Vascular disease and chronic renal failure: new insights

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ABSTRACT

Premature cardiovascular disease (CVD) is a frequent complication in patients with chronic kidney disease (CKD). The traditional (Framingham) risk factors only partly explain the high prevalence of CVD in these patients and nontraditional risk factors/markers such as oxidative stress, persistent inflammation, cardiovascular ossification, endothelial dysfunction and anaemia are prevalent and seem to play an important role in the pathogenesis of CVD in CKD patients. In addition, the so-called reverse epidemiology phenomenon, which occurs in advanced kidney disease, complicates the search for causative mechanisms. Here we review a few recently developed concepts regarding the high incidence of CVD in CKD patients.

KEYWORDS

Chronic renal disease, cardiovascular risk, anaemia, sleep disturbances, reactive oxygen species, inflammation

INTRODUCTION

As in the general population, cardiovascular disease is the major cause of death in patients with end-stage renal disease (ESRD), accounting for about 40% of total mortality.[1,2] Life expectancy is severely reduced in ESRD patients compared with the general population, suggesting that the incidence and case fatality of cardiovascular disease is increased in ESRD patients. Indeed, it has been shown that total and cardiovascular mortality is increased 20- to 30-fold in ESRD patients (*figures 1* and *2*).[1,2] The risk of nonfatal cardiovascular disease is also 10-30

Figure 1. *Epidemiology of cardiovascular disease in haemodialysis patients[2]*
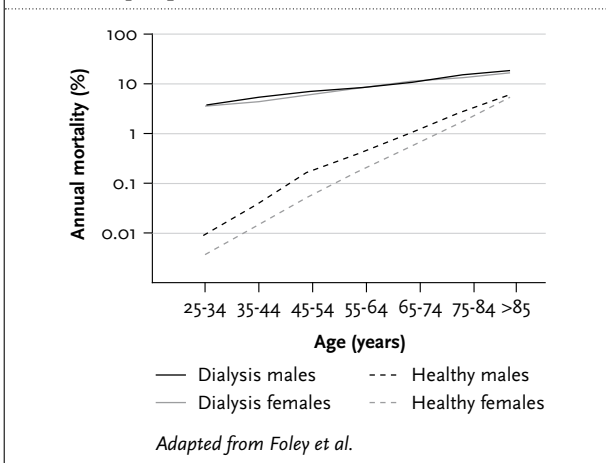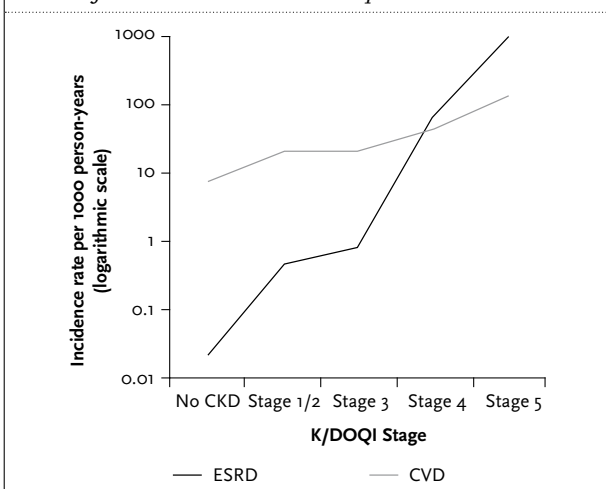

Adapted from Foley et al.

Figure 2. *Incidence of end-stage renal disease (ESRD) and cardiovascular disease (CVD) events according to baseline chronic kidney disease (CKD) stage. Data derived from the PREVEND study[101]*

times higher in patients with ESRD compared with the general population.[3] ESRD patients are therefore prone to the development and/or progression of cardiovascular disease.[4]

Cardiovascular disease (CVD) comprises a group of conditions, which can be divided into ischaemic and nonischaemic conditions. Examples of nonischaemic disease include valvular heart disease and arrhythmia. Ischaemic cardiovascular disease includes coronary artery disease, ischaemic cardiomyopathy, stroke, peripheral vascular disease, ischaemic nephropathy and renovascular disease. Sudden death (cardiac arrest) is also frequently the result of ischaemic vascular disease. Ischaemic vascular disease is generally the result of atherothrombosis. Lipoprotein retention and inflammation play a role in the early phase of this disease leading to arterial narrowing, whereas later on inflammation is implicated in plaque rupture and thrombosis.[5] In United States Renal Data System (USRDS) about 60% of all cardiac deaths in dialysis patients are attributed to cardiac arrest/cause unknown or arrhythmia.[6] Coronary artery disease coupled with diminished tolerance to myocardial ischaemia by left ventricular hypertrophy and ischaemic myocardial fibrosis, rapid electrolyte shifts in haemodialysis patients and derangements in autonomic function may all contribute to this increased risk of sudden cardiac death.[6]
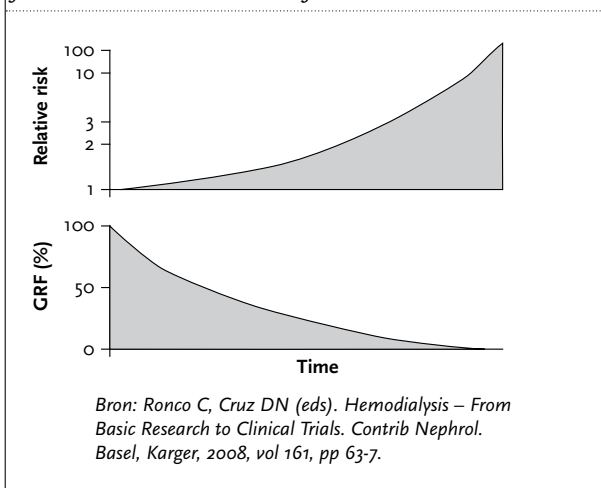
Despite the marked increased risk of cardiovascular disease, several large randomised trials in ESRD patients have consistently failed to show survival benefit from multiple new treatment strategies, which were aimed to reduce cardiovascular disease, such as increased dialysis dose,[7,8] homocysteine-lowering therapy,[9] intensified nutrition,[10] lipid-lowering with statins,[11] treatment with angiotensin-converting enzyme inhibitors,[12] and normalisation of haemoglobin with erythropoietin.[13,14] While some of these interventions do have significant beneficial effects on the incidence of cardiovascular disease in the general population, the reason for the lack of benefit of these interventions in ESRD patients is unclear. One can postulate that the risk factors involved in the atherogenesis in patients with ESRD markedly differ from those of the general population or that the stage of atherosclerosis in these patients is so advanced that it has become resistant to the therapies that have been used.

CARDIOVASCULAR RISK IN MILD TO MODERATE KIDNEY DISEASE

Estimates suggest that prevalence of mild to moderate chronic kidney disease is high in the Netherlands.[15,16] Earlier stages of chronic kidney disease (CKD) have also been associated with increased cardiovascular morbidity and mortality (*figures 1* and *2*).[1,17-21] A recent review of

85 publications, involving a total of 552,258 subjects, concluded that an undeniable link exists between the deterioration of renal function and the development of cardiovascular disease.[22] The risk of cardiovascular disease is already increased in very early stages of chronic kidney disease (at an estimated glomerular filtration rate (GFR) of approximately 75 ml/min) and increases continuously with decrease in renal function (*figure 3*).[22] In addition, recent studies have shown that patients with moderate chronic kidney disease are at a high risk of developing congestive heart failure[23] and that the majority of these patients have coronary heart disease.[24,25] A Norwegian study with 65,604 stage 2 to 3 CKD patients demonstrated that these subjects had a higher risk for development of premature cardiovascular death than progression to ESRD[26] and Keith *et al.* confirmed these findings in patients with stage 2, 3, and 4 CKD.[27]

Figure 3. *The relationship between estimated glomerular filtration rate and the risk of cardiovascular death*

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TRADITIONAL AND NONTRADITIONAL RISK FACTORS

The clear association between reduced kidney function and cardiovascular risk may, at least partly, be the result of a relationship between total atherosclerotic burden and decreased renal function, because intrarenal atherosclerosis (ischaemic renal disease) is a common cause of reduced renal function in patients with atherosclerosis.[28] However, even patients with a primary nonatherosclerotic renal disease such as polycystic kidney disease have an elevated risk of cardiovascular disease.[29,30] Traditional atherosclerotic risk factors such as age, dyslipidaemia, hypertension, diabetes mellitus, smoking and sedentary lifestyle play an important role in the occurrence of cardiovascular mortality in patients with chronic kidney disease.[31] However, these factors only partially explain the

Nanayakkara, et al. Vascular disease and chronic renal failure.

JANUARY 2010, VOL. 68, NO 1

6

cardiovascular morbidity and mortality in patients with mild to advanced chronic kidney disease, suggesting a pathophysiological role for additional risk factors.[32-35]

The so-called novel risk factors are markers of putative mechanisms involved in cardiovascular risk such as oxidative stress, endothelial dysfunction, cardiovascular ossification (calcification), inflammation, anaemia and disturbances in the sleep pattern. These novel markers are thought to play a role in the development of atherosclerosis in patients with CKD.[33,36,37] However, it should be emphasised that these traditional and nontraditional risk factors do overlap and do not operate in separate rigid compartments. While numerous studies have demonstrated that the traditional (Framingham) risk factors only partially explain the excess CVD in advanced CKD patients,[32-35] in a population of elderly CKD patients Shilpak *et al.* demonstrated that traditional CV risk factors had a stronger association with CV mortality than nontraditional risk factors.[31] The association between traditional and nontraditional risk factors and CVD is also complicated by the reverse epidemiology phenomenon seen in patients with CKD.[38] Reverse epidemiology refers to alterations in the normal relation between risk factors and clinical outcome. In specific populations, such as patients with ESRD, this abnormal relation can be so strong that more or less reversal of the usual association between risk factor and clinical outcome occurs. For example, in dialysis patients high body mass index (BMI) and higher serum cholesterol are correlated with decreased cardiovascular morbidity and mortality. Also the association between blood pressure, serum homocysteine, serum parathyroid hormone, serum creatinine and cardiovascular morbidity and mortality is reversed in dialysis patients compared with the general population.[38] The common occurrence of persistent inflammation and protein energy wasting in advanced CKD seems to a large extent to account for this paradoxical association between traditional risk factors and CV outcomes in this patient population.[39] Preliminary studies suggest that the reverse epidemiology phenomenon is also present in patients with CKD not yet on dialysis.[40] This phenomenon of reverse epidemiology sometimes makes it difficult to target traditional risk factors in an effective manner because determination of an optimal target for risk factors such a blood pressure and LDL cholesterol is uncertain, especially in patients with advanced CKD. In this review, we aim to discuss some new concepts on this complex association between CKD and CVD.

Oxidative stress

Imbalance between production of reactive oxygen species (ROS) and antioxidant defence results in oxidative stress (*figure 4*), which may arise either from deficiencies of antioxidants (such as glutathione, ascorbate or α-tocopherol) or increased formation of ROS such as peroxynitrite ($ONOO^-$), hypochlorous acid (HOCL) or superoxide anions.[41] High levels of oxidative stress markers such as F_2-isoprostanes, advanced glycosylation end products, malonyldialdehyde and oxidised LDL have been demonstrated in patients with mild to moderate CKD and in ESRD patients.[42] Oxidative modification of low-density lipoproteins (LDL) is thought to be a key step in the initiation of atherosclerosis.[43] Therefore, one may consider the oxidative stress hypothesis as a unifying concept of increased CVD risk in CKD patients.[36] Numerous studies have demonstrated an inverse association between different markers of oxidative stress and eGFR and in addition graded increase in oxidative stress has been demonstrated with longer duration of dialysis therapy.[44,45] This increased oxidative stress is probably due to increased production of ROS as increased NAD(P)H oxidase activity has been reported in patients with even mild CKD.[46] Whether there is also a deficiency in the antioxidant defence system is still a matter of debate.[42] While some studies demonstrate a reduction in intracellular or plasma antioxidant factors such a superoxide dismutase, catalase or glutathione peroxidase other studies showed no reduction in total antioxidant capacity.[47,48]

Even so, the causal relation between oxidative stress and CVD in CKD patients has not yet been established. Only a small number of epidemiological studies that evaluate the association between surrogate markers of oxidative stress and CVD have been performed and results have been inconclusive.[49] Even fewer data are available on intervention trials aimed at reducing the oxidative stress. Most of the intervention trials aimed at reducing cardiovascular disease in ESRD patients yielded disappointing results, but the SPACE study, in which 196 patients with ESRD were treated with 800 IU vitamin E, demonstrated encouraging results on composite CV endpoints and myocardial infarction.[50] In the Antioxidant Therapy in Chronic Renal Insufficiency (ATIC) study 18 months of a stepwise treatment strategy with pravastatin, vitamin E and homocysteine lowering therapy on top of well-controlled blood pressure lowering led to a significant increase in endothelial function and a significant reduction in carotid intima-media thickness.[51] However, whether the reduction in oxidative stress was primarily responsible for these favourable effects was unclear. In another small study, N-acetylcysteine was shown to reduce cardiovascular events in ESRD patients.[52] However, these studies were too small and too short and the effects on oxidative stress biomarkers were not well documented. Therefore, although existing data suggest a probable role for oxidative stress in increased atherogenecity in CKD patients, further studies are needed to examine the pathophysiological role of oxidative stress and the effects of oxidative stress reducing treatment strategies in CKD.

Nanayakkara, et al. Vascular disease and chronic renal failure.

JANUARY 2010, VOL. 68, NO 1

7

Figure 4. *Schematic simplification of the generation, disposal and effects of reactive oxygen species in renal disease*
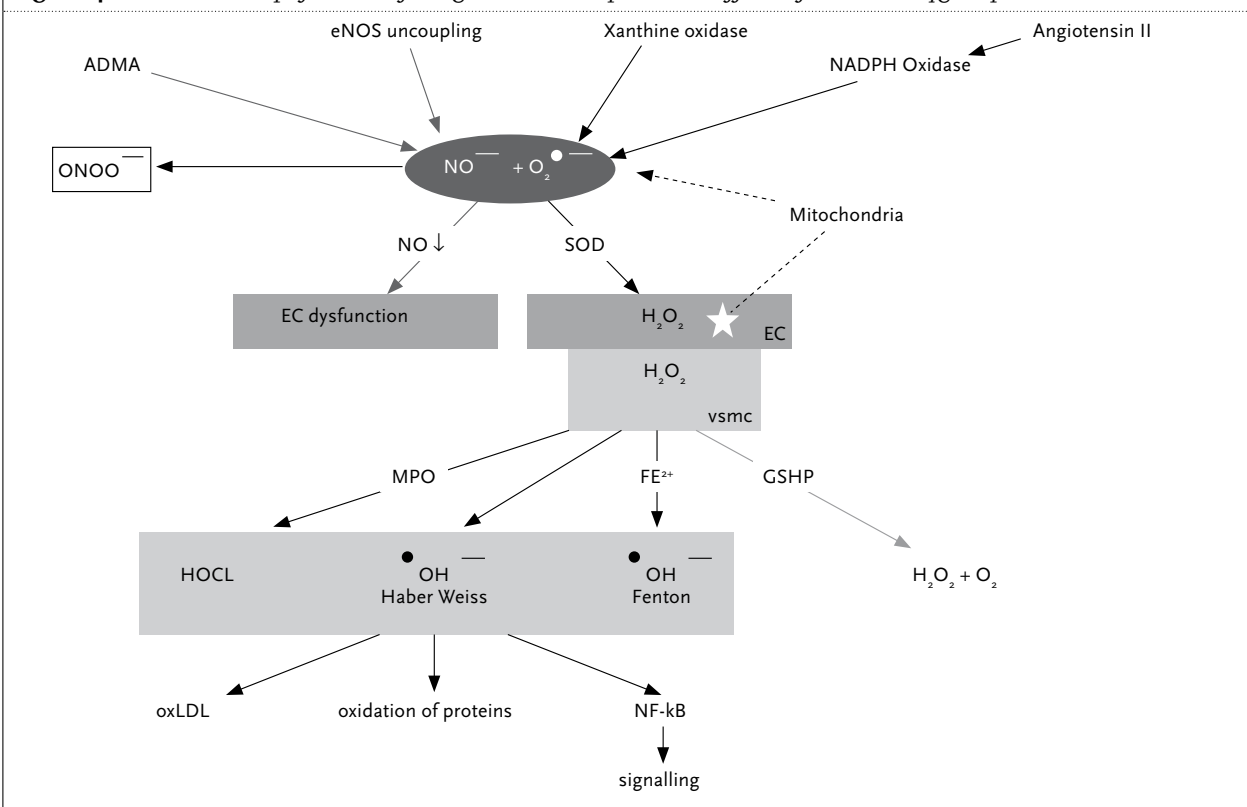
This figure shows a simplified representation of superoxide (O_2^-) and hydrogen peroxide (H_2O_2) generation and effects. In renal dysfunction, the availability of NO is already jeopardised by increased levels of ADMA. Angiotensin II (Ang II) stimulates intracellular formation of ROS such as the superoxide anion and hydrogen peroxide. Ang II activates several subunits of the membrane-bound multicomponent NAD(P)H oxidase and also increases ROS formation in the mitochondria. The increased O_2^-, which are formed by NADPH oxidase and xanthine oxidase, will further decrease the available NO levels, inducing EC and vascular VSMC dysfunction. Also superoxide reacts with NO to form peroxynitrite ONOO- which is damaging to tissues and induces mitochondrial dysfunction.

SOD converts superoxide is into H_2O_2 which can freely enter the cell. The less reactive oxidant hydrogen peroxide (H_2O_2) is then reduced to water and oxygen by catalase or glutathione peroxidase The glutathione system is paramount for protection against oxidative threats. Alternatively, H_2O_2 may be converted into hydroxyl (OH--) radicals, the most reactive and toxic of the ROS, through the Haber–Weiss or the Fenton reactions. These radicals are highly unstable and will interact with proteins, lipids or nucleic acids. In the presence of myeloperoxidase (MPO, from neutrophils), H_2O_2 forms additional oxidants.

Finally, ROS-dependent signalling events, mostly related to NF-kB, will have detrimental effects on the cell's function and the possibility of (irreversible) oxidation of proteins and other molecules in the cells (e.g. AGEs).

ADMA = asymmetric dimethylarginine; ROS = reactive oxygen species; SOD = superoxide dismutase; EC = endothelial cell; VSMC = vascular smooth muscle cell; GSHP = glutathioneperoxidase; MPO = myeloperoxidase; NF-kB = nuclear factor kB; AGE = advanced glycosylation end products.

Inflammation

Numerous studies have reported an association between chronic renal failure and different markers of inflammation such as C-reactive protein (CRP), IL-6, TNF-α, fibrinogen suggesting that CKD is a low-grade inflammatory process with leucocytes being the key mediators in this process.[42,53] Moreover, inflammatory markers are predictors of kidney function deterioration implying that persistent inflammation may also be a risk factor for further deterioration of kidney function.[54] CRP formed locally in the kidney reduces nitric oxide production and induces monocyte recruitment and foam cell formation.[55] In addition, it has been demonstrated that elevated CRP, IL-6 and fibrinogen are independent predictors of CV outcomes in patients with CKD.[56] Therefore, one could postulate that inflammation promotes both deterioration in renal function and CVD. Although precise mechanisms that contribute to the high prevalence of inflammation in CKD are unknown, ROS have been proposed as a potential contributor. Oxidative stress is able to activate transcriptor factors such as NF-κB which regulates inflammatory mediator gene expression.[57] Presence of antioxidants has been shown to prevent NF-κB activation by ROS and depletion of reduced glutathione facilitates activation of NF-κB.[58]

Both dialysis-related and dialysis-unrelated factors may contribute to the high prevalence of inflammation in CKD patients. Intercurrent clinical events, chronic infections with *Chlamydia pneumoniae*, peridontitis, biofilm formation in haemodialysis patients, truncal obesity, and volume over load have all been implicated as culprits in this process. In addition, there is a significant interindividual variation in the prevalence of inflammation which may point to genetically determined variations in the inflammatory response.[56]

Nanayakkara, et al. Vascular disease and chronic renal failure.

JANUARY 2010, VOL. 68, NO 1

8

Endothelial dysfunction

Endothelial dysfunction reflects decreased bioavalability of nitric oxide (NO) and precedes structural changes and clinical manifestations of atherosclerosis.[59] Levels of asymmetric dimethylarginine (ADMA), a methylated product of L-arginine, are elevated in CKD. ADMA is known to inhibit endothelium-dependant NO bioavailability and high ADMA concentrations are associated with higher carotid intima media thickness (IMT) and CV events in patients with CKD.[60] In addition, Ravani *et al.* demonstrated that ADMA represents a strong and an independent risk marker for progression of CKD.[61] Pharmacological interventions with statins, vitamin E, and homocysteine-lowering therapy aimed at reducing plasma ADMA have shown inconsistent results.[62] However, improved endothelial function after administration of both soy protein and α-lipoic acid in CKD patients has been linked to decreased ADMA levels.[49]

The pathophysiological mechanisms leading to albuminuria in renal disease are complex and manifold.[63] However, albuminuria is also thought to be a reflection of generalised increase in endothelial permeability or endothelial dysfunction.[64] The association between albuminuria and CV risk is independent of an association between impaired kidney function and CV risk.[65] In addition, albuminuria is a much stronger predictor of decline in kidney function than mild kidney failure, and other cardiovascular risk factors such as inflammation, abnormalities in fibrinolysis, and dyslipidaemia are strongly associated with both albuminuria and endothelial dysfunction.[49]

Thus, in early CKD both the estimated glomerular filtration rate (eGFR) and low-grade albuminuria seem to play a pathophysiological role in increased CVD. Results from the HUNT II study, performed in 9000 Norwegians, demonstrated that mild changes in both eGFR and albuminuria were independently associated with increased CVD.[66] Stam *et al.* demonstrated that for each decrease of 5 ml/min/1.73 m^2 of GFR, the relative risk of CV death increased by 22% (relative risk 1.22; 95% CI 1.09 to 1.36) and much of this risk was accounted for by albuminuria (adjusted models relative risk 1.17; 95% CI 1.04 to 1.31). Rodondi *et al.* also demonstrated that albuminuria had a stronger association with atherosclerosis than eGFR.[67]

Although in early stages of CKD, an increase in albumin excretion seems to be more important than a small decrease of eGFR, it seems unlikely that albuminuria accounts for the exponential increase in CVD risk once the eGFR decreases to under 60 ml/min/1.73 m^2. However this is still a matter of debate.

Interruption of the renin-angiotensin axis with ACE inhibitors or angiotensin II receptor blockers (ARBs) seems to be pivotal in reducing albuminuria. In the PREVEND intervention trial, patients with albuminuria and without hypertension were randomised to one of two arms, an ACE inhibitor *vs* placebo or a statin *vs* placebo.[68] Use of an ACE inhibitor reduced albuminuria and CV mortality, although this improvement could have been related to reduction of blood pressure.

In response to endothelial injury, endothelial progenitor cells (EPC) are mobilised from the bone marrow to act as repair cells. In CKD there is impaired migratory activity and a decreased number of EPC in the circulation, which may play a role in the progression of atherosclerosis.[69] In fact, low levels of EPC predicted the occurrence of CV disease and death in patients with coronary artery disease.[70]

However, a causal association between endothelial dysfunction and CVD in CKD patients remains to be established. Therefore endothelial dysfunction should be considered a cardiovascular marker until such time that more studies illuminating this issue become available.

Anaemia

Anaemia frequently occurs in CKD and becomes more prevalent as renal function deteriorates. The prevalence of anaemia reaches about 50% in stage 4 CKD whereas in stage 5 anaemia is almost universal.[71] In patients with CKD, anaemia is a common contributor to poor quality of life (QOL), hospitalisation and mortality. There are several physiological explanations for this finding: anaemia is associated with a poor delivery and utilisation of oxygen, a decreased immune response and impaired cognition. Moreover anaemia in CKD is linked to left ventricular hypertrophy (LVH), angina and congestive heart failure (CHF).[71,72]

The severity of anaemia depends both on the cause of the CKD and the degree of GFR loss. In CKD the primary cause of anaemia is insufficient erythropoietin (EPO) production in combination with insufficient response to EPO caused by the mechanism usually described as 'anaemia of chronic disease'. Secondary causes that contribute to the development of anaemia include absolute iron deficiency, hyperparathyroidism and a shorter lifespan of red blood cells caused by uraemia.[71-73]

Anaemia of chronic disease develops as the result of a chronic inflammatory disorder.[74] In CKD the overall inflammatory response is enhanced and inflammatory cytokines such as hepcidin and Il-6 are increased.[75] Enhancement of erythropoiesis by EPO requires intact EPO signalling (EPO receptor, downstream JAK/STAT signalling and transcriptional response) and effective mobilisation of iron stores.[73] Hepcidin inhibits the efflux of iron into plasma transferrin by downregulating ferroportin, the efflux channel for iron in macrophages and in enterocytes (*figure 5*).[76] Enhanced synthesis of hepcidin thus leads to inhibition of iron absorption in the small intestine and sequestering of iron in macrophages, resulting in limited iron availability for erythropoiesis. In addition to its effect on iron metabolism, hepcidin may contribute to EPO

Nanayakkara, et al. Vascular disease and chronic renal failure.

JANUARY 2010, VOL. 68, NO 1

9

Figure 5. *Mechanisms leading to EPO resistance in patients with various degrees of renal dysfunction*
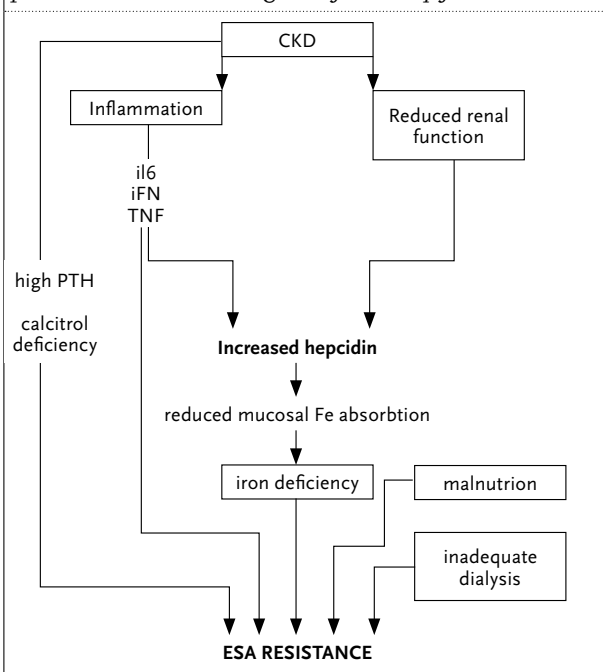
Inflammation and hepcidin, which links inflammation and iron metabolism, are pivotal factors involved in EPO resistance. Both inflammation and reduced renal function increase plasma hepcidin levels. Hepcidin reduces iron availability in among other ways through a reduction in mucosal iron uptake. Furthermore, inflammation per se as well as disturbed phosphate and vitamin D metabolism directly reduce bone marrow response to EPO. When renal function further deteriorates additional factors that induce EPO resistance become important such as inadequate renal replacement therapy and protein energy wasting. ESA = erythropoiesis stimulating agents.

outcomes. Following the large amount of observational data suggesting a 'cause and effect' relationship between anaemia and outcomes, a series of erythropoietin treatment trials was undertaken. Starting in the late 1990s, different hypotheses were investigated in clinical trials: early *vs* late anaemia correction and higher *vs* lower haemoglobin targets in both dialysis and predialysis CKD patients.[81] It is important to note that these studies compared actively treated groups with different target haemoglobin levels and that no placebo-controlled trials were performed. The main overall result is that these studies failed to demonstrate that normalisation of haemoglobin levels using EPO is beneficial and, importantly, that normalisation of haemoglobin levels may be associated with worse outcomes.[82] As an example three major clinical trials investigating the effect of different target haemoglobins on anaemic CKD patients (the Anaemia CORrection in Diabetes (ACORD),[83] Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)[84] and Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE)[85] are shown in *table 1*.

The mechanisms underlying the higher mortality rate are unclear. Increased tendency for developing thrombosis or an elevated blood pressure may contribute to an increase in lethal CV events. Other mechanisms such as deregulation of production/responsiveness of vasoactive factors may also play a role. In addition, it is still unclear whether the higher mortality is related to the higher haemoglobin target itself or to the means by which the haemoglobin level is achieved. A secondary analysis of the CHOIR study points to the dose of EPO used rather than the achieved haemoglobin level.[86]

The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) is the first randomised, placebo-controlled study to investigate whether raising haemoglobin in CKD patients with erythropoietin is beneficial.

resistance through a direct inhibitory effect on erythroid progenitor proliferation and survival.[77] In patients with CKD and in haemodialysis patients, it has been shown that hepcidin levels are higher than in healthy controls.[78-80]

From a biological point of view, it is plausible that anaemia has an impact on cardiac structure, function and

Table 1. *Major clinical trials investigating the effect of different target levels of haemoglobin on anaemic CKD patients*

Study	Primary endpoint(s)	Secondary endpoints
ACORD	Change in LVMI from baseline	LV volumes; LV ejection fraction (LVEF); fractional shortening
CHOIR	Time to death; MI; hospitalisation for CHF and stroke	Time to renal replacement therapy; hospitalisation following CV and any cause; QOL
CREATE	Time to first CV event (incl. sudden death, MI, acute HF, stroke, transient ischaemic attack, angina pectoris) resulting in hospitalisation for ≥24 h or prolonged hospitalisation; complications of peripheral vascular disease (necrosis, amputation)	Death from CV and any cause; CHF; the need for CV intervention; hospitalisation following CV and any cause; changes in LVMI and LV volumes; time to initiation of renal replacement therapy; changes in BMI; serum albumin level; C-reactive protein level; changes in QOL, Hb level and weekly epoetin dose; the need for dialysis and transfusion and decreases in eGFR

LVMI = left ventricular mass index; MI = myocardial infarction; CV = cardiovascular; (C)HF = (congestive) heart failure; LVEF = left ventricular ejection fraction; QOL = quality of life; Hb = haemoglobin; eGFR = an estimated glomerular filtration rate.

Nanayakkara, et al. Vascular disease and chronic renal failure.

JANUARY 2010, VOL. 68, NO 1

10

In summary, although it is clear that anaemia and EPO resistance is associated with increased morbidity and mortality, the beneficial effect of treatment of anaemia using EPO on mortality in CKD remains to be established.

CARDIOVASCULAR OSSIFICATION

In the search for factors that might contribute to the enhanced cardiovascular risk in recent years, the role of renal disease-induced abnormalities in calcium-phosphorus metabolism has become apparent. A strong association has been described between hyperphosphataemia, hyperparathyroidism and CV disease.[87] This increased CV disease is probably caused by increased vascular calcification and evidence is emerging that optimising treatment of calcium and phosphate alterations may decrease CV risk in CKD patients.[88] Likewise in patients with CKD, phosphorus levels are also associated with cardiovascular outcome. Several factors including parathyroid hormone (PTH) and vitamin D play a critical role in maintaining plasma phosphate levels.[89] Fibroblast growth factor 23 (FGF23) has recently been identified as an important regulator of systemic phosphate balance.[90] FGF23 is a 32-kDa protein that is predominantly expressed in osteocytes in the bone and in the endothelial cells that line the venous sinusoids of the bone marrow.[91] Under physiological conditions FGF23 promotes phosphaturia and suppresses the 1 α-hydroxylase activity, thus leading to a reduction in 1,25-dihydroxyvitamin D levels. Transgenic mice over-expressing FGF23 have reduced plasma phosphate concentration, phosphaturia and reduced renal phosphate sodium co-transporter.[92] The phosphate balance is altered in CKD and in these patients very high levels of FGF23 have been demonstrated.[93] As the number of viable nephrons decreases in CKD, in spite of the high FGF23, the net phosphate excretion does not increase sufficiently. This high phosphate level in combination with the reduction in 1,25-dihydroxyvitamin D levels leads to secondary hyperparathyroidism. However, the exact role of FGF23 in renal osteodystrophy has not been established. Fliser *et al.* demonstrated a correlation between increased FGF23 concentration and progression of chronic renal failure suggesting that FGF23 may play a role in progression of renal failure.[94] Other related factors such as calcium phosphate product and PTH also correlated with progression of renal failure in these subjects. Therefore, further studies are needed to better understand the role of FGF23 in patients with CKD.

Disturbances in circadian rhythm
An upcoming field of interest is the effect of disturbances in circadian rhythms in CKD. Circadian rhythms are fluctuations in nearly all bodily functions with a period of about 24 hours. In renal patients some of these circadian processes are disrupted. For example, sleep disturbances are much more prevalent in ESRD patients than in the general population.[95] In dialysis patients several studies on the impact and importance of sleep problems on quality of life revealed that sleep disturbances have a major effect on vitality and general health of these patients.[96] These sleep disturbances can have multiple causes, e.g. sleep apnoea and/or restless legs/periodic limb movement disorder, dialysis treatment or pathology of renal disease.

A key mechanism for the circadian sleep-wake rhythm disorders in CKD might be the disturbance of the circadian rhythm of the pineal hormone melatonin. The nocturnal melatonin rise above a certain threshold (Dim Light Melatonin Onset) declines with decreasing kidney function and is absent in many daytime haemodialysis (HD) patients. Exogenous melatonin intake in HD patients led to significant improvement of sleep parameters and melatonin rhythm.[97] In addition to the modulation of the circadian sleep-wake rhythm, several functions of melatonin have been put forward, such as influences of melatonin on the cardiovascular system. Firstly, melatonin shows antioxidative properties.[98] Secondly, the absence of a dipping blood pressure profile was associated with the absence of a nocturnal melatonin rise and administration of melatonin was associated with lowering of both systolic and diastolic blood pressure.[99,100] Further research on the effect of melatonin on blood pressure regulation and cardiovascular risk profile is warranted.

Future directions
Although in CKD many both traditional and nontraditional risk factors are associated with increased morbidity and mortality, data substantiating that intervention in these risk factors improves outcome is limited. In contrast, recent studies have shown that, for instance, cholesterol reduction and haemoglobin normalisation fails to improve prognosis. Therefore randomised controlled trials are indispensable to ascertain the optimal levels and optimal interventions for traditional and nontraditional risk factors in CKD and ESRD patients. There are clear indications that impaired renal function is an independent risk factor for developing cardiovascular disease in the general population. However, in spite of numerous studies in patients with CKD the pathophysiological mechanisms leading to this increased risk are unclear. Future research should in our opinion focus on studying mechanistic pathways rather than cross-sectional associations between the individual risk factors and CV mortality and morbidity in CKD patients. Ideally, determinants of the excess cardiovascular risk in patients with CKD will be compared with patients without CKD, in a prospective population-based study with the exclusion of patients with CV disease at the baseline. Furthermore, experimental mechanistic studies in patients with mild kidney failure may also help to

Nanayakkara, et al. Vascular disease and chronic renal failure.

JANUARY 2010, VOL. 68, NO 1

11

identify the impact of traditional risk factors such as hypertension, obesity and diabetes and their interaction with nontraditional risk factors in CKD patients. Finally, randomised controlled trials are necessary to ascertain the optimal levels and optimal intervention for traditional risk factors in CKD and ESRD patients.

In conclusion, factors such as endothelial dysfunction, oxidative stress, vascular ossification, inflammation and anaemia are strongly interrelated and thought to play an important pathophysiological role in the initiation and progression of CVD in patients with CKD. However a causal relation between these factors and increased CVD in CKD patients remains to be further elucidated. Intervention studies designed to test whether the above-mentioned factors are not only markers but also aetiological risk factors may provide further information that may lead to novel therapeutic options.

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JANUARY 2010, VOL. 68, NO 1

12

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13

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