CHAPTER 1

Dialysis and the chronic renal failure patient

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Overview

The end-stage renal disease (ESRD) population has been increasing steadily in all parts of the world [1–3]. Data from the 2000 U.S. Renal Data System Annual Data Report (USRDS-ADR) show a linear rise in the incidence of ESRD, with a projected increase to more than 170,000 and a prevalence of 660,000 by the year 2010 (Figure 1). This rise has been partly due to the increasing longevity of the population contributed to by improvements in the quality of health care delivery. When the incident rate is broken down by age and the disease process, the largest increases are seen in diabetics and patients 65 years and older (Figures 2 and 3). In contrast to all other causes of ESRD, where a gradual leveling off has been observed, the incidence of ESRD due to diabetes mellitus continues to rise in a linear fashion [1]. Reasons for this phenomenon are currently unclear.

Concomitant with the rise in the incidence of ESRD has been a fall in death rates within the dialysis population. This decline has been observed in all age groups, regardless of the modality of renal replacement [1]. The declining death rate is again felt to be a consequence of improvements in health care specific to this population, including the use of kinetic modeling to quantify dialysis dose, improved anemia control with the routine use of erythropoietin and parenteral iron preparations, improved dialysis access, and use of biocompatible dialyzer membranes. Despite these improvements in the care of dialysis patients, morbidity and mortality remain unacceptably high. The five-year survival for patients more than

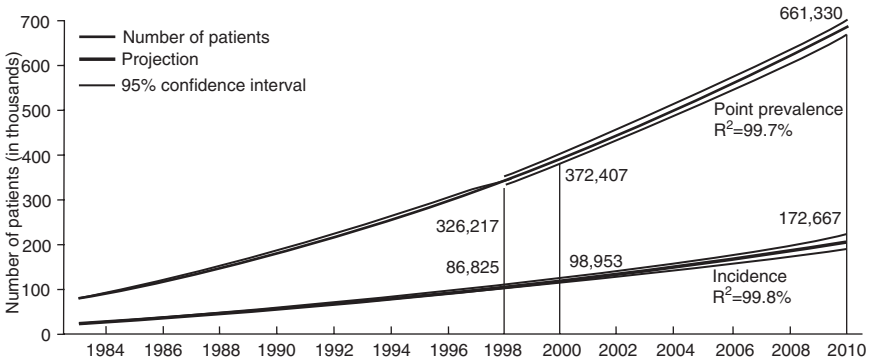

Figure 1 Number of incident and pain prevalent ESRD patients, projected to 2010. The data reported here have been supplied by the U.S. Renal Data System (USRDS). The interpretation and report of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. Government. From U.S. Renal Data System, USRDS 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2001, with permission.

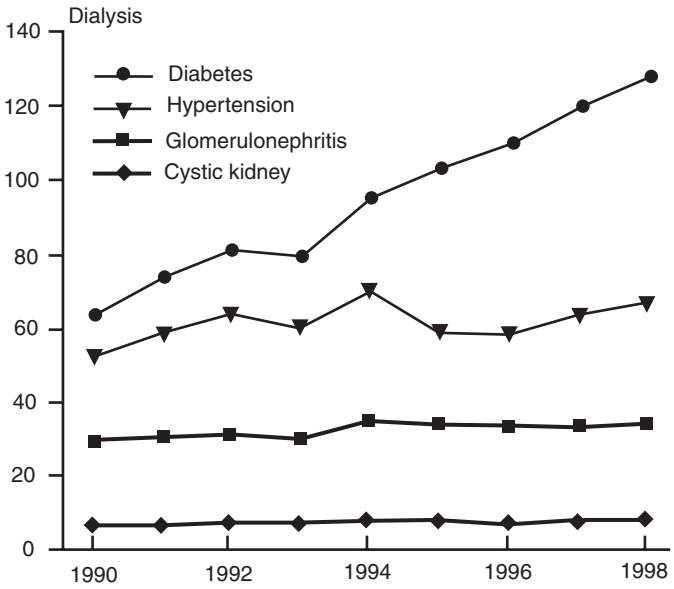

Figure 2 Incident rates by primary diagnosis per million population; unadjusted. The data reported here have been supplied by the U.S. Renal Data System (USRDS). The interpretation and report of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. Government. From U.S. Renal Data System, USRDS 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2001, with permission.

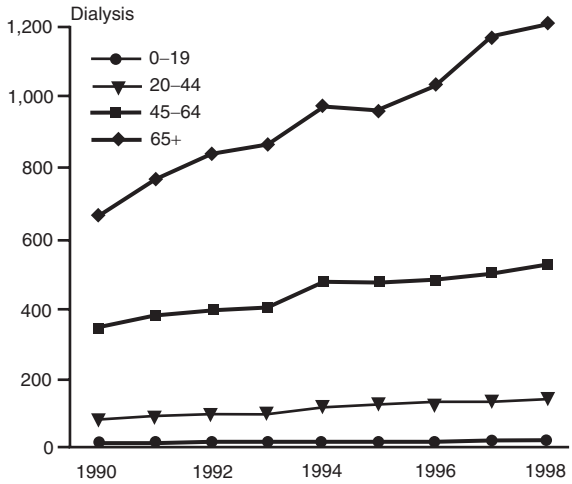

Figure 3 Incident rates by age per million population; unadjusted. The data reported here have been supplied by the U.S. Renal Data System (USRDS). The interpretation and report of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. Government. From U.S. Renal Data System, USRDS 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2001, with permission.

64 years of age starting dialysis is worse than that of breast, colon, or prostate cancer [4].

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in dialysis patients, accounting for between 36 and 50% of deaths [4–9]. Even after stratification by age, gender, race, and presence of diabetes, CVD mortality is 10–20 times higher than in the general population [10]. The pathogenesis of CVD in renal failure is more complex than in the general population. Traditional risk factors associated with CVD such as old age, male gender, family history, smoking, hyperlipidemia, hypertension, and diabetes mellitus [11] are also present in chronic renal failure patients. The relationship between risk factors and CVD is often modified by confounding factors and is different, especially for ESRD patients [12,13]. There are, in addition, factors specific to ESRD and the dialysis population that contribute to increased morbidity and mortality. It is, therefore, important to evaluate risk factors for CVD in the context of chronic renal failure and recognize differences between this population and those with intact renal function.

CVD risk factors in ESRD patients

Diabetes mellitus

Diabetes mellitus is the leading cause of ESRD, representing 42% of newly diagnosed cases [4]. It is an independent cause of CVD in both the general population and those with ESRD [10]. Multiple cardiovascular risk factors such as hypertension, lipid abnormalities, proteinuria, and hyperglycemia are present in diabetics early on in the course of their illness. Many of these patients will have developed heart disease even before the renal disease progresses to ESRD [14]. There is a higher incidence of ischemic heart disease, left ventricular hypertrophy (LVH), and heart failure in diabetics on dialysis compared to nondiabetics [14]. Diabetes is associated with more severe and extensive coronary artery disease than that observed in nondiabetics [15]. These patients also have a worse prognosis after myocardial infarction [11,6], with overall mortality twice that of nondiabetics, regardless of dialysis modality [17]. CVD in diabetics is thought to be mediated in part by the formation of advanced glycation end products (AGEs), which accumulate in both diabetic and nondiabetic chronic renal failure patients [18] and are poorly removed by both hemodialysis and peritoneal dialysis [19]. AGEs cross-link and trap low-density lipoprotein (LDL) on arterial collagen [20], leading to increased vascular permeability and damage [21]. They also inactivate nitric oxide, which results in impaired coronary vasodilatation [19,21] and contributes to CVD.

Hypertension

The prevalence of hypertension in ESRD is estimated at between 60 and 100% [10]. It is both a cause of ESRD and a complication of chronic renal failure. A majority of ESRD patients have been exposed to the deleterious effects of an elevated blood pressure for several years before initiation of dialysis [10,22]. The pathogenesis of hypertension in chronic renal failure is often one or a combination of fluid retention with an expanded extracellular volume, increased vasoconstriction, or activation of the renin angiotensin system [23]. In ESRD patients, hypertension is, to a varying degree, volume sensitive. With careful attention to fluid balance and optimal ultrafiltration during dialysis, it is possible to maintain normal blood pressure in many ESRD patients [24]. Systolic hypertension is the commonest pattern of blood pressure elevation in hemodialysis patients [25], and has been identified as a risk factor for the development of LVH [26–29], which is present in 60–80% of hypertensive dialysis patients. LVH has emerged as a potent and an independent predictor of cardiovascular mortality in ESRD patients and has been associated with a threefold increase

in the risk of subsequent heart failure independent of age, diabetes, and ischemic heart disease [30,31]. ESRD patients at the lower end of the blood pressure scale have also been shown to have an increased risk of cardiovascular mortality [32,33]. This apparent paradox is explained by recognizing that hypotension is actually a surrogate marker of underlying heart failure. Heart failure is a strong predictor of mortality in ESRD patients [33].

Dyslipidemia

Abnormalities in the levels and composition of plasma lipoproteins are common in patients with renal insufficiency [34–36]. The prevalence of these abnormalities is higher than in the general population and increases with deteriorating renal function [37]. Both the prevalence and specific type of lipid abnormality vary, depending on the cause and degree of renal disease as well as the modality of renal replacement. The commonest lipid abnormality in renal failure patients is hypertriglyceridemia, often accompanied by low high-density lipoprotein (HDL) cholesterol levels. Patients with the nephrotic syndrome and those on peritoneal dialysis have elevated total and LDL cholesterol levels, with a prevalence approaching 100%. Lipoprotein analyses in renal failure patients reveal qualitative abnormalities characterized by an increase in the levels of apo-B containing LDL and very low density lipoprotein (VLDL) particles [36] even in patients with normal plasma cholesterol levels. These lipoproteins are cholesterol deficient, triglyceride rich, smaller and denser than their counterparts in patients without renal disease. This qualitative abnormality is felt to increase the atherogenic potential of chronic renal failure patients and therefore their risk of developing CVD. Levels of lipoprotein (a), another small dense lipoprotein, have similarly been found to be elevated in renal failure patients [35,38]. An elevated lipoprotein (a) level has been demonstrated to be an independent risk factor for CVD in hemodialysis patients [39].

Hyperhomocysteinemia

Plasma homocysteine levels are elevated in patients with ESRD [40], and have been independently associated with atherosclerotic heart disease and increased mortality in the dialysis population [41–43]. Lowering homocysteine levels in patients that have undergone coronary angiography with angioplasty has been shown to result in decreased restenosis rates [44], further strengthening the association between hyperhomocysteinemia and atherosclerotic heart disease.

Abnormal divalent cation metabolism

Alterations in mineral metabolism, manifesting as hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, and hypovitaminosis D are common in ESRD. Although most often viewed in the context of renal osteodystrophy, accumulating evidence suggests that these abnormalities may contribute to the increased cardiovascular mortality observed in this population [45,46]. Mitral and aortic valve calcification has been reported to be higher in dialysis patients than in appropriately matched controls [47] and correlates with the calcium phosphate (Ca_xPO_4) product [48]. The predominant cardiac lesion, however, is coronary calcification, which can be demonstrated in up to 60% of dialysis patients on autopsy [49]. Coronary calcification is more common, more severe, and occurs at an earlier age in dialysis patients [48,49–51]. The extent of coronary calcification correlates with the severity of coronary atherosclerosis [52]. Hyperparathyroidism is also felt to contribute to left ventricular hypertrophy, perhaps through cardiac fibrosis and increased cytosolic free calcium levels [53].

Anemia

Anemia in ESRD patients is predominantly a consequence of insufficient erythropoietin production [54], though it could be contributed to by iron deficiency, decreased erythrocyte survival, aluminum intoxication, and bone marrow fibrosis [55]. Untreated, anemia leads to tissue hypoxia with compensatory vasodilatation, increased cardiac output, and eccentric left ventricular hypertrophy [56,57]. LVH is seen in up to 75% of patients initiating dialysis [58], and its association with cardiovascular morbidity and mortality is well described [56,59]. An inverse correlation between hemoglobin levels and LVH by echocardiography has been noted [19,56,60], and correction of anemia leads to a partial regression of LVH [54], suggesting a direct effect of anemia. There appears to be a dose-response association between the severity of anemia, hospitalization, and mortality in ESRD patients [61–64]. Anemia aggravates preexisting coronary artery disease, with an improvement in signs and symptoms following treatment [56].

Malnutrition

Following the National Cooperative Dialysis Study in 1981 [65], malnutrition was recognized as a contributory factor to the increased morbidity and mortality of dialysis patients. Hypoalbuminemia used as a marker of poor nutritional status has emerged as a strong predictor of death in the ESRD population, regardless of dialysis modality [66–68]. It has been linked with vascular disease [69], de novo and recurrent heart failure as