far in excess of the non-uremic population (1-5). Numerous studies have investigated the factors that contribute to this high incidence of cardiac disease amongst dialysis patients, and this paper focuses on a wide variety of such factors, particularly as they relate to peritoneal dialysis (PD) patients (Table 1).

Emphasis in this paper is on the etiologies of atherosclerosis (ASHD), it being the most important cause of morbidity and mortality. However, left ventricular hypertrophy (LVH) has a high prevalence amongst ESRD patients and should be noted as an important and independent risk factor for death (6,7). Hypertension and anemia are treatable major determinants of LVH.

Additional contributing factors have been variably reported to include hyperparathyroidism and fluid overload. Congestive heart failure is also frequent and usually a symptom of advanced ASHD, or persistent cardiac overload, or both.

DYSLIPIDEMIAS

Hyperlipidemia, most importantly, hypercholesterolemia, is associated with the development of ASHD. This is clearly apparent for patients with familial hypercholesterolemia who have a defect in the low-density lipoprotein (LDL) receptor. These patients have premature CAD, usually presenting between their third and fifth decades; homozygote patients have clinically significant diseases as early as their teens. However, hypercholesterolemia is a rare disease and of little relevance to the vast majority of sufferers of CAD.

In large population studies, an association exists between elevated cholesterol levels and the incidence of CAD. In the last decade, evidence has emerged that treatment of elevated LDL cholesterol dramatically improves the outcome of patients with respect to ASHD in both primary and secondary prevention trials (8-10). This body of evidence is perhaps the most compelling to link lipids, specifically LDL cholesterol, to CAD.

ESRD is associated with a high incidence of lipid abnormalities (11). Continuous ambulatory peritoneal dialysis (CAPD) patients have elevated levels of total cholesterol, LDL cholesterol, and apolipoprotein B (Apo B), and decreased levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein Al (Apo Al) (11). Because the elevation of Apo B is often greater than the elevation of LDL cholesterol, CAPD patients

| TABLE 1 |
| Risks for Atherosclerosis in Peritoneal Dialysis |

<table>
<thead>
<tr>
<th>Lipid abnormalities</th>
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<tbody>
<tr>
<td>↑ Total cholesterol</td>
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<td>↑ LDL cholesterol</td>
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<tr>
<td>↑ Apolipoprotein B</td>
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<tr>
<td>↓ HDL cholesterol</td>
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<tr>
<td>↓ Apolipoprotein Al</td>
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<tr>
<td>↑ Triglycerides</td>
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<tr>
<td>↑ Lipoprotein(a)</td>
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<td>↑ Oxidized LDL</td>
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Elevated homocysteine
Hyperinsulinemia
Abdominal obesity
Chronic inflammation
Advanced glycosylation end-product formation
Oxidative stress
Conventional risks
Smoking
Hypertension
Sedentary lifestyle

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appear to have small, dense LDL, a particularly atherogenic form of LDL (12). In contrast, hemodialysis (HD) patients have decreased levels of HDL and Apo Al, and their levels of Apo B, total, and LDL cholesterol are relatively normal (13). As such, the lipid profile of a CAPD patient is more atherogenic than that of a HD counterpart.

The lipid abnormalities associated with peritoneal dialysis have multifactorial causes. In uremia, there are abnormalities of lipoprotein lipase and hepatic lipase. In peritoneal dialysis, the loss of protein across the peritoneal membrane mimics to some extent nephrotic syndrome, which is characterized by hepatic overproduction of Apo B lipoproteins (VLDL and LDL). Elevated insulin levels also enhance the production of LDL particles, and the constant glucose loading in PD patients produces a hyperinsulinemic state. In cell culture studies, diminished amino acids increased hepatocyte Apo B production (14), but addition of amino acids to peritoneal fluid has not consistently corrected the lipid abnormalities (15).

Triglycerides are elevated in PD and HD patients, although significantly more so in PD patients (13). An increased level of triglycerides has a less clear causal relationship to ASHD. It is rarely found as an isolated risk factor, but it is rather found in association with decreased HDL and elevated Apo B protein levels. In a recent eight-year follow-up in the Copenhagen Male Study, triglycerides were a strong risk factor for ASHD independent of other risk factors, including HDL cholesterol (16). As such, the frequently and significantly elevated triglyceride levels of CAPD patients may contribute to their risk profile.

Lipoprotein(a) [Lp(a)] is a cholesterol-rich lipoprotein that has an LDL particle linked by disulfide bridges to apolipoprotein(a) [Apo(a)], which is a glycoprotein with high homology to plasminogen. In 1990, Lp(a) was reported in a case control study to be associated with an increased risk of coronary heart disease (17). This effect has been further demonstrated in a number of subsequent studies. In dialysis patients, Lp(a) levels have consistently been reported as elevated, often more in CAPD than in HD patients (18-22).

In the CAPD population, elevated Lp(a) levels have been further associated with malnutrition as judged by subjective global assessment and other nutritional markers such as albumin (23). Markers of inflammation are also associated with Lp(a) elevation (24,25). Chronic inflammation as a risk factor for ASHD is discussed elsewhere in this paper.

In summary, with respect to lipid abnormalities, PD patients have elevated total cholesterol, LDL cholesterol, apolipoprotein B, protein, triglycerides, and Lp(a). They have decreased HDL cholesterol and Apo Al levels. This constellation of abnormalities represents a highly atherogenic profile.

HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia is an independent risk factor for vascular disease in the non uremic population (26,27). Homocysteine is a highly reactive amino acid. It is toxic to vascular endothelium, it potentiates the auto-oxidation of LDL cholesterol, and it promotes thrombosis. In patients with established CAD, elevated total plasma homocysteine is a strong predictor of mortality. For renal failure patients, homocysteine has been demonstrated to be an independent risk factor for vascular disease (28-30). In one report, the ESRD patients in the upper two quintiles of homocysteine compared with those in the lower three quintiles gave an odds ratio of 2.9 for vascular events. Another report attributed an increased relative risk of 1% per 1 μmol/L increase in homocysteine concentration in ESRD patients (31).

The incidence of abnormally elevated homocysteine levels is high in ESRD patients. The cause is multifactorial, but deficiencies of folate, vitamin B6, and vitamin B12, as well as reduced clearance of homocysteine by the kidney are all contributing factors (32,33). Thus, treatment includes adequate vitamin replacement and transplantation (34,35). Of note is the fact that supernormal levels of folate, B6, and B12 are often required; and even then, some patients retain elevated levels of homocysteine. Furthermore, abnormalities of endothelial function can persist even after correction of homocysteine level (36). A study in PD patients treated with fish oil demonstrated persistent elevation of homocysteine despite the treatments (37).

HYPERINSULINEMIA AND ABDOMINAL OBESITY

Hyperinsulinemia has been identified as an independent risk factor for ischemic heart disease (38). Often, hyperinsulinemia is a signal of insulin resistance and is associated with abdominal obesity. The latter has emerged as a risk factor, and attention has thus focused on the ratio of hip measurement to waist measurement as a predictor of ASHD risk (39).

Renal failure has long been known to be associated with insulin resistance and elevated insulin levels (40). Peritoneal dialysis patients are further disadvantaged in this regard because of constant glucose loading. Fernström et al have reported an increase of intra-abdominal fat in patients treated with CAPD (41), and they suggest that this increase may confer additional cardiovascular risk in these patients.
INFLAMMATION

Peritoneal dialysis has been implicated as a state of chronic inflammation, particularly in patients using conventional, non physiologic dialysate solutions (42). This state of chronic inflammation may contribute to the low serum albumin seen in many patients. Elevated C-reactive protein (CRP) is reported with hypoalbuminemia.

With respect to cardiovascular disease, CRP has been shown to add to the predictive value of total cholesterol and HDL cholesterol in determining risk of first myocardial infarction (43,44). Helnrich et al demonstrated a significant increase in CRP with increasing severity of ASHD. Elevated CRP was associated with an increased relative risk of mortality in hemodialysis patients (45). In a study of CAPD patients, elevated fibrinogen and fibrinolytic activity was associated with ASHD and low serum albumin levels (46). Inasmuch as these are acute phase reactants, their presence may implicate the inflammatory aspect of PD as a predisposing factor for vascular disease.

OXIDATIVE STRESS

In the general population, a decreased relative risk for fatal myocardial infarction has been reported in patients with the largest vitamin E and betacarotene consumption (47-49). In clinical trials, patients receiving antioxidants or antioxidants plus lipid-lowering therapy showed improvement in endothelial function. Conversely, high oxidant stress and oxidized LDL is implicated in the development of atherosclerosis.

In uremia, increased oxidant stress exists, perhaps secondary to the impact of uremia alone, or to dietary deficiencies, or both (50). Oxidized LDL levels are measurable in uremia and are presumably taken up by the scavenger receptor that causes endothelial injury.

MALNUTRITION, ADVANCED GLYCOXYLATION END-PRODUCTS, CALCIUM, PHOSPHATE

Malnutrition, as indicated by hypoalbuminemia, is common in PD patients. As noted elsewhere in this paper, hypoalbuminemia is associated with elevated levels of Lp(a), CRP, and fibrinogen, all of which may predispose to vascular disease. Foley et al report hypoalbuminemia as an independent factor for the development of de novo ischemic heart disease in renal failure (51).

Advanced glycosylation end-products (AGEs) form between aldose sugars and lipids or proteins. AGEs exacerbate oxidative stress and accumulate in the vessel wall. Peritoneal dialysis promotes the production of AGEs in the peritoneal vascular space and may do so systemically through glucose loading and insulin stimulation.

Heavy calcification of the peripheral and coronary vessels has been observed for years in uremic populations. Recently, Block et al have implicated elevated phosphate as a risk factor for mortality (52).

A further, poorly defined, high-risk group appears to be high transporters and, possibly, their chronic fluid overloaded state (53,54).

Finally, conventional risk factors for cardiovascular disease -including hypertension, smoking, and passive lifestyle -are all relevant to PD patients.

SUMMARY

Uremia in general and peritoneal dialysis in particular bring with them risk factors for the development of cardiovascular disease. These factors include multiple lipid abnormalities, hyperhomocysteinemia, abdominal obesity, chronic inflammation, hypoalbuminemia, oxidative stress, and AGE formation. When these are combined with conventional risk factors, one can appreciate why the incidence of cardiovascular disease is so high in peritoneal dialysis patients. Treatment strategies should address each of these risks appropriately.

REFERENCES


