



Accelerated atherosclerosis in patients with Chronic Kidney Disease - the role of traditional and non-traditional risk factors

Peer review status:

No

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Previous Article Reference: http://www.webmedcentral.com/article_view/4759

Article ID: WMC004769

Article Type: Review articles

Submitted on: 25-Nov-2014, 11:19:27 AM GMT **Published on:** 26-Nov-2014, 12:29:53 PM GMT

Article URL: http://www.webmedcentral.com/article_view/4769

Subject Categories: MEDICINE

Keywords: Atherosclerosis, Chronic Kidney Disease

How to cite the article: Alam S, Siddiqui MR. Accelerated atherosclerosis in patients with Chronic Kidney Disease - the role of traditional and non-traditional risk factors. WebmedCentral MEDICINE 2014;5(11):WMC004769

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Source(s) of Funding:

None

Competing Interests:

None

Accelerated atherosclerosis in patients with Chronic Kidney Disease - the role of traditional and non-traditional risk factors

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Abstract

It is becoming increasingly more evident that accelerated atherosclerosis is a serious problem in patients with chronic kidney disease (CKD), with more patients dying prematurely from cardiovascular related diseases than progressing to end stage renal disease. A literature review was conducted to investigate the role of both traditional and non-traditional risk factors of atherosclerosis in these patients, to determine which risk factors had more of a significant effect. Findings showed that underlying pathophysiological mechanisms of the non-traditional risk factors such as inflammation were more heavily involved in creating an environment for development of atherosclerosis in CKD patients. It is therefore vital that primary and secondary prevention strategies are implemented early on in CKD, which would inevitably lead to a better prognosis for such patients.

Introduction to Chronic Kidney Disease

Chronic Kidney disease (CKD) represents a progressive decline in renal function which can be caused by numerous conditions such as diabetic nephropathy, hypertension and vascular disease¹. 'The Kidney Disease Outcomes Quality Initiative' (KDOQI) defines CKD as a glomerular filtration rate (GFR) of less than, or equal to 60 ml/min/1.73 m² of one's body weight for at least 3 months, regardless of the underlying aetiology of the kidney damage. This specific GFR marks a 50% reduction rate in kidney function in comparison to healthy adults¹. Despite the rising prevalence of CKD, it is often left undetected until the disease has advanced considerably, due to its largely asymptomatic nature. This leads to an earlier onset of end stage renal disease (ESRD) in the patient because of lack of secondary preventative measures². For this reason, the NICE guidelines in relation to CKD management aim to actively detect CKD and, wherever possible, prevent progression to renal failure³.

Furthermore, CKD often presents with a multitude of extra-renal complications. Amongst these complications are those that contribute to the acceleration of atherosclerosis and CVD, facilitated by the presence of traditional and non-traditional risk factors for CVD in CKD patients.

Classification of CKD

'The Kidney Disease Outcomes Quality Initiative' (KDOQI) have classified the stages of CKD solely on glomerular filtration rate (GFR). However, it has been revised by 'National service framework for renal services' to include the clauses of persistent proteinuria, albuminuria, haematuria or structural abnormalities in stages 1 & 2 as well as the stated low GFR³.

Stage	Description	GFR (mL/min/1.73m ²)
1	Kidney damage with normal or increased GFR	>or equal to 90
2	Kidney damage with mild decrease in GFR	60 – 89
3	Moderate decrease in GFR	30 – 59
4	Severe decrease in GFR	15 – 29
5	Kidney failure	< 15 (or dialysis)

Figure 1: Adapted from NKF-NDOQI CKD guidelines^[2]

Epidemiology of CKD

Chronic kidney disease affects approximately 20 million people in the USA - equating to ~10% of the population⁴. According to statistics, women are more likely to develop CKD, though men are 50% more likely to progress to kidney failure than women⁴. In the USA, the prevalence of the stages of CKD in proportion are: 1.8% for stage 1, 3.2% for stage 2, 7.7% for stage 3, and 0.35 % for stages 4 and 5⁵. A cross sectional survey was conducted to investigate the prevalence of CKD in adults in England in 2009⁶. This was determined by the use of the 'Chronic Kidney

Disease Epidemiology Collaboration' (CKD-EPI) formula and Modification of Diet in Renal Disease' (MDRD) equation. Participants were categorised in terms of age, gender and socio-economic status to compare the difference in disease prevalence. Results showed a strong correlation between increasing age and prevalence of CKD; the figures rising from 6% in the 16-54 age group and to an average of 33.5% in people aged 75 and older ⁶.

Complications of CKD

Anaemia

The type of anaemia seen in CKD patients is often normochromic and normocytic ⁵. Low red blood cell count/haemoglobin level is present in 50% of CKD sufferers and can be caused by multiple mechanisms including iron/folate deficiency, gastrointestinal bleeding secondary to uremia, and inflammation⁵. It has been hypothesised that anaemia may lead to the further progression of kidney disease. This can be caused by renal ischemia as a result of decreased oxygen reaching the kidneys⁷.

CKD related bone disorders

Renal osteodystrophy and metabolic bone diseases are common complications of CKD ¹⁵. Hyperplasia of the parathyroid glands in CKD, due to mechanisms relating to phosphate retention for example, causes increased bone turnover⁸. This leads to abnormalities in the structure of the bone. Hyperphosphatemia, due to bone disorders in CKD, also increases mortality. This is because elevated serum phosphate levels augment the risk of developing cardiovascular disease, most commonly leading to an increase of atrial and mitral stenosis⁵. Studies have also shown that hypocalcaemia secondary to vitamin D deficiency in CKD is a main contributor to renal osteodystrophy, especially in CKD stage 4 and dialysis patients⁹.

Nutritional problems

Issues pertaining to nutritional deficit and ineffective metabolism are common in CKD patients on dialysis, especially those who have progressed to stages 4 and 5 because of seriously diminished kidney function¹⁰. These changes can lead to inadequate energy generation, anorexia, and in more severe cases, uraemic malnutrition⁵.

It is therefore important that when treating CKD patients, the kidney should not be treated in isolation. Rather, the wider, systemic effects of CKD must also be considered, to prevent premature death and other morbidities.

This review will introduce the topic of atherosclerosis and then begin to discuss the complications of CKD in relation to atherosclerosis.

Atherosclerosis and CKD

Introduction to Atherosclerosis

It was initially thought that atherosclerosis is a degenerative process of the arteries due to aging ¹¹. Russell Ross ¹¹ put forward his 'response to injury hypothesis' of atherosclerosis in the 1970's and revisited it again in 1986. He came to the conclusion that even subtle damage to the endothelium could spark off a cascade of events, leading to atherosclerosis¹². It is now widely accepted that atherosclerosis is an inflammatory response to endothelial wall damage and dyslipidemia, often leading to plaque and subsequent thrombus formation within the vascular wall ¹³. Endothelial injury itself may be enough to initiate atherogenesis in the absence of dyslipidemia. This is because injury compromises intimal permeability to LDL cholesterol, therefore even at normal levels, cholesterol may be deposited in the arteries ¹³.

The rupture of lipid-rich plaques is the most common cause of coronary thrombosis, leading to partial or complete arterial occlusion. It triggers a cascade of further inflammatory events such as the recruitment of macrophages, angiogenesis and remodeling; consequently accounting for 76% of all fatal coronary thrombi ¹⁵.

According to the British Heart Foundation, coronary heart disease (CHD) has been found to be the biggest cause of death in the UK than any other single disease ¹⁵, costing the National Health Service £3500 million annually ¹⁶. In England, over 1.2 million people have had a heart attack and a further 1.7 million suffer from angina. In 2010, CHD caused around 65,000 deaths in the UK ¹⁵.

It has also been reported by the American Heart Association (AHA) that approximately 700,000 people in America have their first coronary incident every year and 500,000 have a recurrent event ²¹. The people who survive the event have an increased mortality and morbidity thereafter, increasing the likelihood of suffering from stroke, recurrent coronary incidents and heart failure ¹⁶.

Though there is a genetic basis to atherosclerosis that increases the manifestation of and susceptibility to the disease ¹³, many environmental risk factors can be targeted as a primary prevention method. The term 'primary prevention' denotes the delaying and

minimising the risk of the manifestation of a first event in individuals who are yet to be diagnosed with a disease¹⁷. In the case of CVD, a primary prevention measure would therefore lie in lowering the prevalence of risk factors, thus preventing the onset of atherosclerosis.

Pathogenesis of atherosclerosis

There are many atherogenic stimuli that act as precipitating factors and drive the process of atherosclerosis (atherogenesis). Having an excessive amount of cholesterol in the blood, in particular, has a very profound effect¹³. Other risk factors include hypertension, diabetes mellitus and smoking¹⁵.

The process of atherosclerosis is initiated following endothelial injury, causing endothelial cell activation and dysfunction, compromising the permeability of the endothelial wall. Activated endothelial cells within the inflamed arterial wall display surface adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), which leads to the binding and recruitment of monocytes in the vascular wall^{11, 18}. Disturbed blood flow and increased wall shear stress can lead to the activation of endothelium and increased expression of leukocyte adhesion molecules. This subsequently causes the retention of lipoproteins in the blood, as they are phagocytosed by monocytes and macrophages¹⁸. Chemo-attractant molecules, such as monocyte chemo-attractant protein-1 (MCP-1), facilitate the penetration of the monocytes into the vascular tunica intima, where it is activated¹⁸.

Once in the vascular wall, pro-inflammatory cytokines released by macrophages begin the chronic inflammatory process¹². Fatty streak lesions eventually occur when macrophages continue to take up lipids, forming lipid-laden foam cells in the intima. This marks the pathological basis for early atherosclerosis¹².

The types of atherosclerotic lesions can be classified into 5 different categories, I, II, and III describing the new, undeveloped lesions, and IV and V describing the lesions at more advanced stages^{19, 20}.

Development of the atherosclerotic lesions

The first of the advanced lesions, type IV, is characterised by a dense accumulation of extracellular lipid with well-defined boundaries²⁰. The smooth muscle cells and intercellular matrix, now replaced with lipid, become dispersed and develop thick basement membranes. The lipid core of the plaque is highly thrombogenic and contains collagen and tissue factor²¹. Following the stabilization of the foam cells in the intima, inflammatory mediators such as T-lymphocytes penetrate the intima wall, secreting

cytokines which subsequently leads to the release of extracellular matrix. This forms the fibrous cap of the advancing plaque¹⁶. Multiple histological studies have found that the formation of connective tissue occurs in those intimal regions in which the extensive accumulation of lipid has caused disarrangement or damage to the intercellular matrix²⁰. As the plaque develops, the gradual narrowing of the lumen leads to a restricted blood flow through the artery, often causing tissue ischaemia²².

Multiple factors can increase the development and growth rate of the atherosclerotic lesions. These include hypertension, diabetes and the presence of CKD^{22,23}.

Plaque rupture

Degradation can cause thinning of the thick fibrous cap. This occurs via the secretion of proteolytic enzymes such as matrix metalloproteinases from the activated macrophages, or through the direct action of cytotoxic T-cells infiltrating the plaque. This makes the plaque unstable and susceptible to rupture¹⁸. Activated CD8+ T cells, as well as a sub-class of CD4+ cells known as CD4+/CD28 null cells, are capable of directly lysing the smooth muscle cell component of the plaque cap presenting autoantigens, also leading to plaque destabilisation and rupture²⁴.

Rupture of the plaque occurs at the weak base of the fibrous cap and acts as a platform upon which coagulation and platelet aggregation begins to occur. The release of Von Willebrand factor alongside the production of thrombin and fibrin creates the ideal environment for the development of a thrombus¹⁶.

The question now arises as to what is the link between CKD and CVD and why are people with CKD more likely to suffer from CV related diseases?

The relationship between CKD and CV

It has been well documented that patients with CKD are more likely to die of cardiovascular disease than of kidney failure²⁵. In fact, patients with CKD are 16 to 40 times more likely to die prematurely of cardiovascular related diseases than progress to ESRD⁴. It has been recently discovered that atheroma begins to develop during the early stages of CKD, leading to the formation of atherosclerotic plaques before ESRD has been reached²⁶. It has been suggested that this is primarily due to a higher prevalence of cardiovascular related risk factors that are often present in CKD patients, such as diabetes²⁷. This will be described in

more detail later on in the paper.

The link between cardiovascular disease and mild renal insufficiency has also been suggested by the results of the Framingham heart study, where it was found that there was a trend of more cardiovascular events in the 246 men that participated with mild renal insufficiency in comparison to those without it ²⁵.

The further the progression from CKD to ESRD, the higher the risk of CV related pathology. It was found that CV mortality is increased by 500 fold in ESRD, in comparison to age-matched individuals with normal renal function ²⁵. Therefore, the likelihood of mortality from CVD increases in proportion to decreasing GFR ²⁸.

A randomized control trial conducted by Lewis et al ²⁹, followed women for a period of 10 years and recorded eGFR scores using both the MDRD equation and the CKD-EPI formula. The results of the study demonstrated that the atherosclerotic vascular disease (ASVD) related hospitalisation and mortality increased markedly with decreasing eGFR, regardless of which formula was used for the calculation of eGFR. Furthermore, it was found that the inversely proportional relationship between eGFR and AVSD events was independent of other factors, relating to an increased ASVD risk ²⁹.

Cardiovascular complications in Chronic Kidney Disease

There are multiple mechanisms through which reduced glomerular filtration rate may accelerate cardiovascular morbidity through endothelial dysfunction. For example, a decline in kidney function and a subsequent inability to excrete and produce substances, such as reninase, could affect the heart's ability to operate effectively ³⁰.

As previously mentioned, atherosclerotic lesions are highly prevalent in CKD patients. In CKD, these lesions are characterised as being calcified in contrast to the familiar fibroatheromatous plaques that are present in other atherogenic diseases. These calcified lesions can lead to ischaemic heart disease, presenting clinically with angina, myocardial infarction, or sudden cardiac death ²³.

The low GFR in CKD patients also leads to inefficient water regulation which exposes stressors, such as volume overload, on the heart. An overload of pressure on the heart can also result due to a combination of hypertension and arterial stiffening. These mechanisms play an important role in cardiomyopathy, consequently leading to left ventricular failure ³¹. A study conducted by Paoletti et al³² also found that left ventricular hypertrophy (LVH) was highly prevalent in non- diabetic CKD patients,

with evidence of LVH occurring at even the early, pre-dialysis stages of CKD ³².

Furthermore, there is a possibility that glomerular cells and cells in the endothelium of vasculature are very much alike in character and in the way they respond to insults. This explains why atherosclerosis and glomerulosclerosis have been suggested to be processes of a similar nature ^[27].

Endothelial dysfunction is a common pathway through which multiple mechanisms of CVD converge with CKD related abnormalities ³⁰. The extent of the effect of endothelial cell dysfunction can be estimated through the measuring of circulating markers of processes that damage the endothelial cell lining and interfere with their function. Endothelial cell function can be compromised by processes such as oxidative stress, inflammation and dyslipidemia ³⁰.

Pro-inflammatory mediators that are present within CKD and end stage kidney disease (ESKD) patients contribute to their chronic inflammatory state and consequential morbidity and mortality. Examples of these mediators include lipopolysaccharides, beta glucans and acetate ³⁴.

The role of inflammation in the acceleration of atherosclerosis in CKD patients will be discussed again at a later stage.

The risk factors for the progression of CVD and acceleration of atherosclerosis in CKD patients have been grouped into two broad categories:

1. **Conventional, traditional risk factors.** Traditional risk factors are gathered from prospective cohort studies like the Framingham Heart Study (1948) and are taken into account when estimating the risk of developing CHD through the use of the Framingham predictive instrument ³⁵. Examples of traditional risk factors include: age, gender (male), hypertension, diabetes mellitus, smoking and menopause ⁶⁶.
2. **Novel, non-traditional risk factors.** These risk factors are defined by the metabolic and haemodynamic discrepancies that CKD exposes on an individual. For example, inflammation, endothelial dysfunction and oxidative stress, dyslipidaemia, calcium phosphate imbalance, anaemia, malnutrition and albuminuria ³⁵.

Traditional risk factors

Age

The inverse relationship between increasing age and decreasing GFR has been supported by many studies ⁶. Studies have shown that the risk of developing CKD is increased by four times over the age of 65 ³⁷. Similarly,

the National Health and Nutrition Examination Survey (NHANES) conducted in 1999 found that moderate or severe CKD was present in over one third of persons aged 70 and older (GFR < 60 mL/min/1.73m²)⁶⁷.

However, it is still unclear whether this decline in kidney function is a consequence of the natural physiological deterioration that comes with age, or a disease process that reduces the functional capacity of the kidneys. Age-related renal dysfunction and decrease in GFR is related to kidney and tubular atrophy, renal vascular/glomerular sclerosis and thinning of the renal cortex³⁷. Pathological disease processes include diseases of the glomerulus³⁷ alongside chronic diseases such as hypertension and diabetes⁶⁷.

Despite the underlying aetiology of the decline in renal function with age, the physiological consequences of the deterioration may result in multi-organ dysfunction, including CV events.

In a similar fashion, the risk of CVD also increases with age. This is due to a gradual degeneration in the cardiovascular system such as a decline in arterial elasticity and compliance³⁸. Collectively, these changes lead to an increase in vascular resistance, which itself is a risk factor for CVD³⁸.

Hypertension

The presence of hypertension in CKD presents as another important risk factor for CVD. This is due to multiple mechanisms, with activation of the renin-angiotensin-aldosterone system (RAAS) being the most prominent²⁵.

The chain of events in the RAAS begins with the detection of the decreased sodium and chloride levels by the macula densa of kidney and the subsequent secretion of the enzyme renin from the juxtaglomerular apparatus. This facilitates the conversion of circulating angiotensinogen to angiotensin-I. Angiotensin converting enzyme (ACE) acts on angiotensin-I to generate angiotensin-II and simultaneously inactivates bradykinin, a potent vasodilator. Angiotensin-II has multiple functions, primarily causing systemic vasoconstriction and increasing the production of the mineralocorticoid, aldosterone. This has the principle role of causing sodium and water retention, resulting in hypervolemia. Together, therefore, angiotensin-II and aldosterone increase blood pressure. In the kidney, angiotensin-II predominantly causes a greater constrictive effect of the efferent glomerular arteriole rather than the afferent arteriole. This consequently increases glomerular capillary hydrostatic pressure, in attempt to normalise GFR levels³⁹. Angiotensin-II also facilitates the process of atherosclerosis due to

increased oxidative stress through the stimulation of enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. In addition to this, it also activates NF- κ B, adhesion molecules and transforming growth factor, accelerating atherosclerosis through the induction of inflammation and vascular growth^[27].

Glomerular capillary hypertension also occurs in CKD to increase filtration pressure and compensate for the loss of functioning glomeruli due to kidney damage. Despite the short-term solution this provides of maintaining the GFR, the long term effects of continual adaptation lead to a decline in kidney function³⁹. Another cause of hypertension involves the implication of raised endothelin-1 [ET-1] in CKD⁴⁰. The increased synthesis of renal ET-1 is mediated by substances such as cytokines and vasoactive factors that are present in CKD. ET-1 has a potent vasoconstrictive effect and can stimulate pathological vascular remodelling and fibrosis in the kidney⁴⁰.

Inappropriate activation of the RAAS and ET system takes a toll on the heart by increasing preload through hypervolemia, and afterload due to vasoconstriction and eventual atherosclerosis and LVH³⁰. The relationship between hypertension in CKD and CVD is also supported by the outcomes of the Hypertension Optimal Treatment (HOT) study, (analysed by Ruilope et al, cited by Schiffrin)²⁵.

This randomised, prospective trial followed a large sample of 18 790 hypertensive individuals for an average of 3.8 years, after which relative risks for major cardiovascular events and total mortality were calculated. Results demonstrated that patients with a GFR < 60mL/min had an adjusted relative risk of 1.65 and those with a GFR of greater than this had a relative risk of 1.58. This means that there was an increase of 7 % in mortality and CVD related morbidity in hypertensive patients with moderate and severe CKD in comparison to those with a mild decrease in GFR²⁵.

Diabetes

Diabetes induced renal disease is primarily categorised by microalbuminuria and reduced GFR⁴¹. Diminished kidney function is highly prevalent in diabetic patients, shown by the results of the NHANES III, in which renal insufficiency was seen in 30% of adults with type 2 diabetes⁴¹. Diabetes also increases the risk of all-cause mortality and cardiac death, with CVD accounting for three quarters of the deaths of diabetic patients⁴².

The pathophysiology of diabetic kidney disease is believed to occur through the generation of

morphological changes in renal tubules, arterioles and interstitium and through the process of glomerulopathy⁴¹. Understandably, it is the latter process that causes the decline of GFR, most notably through mesangial expansion. Furthermore, the severity of the changes is exacerbated by albuminuria⁴¹. Studies in rats have shown that renal vasodilatation and intraglomerular hypertension can be caused by metabolic anomalies present in hyperglycaemic and insulin deficient states⁴³. These changes can be reversed initially, if insulin is monitored and controlled properly, as they occur early in the disease before signs of nephron loss⁴³.

A study by Ohtake et al⁴⁴ was carried out on 30 CKD stage 5 patients with no history of angina and myocardial infarction before initiation of renal replacement therapy. Procedures included measurement of the intima-media thickness of the carotid arteries and ankle-brachial index. Markers of coronary artery stenosis were also evaluated. Observations showed more than 50% stenosis in 16 of the 30 CKD patients. Further analysis showed that diabetes was significant in the patients and acted as an independent risk factor for cardiac events. Atherosclerotic lesions were seen in 83% of diabetic patients^{42,44}.

The presence of diabetes in an individual leads to a prolonged exposure of proteins to glucose, or glucose-derived species. This induces the production of advanced glycation end products (AGEs) in the vascular system, which is increased in CKD. AGEs can cause oxidation of LDLs, the accumulation of cholesterol in macrophages and subsequently increase foam cell formation. This can lead to atherogenesis, consequently accelerating the process of atherosclerosis²⁷. Furthermore, diabetic patients express higher levels of mediators that enhance the activation and adhesion of platelets. For example, there is an increased surface expression of the integrin complex glycoprotein IIb/IIIa which binds to Von Willebrand factor during the process of platelet adhesion⁴². Diabetes most commonly exerts its effects on the large arteries of the body, the three main sites being the coronary, cerebral and peripheral arteries⁴¹.

Diabetes increases the risk of CKD just as it increases the risk of CVD through the acceleration of atherosclerosis. In the same way, the presence of diminished kidney function also causes the development of atherosclerosis in patients with diabetes, acting as an independent risk factor for the formation of atheroma²⁷.

Smoking

Smoking is from amongst the most easily preventable

risk factors for an array of chronic, systemic diseases such as CKD and CVD. This has been demonstrated by increasing evidence through trials, observations and cohort studies. In a trial conducted by Halimi et al⁴⁵, a sample of 28 409 volunteers from the general population, including current and former smokers, were studied. Smoking-related non-reversible nephropathy was noted, with an increased relative risk for macroalbuminuria. Furthermore, there was a higher Creatinine Clearance (CR) in participants who were smokers in comparison to non-smokers, indicating towards renal hyperfiltration induced by smoking^{45,46}.

Epidemiological studies also show that there is also a positive correlation between smoking and the incidence of coronary artery disease and MIs⁴⁷.

Cigarette smoke is made of 92% gaseous substances and 8% tar, which contains the addictive substance, nicotine. Both phases contain billions of free radicals per puff⁴⁷. In general, the pathophysiological mechanisms involved in smoking-induced acceleration of disease broadly fall in to 2 categories, namely haemodynamic and non-haemodynamic⁴⁶. Haemodynamic mechanisms include the increase of blood pressure (BP) and heart rate (HR), due to the effect of nicotine acting on nicotinic receptors on sympathetic nerve endings. This increases the concentration of adrenaline and noradrenaline in the blood⁶⁵. In vitro studies show that components of cigarette smoke also mediate a decrease in nitric oxide mediated vasodilatation⁴⁷. The overall increase in BP leads to further decline in kidney function⁴⁶.

Non-haemodynamic mechanisms include inappropriate activation of growth factors such as TGF- β 1, ET-1 and Angiotensin II, oxidative stress pathways and renal mesangial cell proliferation⁴⁶.

The process of atherosclerosis is specifically enhanced by cigarette smoking primarily by impairment of lipid profiles, vasomotor dysfunction and inflammation⁴⁷. Due to such effects, the Canadian Coronary Atherosclerosis Intervention trial results branded smoking to be an independent risk factor for the formation of new coronary atherosclerotic lesions⁴⁷. The prevalence of smoking-induced atherosclerosis in CKD patients is most commonly expressed in the form of peripheral arterial disease⁴⁶.

A longitudinal cohort study in the United States aimed to identify risk factors as predictors of CVD in 5808 patients living in the community. The mean follow-up time was 8.6 years. The traditional risk factors in CKD were shown to have the most significant absolute risk for CVD. From amongst these, smoking was found to have caused 20 deaths per 100 person years⁴⁸.

Non-traditional risk factors

Inflammation

Inflammation is a vascular response to stimuli, triggered by the immune system. Though it is involved as part of the natural healing process, it can often become maladaptive, acting as a detriment to normal systemic functions³⁴.

Inflammation is thought to be a major risk factor in increasing the onset of atherosclerosis and other cardiovascular diseases in CKD patients^{5, 27, 34}. The results of a study⁴⁹ carried out in 2004 found that, during a 10 year follow-up period, mortality from CVD was 10 % for patients with CKD stages 3,4 and 5 at enrolment. Inflammatory markers, such as C-reactive protein (CRP) were found to be elevated in these patients. It was concluded that raised CRP levels acted as an independent risk factor and predictor of CV, as well as all-cause mortality in CKD patients. Studies have also shown that there are signs of inflammation in up to half of both CKD pre-dialysis and dialysis patients²⁷.

Inflammation can be caused by abnormalities in the body's internal environment and dysfunctional homeostatic processes. This means that disease processes that subsequently cause renal damage can activate the inflammatory cascade, due to the role of the kidneys in maintaining a constant environment in the body³⁴. For this reason, one of the mechanisms that may lead to the increase in inflammatory mediators has been suggested to be the level of malnourishment caused by onset of CKD²⁵. Malnourishment in these patients can be demonstrated by the low levels of plasma pre-albumin, albumin and transferrin²⁵.

Following endothelial damage, the inflammatory response takes place, occurring through the activation of leukocytes, cytokines and other mediators. This leads to the initiation and formation of atherosclerotic lesions¹⁸. Chronic disease states such as hypertension, diabetes and dyslipidemia provide an environment which can trigger the inflammatory cascade, consequently contributing to atherogenesis¹⁸. For this reason, inflammation has been found to be a common causal pathway for CVD in multiple diseases.

A study conducted at St George's Hospital in London⁵⁰ studied 76 CKD patients of different stages and compared results with controls matched for age and gender. Observations showed an increased intima-media thickness and CRP levels, alongside

decreased brachial flow mediated dilatation in the CKD patients in comparison to controls. All measurements had a p value of < 0.001, which demonstrated statistical significance. The findings support the pro-inflammatory state of CKD patients and suggest the progression of atherosclerotic lesions in these circumstances⁵⁰.

Whilst inflammation remains an important risk factor for the development of CKD, it seems that CKD may also be the cause of an amplification of further pro-inflammatory effects. An example of this is that CKD induces the accumulation of uraemic toxins, which have the capacity to trigger inflammatory events²⁷. Inflammatory stimuli then cause the production of reactive oxygen species from phagocytic cells within the kidneys. Therefore, this acts as a vicious cycle, eventually leading to the process of atherogenesis²⁷. Excessive oxidative stress increases circulating inflammatory biomarkers and can cause activation of NADPH oxidase, a complex implicated in atherogenesis²⁵. Inflammation in CKD patients can also cause an increase in coagulation and activation of platelets, via p-selectin and von Willebrand factor, leading to vascular abnormalities³⁴. CKD induced CVD as a result of inflammatory processes is also a problem in paediatric patients, as well as in adults. A study by Matteucci et al³⁴ found 10.2% of the 156 children with CKD (stages 2-4) followed had ventricular remodelling and 21% expressed eccentric LVH.

Endothelial dysfunction

Endothelial dysfunction is an independent risk factor for both CKD and CVD, triggering mechanisms such as inflammation; the hallmark of atherogenesis and renal dysfunction^{27, 34, 25}. Research has shown that vascular endothelium plays the role of an active autocrine, paracrine and endocrine organ, and is vital for homeostatic maintenance of the vascular system¹³. Healthy endothelium does not permit the adhesion of leukocytes. However, factors that damage the endothelium, such as an unhealthy diet, can lead to the expression of adhesion molecules that cause binding of leukocytes¹⁸. Endothelial damage can also result from hypertension. This can cause hyaline thickening of renal vasculature and atherogenesis in larger arteries²⁷. In particular, endothelial dysfunction of the microvasculature is what exacerbates the progression of renal disease²⁵.

The role of endothelial dysfunction as a risk factor in CKD for diseases such as CVD has been explored by many studies. A cross sectional study⁵¹ was conducted using non-diabetic CKD patients of different stages, who were matched against controls for age

and gender. AGE products and AGE receptors were measured in the blood. The activity of endothelial cells was also recorded, after assessment of observed changes in the microcirculation when subject to hyperthermic and ischaemic conditions. Results found that, in contrast to controls, patients with a low GFR (< 80ml/min per 1.73 m²) showed significantly less hyperthermia and post-occlusive reactive hyperemia in response to ischaemia. This shows that with the progression of renal disease, there is a reduction in endothelium-mediated vasodilatation, indicating endothelial dysfunction. Decreasing GFR in the more severe cases of CKD also led to increasing AGE/AGE receptor levels⁵¹. This is significant because the increase in AGEs contributes to the progression of atherosclerosis through production of vasoactive factors and cytokines⁵¹. The contribution of AGEs in CVD has been discussed in more detail at an earlier stage of this paper.

Nitric oxide (NO) is a potent vasodilator of vascular endothelium and is essential in the maintaining a healthy blood flow. Endothelial dysfunction in CKD leads to a decreased synthesis of endothelium-derived NO. In turn, this results in a reduction in the atheroprotective and vasodilatory effects of NO, causing a disturbance to the regulation of blood pressure¹⁴. NO synthesis is mediated by NO synthase (NOS) enzymes and occurs through stereo-specific oxidation of the precursor L-arginine⁵². Animal studies exploring the role of NO in CKD found that glomerular hypertension and ischemia alongside glomerulosclerosis and proteinuria can occur when NOS inhibition is induced⁵³.

The production of NO is disrupted due to multiple mechanisms in CKD. For example, CKD gives rise to elevated levels of circulating NOS inhibitors, such as asymmetric dimethylarginine (ADMA)^{27,25}, synthesised in the endothelium, heart and other tissues in the cardiovascular system²⁵. The overall increase in NOS inhibitors may be due to the decline in dimethylarginine dimethylaminohydrolase (DDAH) metabolism, an enzyme important in the removal of methylarginines such as ADMA²⁵. Nitric oxide is also deficient in CKD patients due to decreased levels of renal L-arginine synthesis⁵³.

Kielstein et al⁵² conducted a study to determine the levels of ADMA and L-arginine with regards to plasma nitrate levels in haemodialysis (HD) and peritoneal dialysis (PD) patients. Dimethylarginine and L-arginine levels in plasma were measured using high-performance liquid chromatography and the presence and role of ASVD was analysed. Results showed that ADMA levels of HD-treated patients were

six times higher than in healthy control subjects. Nitrate levels were also decreased in these patients, suggesting that ADMA may be implicated in NO synthesis. Furthermore, it was also noted that ADMA levels were increased in HD-treated patients who expressed signs of ASVD, in comparison to those patients without atherosclerotic lesions. This could mean that accumulation of dimethylarginines, such as ADMA, can accelerate the rate of atherosclerosis in patients with CKD⁵².

Calcium-phosphate metabolism

Abnormalities of calcium and phosphate metabolism are just a few of the array of mineral metabolism disorders that are present in CKD. These imbalances may cause the acceleration of a number of subsequent disease processes, such as CVD. In the case of CVD, for example, CKD increases the formation of calcified atherosclerotic lesions and gives rise to valvular heart disease²⁵. Studies have shown the prevalence of coronary artery calcification to be 40% in CKD patients compared to subjects with no renal dysfunction²⁵.

Vascular calcification may occur in CKD patients due to abnormally high plasma calcium and phosphate concentrations causing passive accumulation and precipitation in vessels²⁵. Other mechanisms include a reduction in calcification inhibitors, such as fetuin A, and hydroxyapatite formation in CKD²⁵. Renal dysfunction causes a decrease in phosphorus excretion and therefore an increase in plasma phosphorus levels. This results in a reduction in ionised calcium, due to Bricker's 1972 'trade-off hypothesis'⁵⁴, stimulating the release of excess parathyroid hormone (PTH)⁵⁵. This marks the onset of CKD-induced secondary hyperparathyroidism.

Accumulation of excess PTH has detrimental skeletal and extra-skeletal complications⁵⁵. This is because the primary role of PTH is to prevent hypocalcaemia. Therefore, it actively works to increase calcium levels by stimulating the activity of osteoclasts, causing the release of calcium through the process of cell lysis⁵⁶. This also outlines the primary mechanism behind renal osteodystrophy^{5,56}.

Vitamin D also plays a vital role in calcium-phosphate regulation. When activated by the liver and kidneys, Vitamin D, now called 1,25 dihydroxyvitamin D₃, increases calcium absorption from the gut and causes the down regulation of PTH⁵⁶. Therefore, the decline in the number of functioning nephrons in CKD also contributes to the onset of secondary hyperparathyroidism due to the decrease in calcitriol production by the kidney⁵⁶.

In CKD, the production of active vitamin D is further impeded by the reduction of renal 1- α -hydroxylase activity, an enzyme vital for the final hydroxylation reaction⁵⁶. This is why calcitriol and vitamin D supplements can be given as a form of treatment to treat secondary hyperparathyroidism and vascular calcification in CKD patients^{5, 56, 57}.

Increased phosphate levels pose a risk to CKD patients as they are thought to exacerbate calcification in the vascular system²⁵. Due to the increased binding affinity between calcium and phosphorus ions, an increase in the serum concentration of both or either ions increases the possibility of the formation of an insoluble mass⁵⁶.

The impact of hyperphosphatemia on calcification and subsequent mortality from CV related diseases has been supported by a study carried out by Ganesh et al⁵⁸ in 2001. 12,833 haemodialysis patients participated in this 2-year follow up cohort study to determine the degree of the role of phosphate in relation to cause-specific mortality. Overall, there was a total of 4120 deaths within the course of the 2-year follow up. Results showed that an increase of 1mg/dl in serum phosphate was correlated with a risk of mortality from coronary artery disease (CAD) by 9% and a risk of sudden death by 6%. In addition to this, the greatest risk for patients who suffered CAD death was found to be in patients who had an elevated serum phosphate level of > 6.5mg/dl.

Conclusion

There has been a plethora of studies conducted to determine role of risk factors in the acceleration of atherosclerosis in individuals with compromised renal function. Research on this topic provides compelling evidence that both traditional and non-traditional risk factors are of paramount importance when considering pathogenic mechanisms and treatment options to prevent CV morbidity and mortality in CKD patients.

I believe, however, that inflammation in CKD is the primary underlying risk factor for the development of atherosclerosis in these patients. This is because it has been observed that inflammation is the common pathway for the convergence of multiple atherogenic triggers, such as smoking, diabetes and dyslipidemia. In addition to this, inflammatory mediators, such as tumour necrosis factor- α (TNF- α) and other cytokines, are raised in CKD⁵⁹. These mediators directly initiate the formation of atherosclerotic lesions.

Vitamin D therapy has become increasingly popular

for the treatment of inflammation in CKD patients. Receptors for the fat-soluble vitamin D are present on most organs, including the heart, kidney and vascular system⁵⁷. The mechanism of the action of Vitamin D therapy includes inhibition of angiogenesis and smooth muscle proliferation and down-regulation of nuclear factor kappa-b (NF- κ B), a protein complex implicated in the regulation of inflammatory processes⁵⁷. Vitamin D has also been known to regulate the expression of tissue matrix metalloproteinases which cause vascular remodeling as part of the inflammatory cascade⁵⁷. A prospective study⁶⁰ following 158 haemodialysis patients aimed to monitor the effects of vitamin D supplementation over the period of 1-year. Results showed an increase in active vitamin D levels and a reduction in CRP levels, indicating towards the anti-inflammatory actions of vitamin D.

With the rising prevalence of CKD², it is vital that the CKD management and prevention guidelines are continually evaluated and brought in to practice. As part of the primary prevention strategy, the CKD Quality and Outcomes Framework (QOF) was recently introduced, allowing a larger scope for the detection of CKD through primary care management. This has led to a 4% increase in the diagnosis of the adult population since the introduction of the strategy⁶¹. According to the 2011 National Institute of Clinical Excellence (NICE) Guidelines, testing should be offered to individuals with risk factors for CKD and local arrangements should be made to ensure that prevalent CKD patients are assessed for cardiovascular risk⁶². NICE also suggests the use of statins and anti-platelet drugs for secondary prevention of CVD in CKD patients and bisphosphonates for the prevention of osteoporosis in patients with CKD stages 1-3⁶³. For the treatment of hypertension in CKD, recommendations are made to begin with the use of ACE inhibitors. In the case of low ACE inhibitor tolerance, the use of angiotensin receptor blockers (ARBs) are advised⁶³.

During 2009-10, the National Health Service (NHS) in the UK spent an estimated £1.44-1.45 billion on CKD costs; approximately 1.3% of the entire NHS budget in that year⁶⁴. From this, more than 50% was spent on renal replacement therapy, life-extending treatments that are only beneficial to 2% of the CKD patient population⁶⁴.

Primary prevention of CKD onset through careful monitoring for risk factors and secondary prevention of CKD-related complications, such as atherosclerosis and bone disorders, would inevitably reduce costs related to CKD management. To improve mortality rates of CKD patients due to CVD, it is imperative that

we look beyond treating the immediate renal complications of CKD so it is possible to curb the acceleration of atherosclerosis in these patients.

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