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Cardiovascular Disease and Predisposing Factors in Chronic Renal Failure

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The cardiovascular mortality in dialysis patients is 10 to 20 times higher than in the general population. Therefore patients with end-stage renal disease should be considered in the highest risk group for subsequent cardiovascular disease. The excess risk is caused by multiple traditional and non-traditional risk factors for ischaemic heart disease. The evaluation of the specific cardiovascular risk profile in each patient, appropriate prevention, diagnosis and treatment of cardiovascular disease is demanded. *J Clin Basic Cardiol* 2001; 4: 97–100.

Key words: end-stage renal disease, ESRD, dialysis, cardiovascular disease, cardiovascular mortality, cardiovascular risk factors, diabetes, hypertension, dyslipidaemia, inflammation, chronic renal disease

The risk of cardiovascular disease in patients with end-stage renal disease (ESRD) is far greater than in the general population. Thus, among patients treated by haemodialysis (HD) or peritoneal dialysis (PD), the prevalence of coronary artery disease and congestive heart failure is approximately 40 %, compared with 5–12 % in the general population (Table 1). Likewise, the mortality due to cardiovascular disease in dialysis patients is substantially higher than in the general population. It has been estimated to be approximately 9 % per year (Table 2) [1–8].

Up to now clinical investigation focused on coronary artery disease, predisposing risk factors and on echocardiographic findings including left ventricular hypertrophy (LVH), left ventricular dilatation (LVD) and systolic dysfunction.

Left Ventricular Hypertrophy, Left Ventricular Dilatation and Systolic Dysfunction

In a Canadian prospective cohort study [9] 432 dialysis patients had an echocardiogram performed within 1 year of starting dialysis. These data were correlated with clinical outcome and predisposing risk factors. Parfrey et al. found 41 % LVH, 28 % LVD and 16 % systolic dysfunction, only 16 % of patients showed normal echocardiographic findings when entering the haemodialysis program.

The median time until development of heart failure was 38 months in patients with concentric LVH as well as LVD, a substantially worse outcome compared to those patients with normal echocardiogram. However, the median survival was 48 months in patients with LVH and 56 months in patients with LVD, which was not significantly different as compared to those patients with normal echocardiogram. The relative risk of developing heart failure was 3 in LVH and 2.7 in LVD.

Independent predictors of LVH were systolic blood pressure and female gender. Risk factors for the presence of LV dilatation were anaemia and ischaemic heart disease.

LV mass index (LVMI) and LV volume (LVV) could be predicted by anaemia (LVMI + LVV), diabetes mellitus (LVMI), ischaemic heart disease (LVV), higher diastolic blood pressure (LVV) and lower serum albumin (LVV).

Foley et al. [10] found in a prospective cohort study that anaemia is an independent risk factor for clinical and echocardiographic cardiac disease, as well as mortality in end-stage renal disease patients. Anaemia had no independent association with the development of ischaemic heart disease while the patients were on dialysis.

Traditional and Non-Traditional Risk Factors for Ischaemic Heart Disease in Haemodialysis Patients

Diabetes Mellitus

Diabetes has a dramatic impact on cardiovascular disease mortality rates. Diabetic dialysis patients have the highest cardiovascular mortality with 11 % (haemodialysis) and 13 % (peritoneal dialysis) per year (Table 2). Foley et al. [11] prospectively followed a cohort of 433 diabetic ESRD patients. Among this population older age, left ventricular hypertrophy, smoking, clinically diagnosed ischaemic heart disease, cardiac failure and hypoalbuminaemia were independently associated with mortality. Additionally Koch et al. [12] demonstrated in a group of 196 diabetic ESRD patients that serum lipids on admission were the strongest predictors of myocardial infarction or sudden death whereas hypertension, LVH and end-diastolic diameter, smoking, interdialytic weight gain and type of dialysis were not predictive of cardiovascular death or death by all causes. Diabetic patients subsequently dying from myocardial infarction had significantly higher median cholesterol, LDL cholesterol, LDL/HDL ratio and apolipoprotein B than survivors [13]. Finally, another prospective trial enrolling 412 diabetic ESRD patients revealed that older age, lower apolipoprotein A-I, higher fibrinogen, and history of stroke were predictors of death [14].

The rates of *de novo* ischaemic heart disease, overall mortality and cardiovascular mortality were higher in diabetic patients whereas the rates of progression of echocardiographic disorders and development of *de novo* heart failure were similar in diabetic and nondiabetic patients. Accordingly, the excessive cardiac morbidity and mortality of diabetic patients seems to be mediated via ischaemic disease [11].

Hypertension

The prevalence of hypertension in chronic renal disease (CRD) is approximately 60 % to 100 %, depending on the target population, cause of renal disease, and level of residual renal function. Hypertension is associated with cardiovascular disease outcomes in all CRD target populations. Observational studies have shown that hypertension in HD patients is associated with an increased risk of LVH, coronary artery disease, and congestive heart failure [15]. There is also a strong association of LVH, coronary artery disease and congestive heart failure with subsequent mortality [16–18]. However, the association

Table 1. Approximate prevalence (%) of cardiovascular disease by target population

	Coronary artery disease (clinical) %	LVH (Echo) %	Congestive heart failure (clinical) %
General population	5–12 (NHLBI 1996 [6])	20 (Levy et al. [5])	5 (NHLBI 1996 [6])
Chronic renal insufficiency	Not available	25–50 (Levin et al. [2])	Not available
Haemodialysis	40 (USRDS [4])	75 (Foley et al. [3])	40 (USRDS [4])
Peritonealdialysis	40 (USRDS [4])	75 (Foley et al. [3])	40 (USRDS [4])
Renal transplant recipients	15 (Kasiske et al. [7])	50 (Parfrey et al. [8])	Not available

Data are depicted from [1]

Table 2. Cardiovascular mortality by gender, race, and target population (% annual mortality).

	All	Men	Women	White	Black	Diabetic	Non-diabetic
General population	0.28	0.28	0.27	0.29	0.23	0.80	0.26
Haemodialysis	9.12	9.38	8.83	11.18	6.68	11.09	7.78
Peritonealdialysis	9.24	10.27	8.14	10.76	6.07	13.22	7.09
Renal transplant recipients	0.54	0.59	0.43	0.53	0.56	1.11	0.39

Data are depicted from [1].

between blood pressure and subsequent mortality does not appear to be consistent, with a number of studies reporting either positive or negative associations. Zager et al. [19] showed an U-shaped relationship with excess mortality risk in HD patients with normal or low blood pressure as well as in patients with very high blood pressure. The United States Renal Data System (USRDS) database [20, 21] documented excess cardiovascular disease mortality in patients with low predialysis systolic blood pressures. According to these data relative hypotension is a potent marker of mortality in ESRD patients, probably reflective of antemortem cardiac failure.

The blood pressure level that minimizes death risk in dialysis patients has not been determined. In the absence of such studies, the current rationale for the treatment of hypertension in ESRD patients has been extrapolated from the treatment of otherwise healthy essential hypertensive patients in the general population and it appears reasonable to recommend a target predialysis blood pressure of less than 140/90 mmHg [15].

Dyslipidaemia

Secondary dyslipidaemia remains a prominent feature of ESRD. Lipid abnormalities include hypertriglyceridaemia [22], increased levels of cholesterol-rich very-low-density lipoproteins (VLDL) [23], intermediate-density lipoprotein (IDL) [24], apoB, and low levels of high-density lipoproteins (HDL) [25]. Diabetic patients exhibit an enrichment of the highly atherogenic low-density lipoprotein subclass, LDL-6 or small dense LDL. All these lipoproteins contain apoB, thus the complex disorder can be summarized as an elevation in triglyceride-rich apoB-containing complex lipoprotein particles [26]. A defect in postprandial chylomicron remnant metabolism has been associated with decreased lipoprotein lipase activity [27].

Although hypercholesterolaemia is clearly associated with a significantly increased risk of cardiovascular-related disease and mortality in the general population, in haemodialysis patients (except the diabetic ESRD patients), generally it is a low serum cholesterol that is associated with an increased relative risk of mortality [28]. An explanation for this phenomenon has recently been provided by the elucidation of the inflammatory response syndrome (see below). In several studies haemodialysis patients with cardiovascular disease had higher levels of triglycerides [29–31], total and LDL cholesterol [30] and lower levels of HDL [29, 31]. Hypertriglyceridaemia was an independent predictor of cardiovas-

atorvastatin decreases the rate of cardiovascular mortality and morbidity in haemodialysis patients with type 2 diabetes [32].

Lipoprotein(a) and Apolipoprotein(a) Phenotype

Cressman et al. [33] followed prospectively 129 patients for 48 months and found that high serum lipoprotein(a) [Lp(a)] levels predict subsequent cardiovascular disease events. Kronenberg et al. [34] found in a cross sectional study of 167 patients that low molecular weight (LMW) phenotypes of apo(a) and higher serum Lp(a) levels were associated with carotid artery plaques as investigated by ultrasound. They demonstrated that haemodialysis patients with LMW phenotypes of apo(a) had significantly more carotid arterial sites affected by atherosclerotic plaques than those with other phenotypes. The LMW apo(a) phenotype also predicted independently coronary artery disease in a cohort of 440 unselected haemodialysis patients in a prospective study over 5 years [35]. It has been suggested that the apo(a) size and the Lp(a) plasma concentration play a synergistic role in advanced atherosclerosis [36].

Tobacco Use

Approximately 15–18 % of ESRD patients report themselves as active smokers, but a greater number smoked before the onset of ESRD (15–45 %) [37–39]. Nicotine accumulation during smoking has been shown to be greater in chronic renal disease and increases with the degree of renal impairment [40].

In the USRDS Case Mix Severity Study, the relative mortality risk in active smokers compared to non-smokers was 1.3 [37]. In the USRDS Dialysis Mortality and Morbidity Study [38], the relative risk of myocardial infarction in patients who smoked cigarettes with type 1 diabetes was approximately 2.6 compared to patients who did not smoke. Similar data exist for ESRD patients and type 2 diabetes. Tobacco use both directly and indirectly affects normal kidney function, contributes to an intermittent and a persistent elevation of blood pressure and may potentially enhance other known risk factors. It is likely but not proven that smoking cessation will improve cardiovascular disease outcomes in ESRD patients [41].

Inflammation

Inflammation is now considered to play an essential role in the initiation of atherosclerosis as well as in plaque erosion and rupture [42, 43]. Recent prospective studies [44], the MONICA-Augsburg Cohort Study, and data from the Physicians' Health Study have shown that several markers of systemic inflammation such as C-reactive-protein (CRP) may

cular disease death [30]. In multivariate analysis, low levels of HDL cholesterol, high levels of apolipoprotein B, and a low molecular weight phenotype of apolipoprotein(a) were independent predictors of coronary artery disease [31]. Recently IDL was identified as well as an independent risk factor for aortic atherosclerosis in haemodialysis patients [24]. A first prospective, randomized, placebo controlled trial was initiated in Germany to test the hypothesis that

be used to predict future cardiovascular events in the general population.

CRP levels in haemodialysis patients are approximately tenfold higher than in normal subjects [45]. In this population CRP not only predicts the long-term but also the short-term, 2-year, cardiovascular and overall outcome [45]. Corresponding to these data CRP levels are also associated with an increased intima-media carotid artery area in predialysis patients [46]. Other acute phase reactants, such as albumin, fibrinogen, apo A-I [14] and Lp(a) are correlated with CRP and several of these proteins may be additional predictors of the high cardiovascular risk. Hypoalbuminaemia is often interpreted as a marker of poor nutrition shortening the long term survival of haemodialysis patients [47–50]. But serum albumin and cholesterol levels may be low as part of a cytokine-mediated acute-phase reaction. Accordingly Bologna et al. [51] found a significant relationship between TNF α , IL-6 and the degree of hypoalbuminaemia and dyslipoproteinaemia. IL-6 was the strongest predictor of mortality followed by age, albumin, and body mass index.

Since patients with chronic renal failure, not yet on haemodialysis treatment, exhibit a similar degree of elevation in CRP levels [46], the inflammatory process seems to be linked more to uremia dependent processes, such as oxidative stress, rather than haemodialysis. However, the HD-treatment or arterio-venous-grafts may act additionally [52].

Oxidative Stress

Dialysis patients are exposed to enhanced oxidative stress which is based on the generation of oxygen free radicals. One of the best investigated O₂-generating proteins is oxidized LDL (ox LDL) which may be an integral and necessary step for the development of atherosclerosis [53]. It has been suggested that alterations in LDL induced by carbamoylation may act in concert with ox LDL and initiate or participate in atherosclerotic plaque formation [54]. Several studies have documented the presence of ox LDL in chronic haemodialysis patients [55–58]. Itabe et al. [59] showed that ox LDL was increased more than eightfold in chronic haemodialysis patients compared with control subjects. Oxidative and carbonyl stress [60] may stimulate cells and endothelium to produce IL-6 which in turn activates the liver to secrete CRP and other acute phase proteins [52].

Hyperhomocysteinaemia

Moderate elevation of plasma total homocysteine concentration is present in the early stage of chronic renal failure, increases in parallel with the degree of reduction in renal function, and persists after starting dialysis [61, 62]. In several retrospective and prospective trials, hyperhomocysteinaemia was identified as an independent risk factor for cardiovascular morbidity and mortality in ESRD patients on dialysis treatment [63, 64]. In view of this athero-thrombogenic role attempts have been made to lower plasma homocysteine with folate [65–69]. Preliminary data suggest that the reduced forms of folate, ie, methyl-tetra-hydro-folate and folinic acid, are metabolically more active than native folic acid. They are also capable of normalizing plasma total homocysteine concentrations in CRF where the effect of the parent compound is limited [69]. The efficacy, optimal treatment modality and safety of administration must be confirmed in prospective studies [70].

Hyperphosphataemia

Hyperphosphataemia predict reduced survival in HD patients [71]. This is accounted for by an excess of cardiac deaths [72]. The underlying mechanisms may be inadequate dialysis and en-

hanced vascular damage by phosphate and parathyroidhormone (PTH). Hyperphosphataemia may well be a surrogate marker of inadequate dialysis which is known to shorten life expectancy in haemodialysis patients. Bloembergen et al. [73] showed that the relative risk of death due to coronary artery disease and other cardiac causes could be lowered by an increase in Kt/V. Serum phosphate is correlated to angiographic levels of coronary disease and coronary occlusion in non renal patients [74]. Serum phosphate affects the activation of interstitial cells, interstitial fibrosis and thickening of the wall of cardiac arterioles in animals [75–77]. Phosphate induces the production of PTH which is to be considered to act as a potential cardiac and vascular toxin [78].

Body Weight

In contrast to the data in the normal population [79] that suggest an increased risk of cardiovascular mortality associated with being overweight, Fleischman et al. [80] showed in a group of 1346 haemodialysis patients that low body mass index is associated with increased risk of hospitalization and mortality, even after adjusting for such demographic attributes as age and nutritionally-associated serum markers. Furthermore for every one unit increase in BMI above 27.5, the relative risk of dying was reduced by 30 %. However these findings are based on the definition of overweight. As the NHANES II [81] data showed, the distribution of BMI in the normal population varies among race and gender. Thus the finding in this study may result simply from a statistical artifact in defining normal [82]. Similar data was obtained by Kopple et al. [83] in a group of 12,965 HD patients. Multivariate analysis indicate that body weight-for-height relationship is an independent predictor of higher 12-months mortality in those patients who are in the lower 50th percentile for this measurement.

Conclusion

A considerable number of traditional and non-traditional risk factors for cardiovascular disease may be present in haemodialysis patients. Usually one patient is affected simultaneously by several risk factors. According to the Framingham study several factors multiply (not only add) the cardiovascular risk leading to poor long-term survival. Herzog et al. [84] evaluated 34,189 dialysis patients (1977–1995) hospitalized for acute myocardial infarction. They found that the overall mortality was 59 % at one year and 73 % at two years. The one and two year cardiac mortality was 41 % and 52 %, respectively. Therefore the evaluation of the specific cardiovascular risk profile of each patient, appropriate prevention, diagnosis and treatment of cardiovascular disease is demanded. Further clinical trials are needed to elaborate specific guidelines for appropriate treatment.

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