

Pathophysiology of Cardiovascular Disease and Renal Failure

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Observation has repeatedly confirmed the seminal observation of Lindner et al [1] on the excessive cardiovascular (CV) mortality in patients receiving renal replacement therapy. Today it is well established that in patients receiving renal replacement therapy the relative risk of dying from cardiac causes increases by a factor of 10 to 100, depending on age [2]. It has only recently been recognized, however, that even minor renal dysfunction, as reflected by an increase in urinary albumin excretion or a decrease in glomerular filtration rate, is an independent CV risk factor [3–6] in addition to the known risk factors assessed by the Framingham score. Because of the high prevalence of minor renal dysfunction in the general population, such recent insights have enormous public health relevance.

This article discusses the epidemiology of CV events in end-stage and early renal disease, summarizes the profile of classic and nonclassic CV risk factors in renal patients, highlights recent evidence documenting accelerated atherogenesis in renal disease, and closes by providing information on the central arteries and heart as target organs for CV damage in renal disease.

Cardiovascular risk in end-stage renal disease

The seminal observation of Lindner [1] of the high rate of CV events, particularly from ischemic heart disease, has been amply confirmed by numerous studies and registry reports. Fig. 1

shows early observations of the late A. Raine [7] indicating that, compared with the general population, the event rate in dialyzed patients is consistently higher by a factor of 15 to 20, irrespective of gender and country.

To interpret the underlying pathophysiology correctly, it is important appreciate that the most frequent cause of death is cardiac arrest (ie, sudden death [8]) as illustrated in Table 1.

Cardiovascular risk in incipient renal disease

It has recently been recognized that evidence of minor renal dysfunction (ie, microalbuminuria or reduced glomerular filtration rate) is associated with excessive CV risk [3–6]. In a population-based study, Hillege [9] and Borch-Johnsen [10] found that survival is significantly reduced even in non-diabetic, nonhypertensive individuals with microalbuminuria. Microalbuminuria is correlated with classic risk indicators, particularly glycemia and insulin resistance [11,12], but previous studies had documented that microalbuminuria is an independent risk predictor [10]. It is currently uncertain whether microalbuminuria is a marker of a generalized endothelial defect, evidence of minor renal dysfunction, or both. The recent finding that microalbuminuria is related to a polymorphism of podocin (NPHS2), a molecule of the glomerular filtration slit that controls the traffic of proteins into the filtrate, is consistent with the notion that it is related to podocyte dysfunction [13].

Following the observation in the Hypertension Detection and Follow-up Program [14] of a correlation between serum creatinine concentration and mortality, a number of studies confirmed [5,6] that serum creatinine or estimated glomerular filtration

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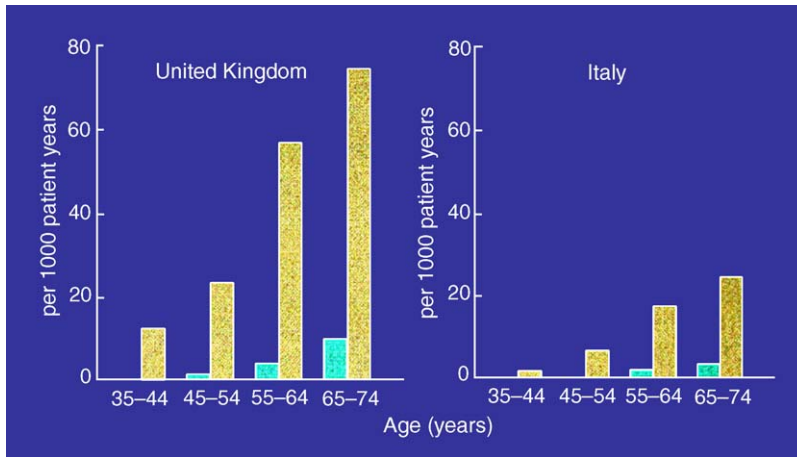


Fig. 1. Rates of ischemic events in patients receiving maintenance hemodialysis according to age and geographic origin. Note that the rate is consistently higher by a factor of 15 to 20 compared with the respective background population (*Data from Raine AE, Margreiter R, Brunner FP, et al. Report on management of renal failure in Europe, XXII, 1991. Nephrol Dial Transplant 1992;7(Suppl 2):7-35.*)

rate is a powerful predictor of CV risk in the general population [15], in hypertensive subjects [16], in patients at high CV risk [17], in patients with heart failure [18], and in patients with acute coronary events [19,20].

Risk factor profile (classic and nonclassic)

There is no doubt that the prevalence of classic risk factors is increased in renal patients [5,6], although the impact on CV events may be confounded by reverse causality. A classic example of the latter is the relationship of cholesterol to CV events. Overall, an inverse relation (the higher cholesterol, the lower the risk) or a U-shaped relationship (both high and low levels are

deleterious) is noted. The recent study of Liu [21] provided evidence that in uremic patients the relationship is confounded by microinflammation: in the absence of microinflammation, the mortality increased with increased concentrations of cholesterol, as it does in the general population.

Box 1 summarizes predictors of high CV risk including lipoprotein (a) genotype [22], low total cholesterol as an index of malnutrition, high non-HDL-cholesterol, a novel index of risk simultaneously incorporating information on low-density and very-low-density lipoprotein [23], high serum phosphate concentrations [24], and, in a complex

Table 1
Adjusted cause-specific death rates 1999 and 2001

Cause	Death per 1000 patient-years (%)
Acute myocardial infarction	19.9 (8.4%)
Cardiac arrest	51.9 (21.9%)
Cardiomyopathy	8.4 (3.6%)
Cardiac arrhythmia	11.2 (4.7%)
Heart-valve disease	1.4 (0.6%)
Cerebrovascular	12.3 (4.7%)
Total	236 ppm (100%)

Abbreviation: ppm, parts per million.

Data from USRDS. National Institutes of Health: annual data report. 1999.

Box 1. Some predictors of high cardiovascular risk in renal patients

- Lipoprotein (a) genotype (not Lipoprotein (a) concentration)
- Low total cholesterol
- High non-high-density lipoprotein cholesterol (~low-density lipoprotein + very-low-density lipoprotein)
- High serum phosphate
- High calcium × phosphorus product
- Parathyroid hormone <65 pg/ml or >495 pg/ml
- Homocystein?
- C-reactive protein, hypoalbuminemia, fibrinogen, interleukin-6, and others

interaction, both low and high parathyroid hormone concentrations [25,26]. Although the causal role of homocysteine is still controversial, there is no doubt about the importance of inflammatory markers in both early [27] and advanced renal failure.

Apart from the indices of microinflammation/malnutrition (malnutrition, inflammation, and atherosclerosis syndrome) [28], novel markers include adiponectin, an adipocyte hormone [29]; asymmetric dimethyl-L-arginine, an inhibitor of nitric oxide synthase [30]; and fetuin, an inhibitor of vascular calcification [31].

Sympathetic overactivity is also an important factor in CV risk [32], because sudden death is the most frequent mode of death in dialyzed patients (see Table 1). Indeed, plasma norepinephrine predicts survival and incident CV events in patients with end-stage renal disease [33].

A novel risk indicator is anemia [34], which is associated with reduced survival and aggravates the risk of increasing left ventricular mass [35]. Possibly lack of erythropoietin per se may be a CV risk factor as well, because erythropoietin increases the number of endothelial cell precursors [36]. In renal failure, one finds increased numbers of endothelial cells in the circulation, possibly reflecting sloughing off of damaged cells [37], as well as reduced numbers of endothelial precursor cells [38].

Accelerated atherogenesis

Lindner [1] speculated that the high incidence of ischemic heart disease reflects accelerated atherogenesis, although later work pointed to the high prevalence of classic risk factors [39,40]. Early work by Tvedegaard [41] in the rabbit cholesterol-feeding model suggested more severe atherosclerosis in uremia, but indisputable evidence for acceleration of atherosclerosis has been presented only recently in the study by Buzello [42] in the apolipoprotein (ε)-knockout mouse, a model of spontaneous rodent atherosclerosis. Even after uninephrectomy, he observed more rapid growth of atherosclerotic plaques that was associated with increased expression of nitrotyrosine (an index of oxidative stress) in non-plaque-bearing endothelial cells. Furthermore, Bro [43] recently showed increased expression of adhesion molecules only a few days after uninephrectomy or subtotal nephrectomy. These experimental studies leave no doubt that even modest impairment of renal

dysfunction aggravates progression of atherosclerosis, independent of classic risk factors.

Central arteries as a target organ

In renal failure, restructuring of the aortic wall is observed [44] with reduction of elastin and increase of collagen content, similar to that seen in aging [45]. Uremia can be interpreted a state of premature and accelerated aging.

The functional consequences of remodeling of aorta and central arteries have been underestimated in the past, but recent work shows that they have a major impact on CV risk. The consequences are both functional, as reflected by impaired reactive hyperemia [46], and structural, as reflected by altered mechanical properties of the vascular wall resulting from changed intrinsic properties of the wall material [47].

An additional factor is the propensity of central arteries to undergo calcification of both the media (elastic fibers) and intima (atherosclerotic plaques) [48]. The increased stiffness of central arteries accelerates the propagation of the pulse wave and earlier return of the reflected wave (augmentation). The altered pressure–volume relationship causes increased peak systolic pressure and accelerated decrease of diastolic pressure. The net result is an increase in peak systolic wall stress and oxygen demand, on the one hand, and reduced coronary perfusion during diastole on the other. This process explains why aortic stiffness is correlated with left ventricular hypertrophy and CV events. Clinically useful indices of aortic stiffness are pulse-wave velocity [49] and central pulse pressure [50], which are predictive of CV death.

A further complication is calcification of both the central elastic arteries and the muscular conduit arteries such as coronary arteries [51]. Calcification is favored by the absence of calcification inhibitors such as fetuin [31,52] and by high phosphate concentrations, which promote expression by vascular smooth muscle cells of genes involved in osteogenesis such as *Cbfa1* [53] or osteopontin [54]. Vascular calcification of either type predicts poor survival [55], as has also been shown using quantification of coronary calcification by electron-beam CT [56].

The heart as a target organ

Although atherogenesis is undoubtedly accelerated in uremia, it is naive (as has often been done in the past) to assume that all CV problems

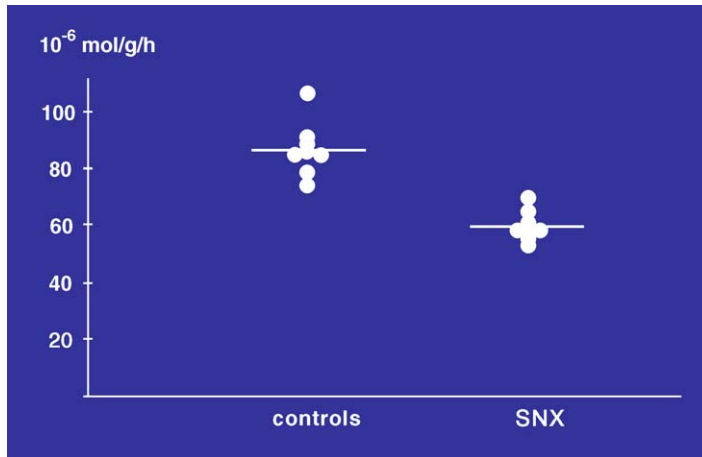


Fig. 2. Insulin-dependent glucose uptake in the isolated perfused Langendorff heart of uremic rats. (Data from Ritz E, Koch M. Morbidity and mortality due to hypertension in patients with renal failure. *Am J Kidney Dis* 1993;21:113–8.)

are explained by ischemic heart disease. In uremia oxygen delivery to the myocardium is reduced, and tolerance of ischemia is also diminished [57]. The issue is further complicated by the occurrence of interstitial fibrosis [58] and microvessel disease [59] in the heart of uremic animals and humans. Cardiac fibrosis reduces left ventricular compliance and electrical stability by favoring re-entry type arrhythmias that may contribute to the higher rates of cardiac death. The abnormalities of vessels distal to the coronary conduit artery (microvessel disease) comprise arteriolar wall thickening, limiting compensatory vasodilatation (when oxygen demand is increased), and capillary deficit with cardiomyocyte/capillary mismatch (increasing the distance for oxygen diffusion between capillary and cardiomyocyte core).

Furthermore, the frequency of heart failure is higher in uremic patients. In dialyzed patients, heart failure carries the worst prognosis of all cardiac abnormalities [60]. The factors causing heart failure have been poorly defined, but cardiomyocyte dropout has been demonstrated in experimental studies [61] and may play a major role in the genesis of heart failure.

Finally, the heart is exposed to excessive sympathetic stimulation [62]. Excess sympathetic activity is caused by stimulatory afferent signals emanating from the diseased kidney. Sympathetic overactivity is seen in renal patients even before the glomerular filtration rate decreases [63]. The causal role of sympathetic overactivity has been demonstrated by an intervention study that showed substantially reduced cardiac death when

dialyzed patients were given the beta blocker carvedilol instead of placebo [64].

The results of the DIGAMI study indicate that administration of insulin and glucose substantially improves the prognosis in patients with myocardial infarction and insulin resistance [65] (although these findings apparently could not be replicated in an unpublished follow-up study). Nevertheless, we were able to document diminished insulin-dependent glucose uptake (Fig. 2) in the isolated perfused Langendorff preparation of the heart of uremic rats [66]. Improved insulin-dependent glucose uptake could be a therapeutic target. Diminished insulin-dependent glucose uptake may not be the only metabolic abnormality interfering with ischemia tolerance in uremia: Raine [67] had found instability of energy-rich nucleotides and abnormal handling of calcium during ischemia.

Given the multifactorial pathogenesis and the complexity of the underlying mechanisms, it is unlikely that there will ever be a single approach that eliminates excess cardiac risk in uremic patients.

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