Inflammation and Endothelial Dysfunction in the Initiation and Propagation of Cardiovascular Disease in Patients with Chronic Kidney Disease

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Authors' contributions

Review Article

ABSTRACT

Background: There are many different theories on atherosclerosis pathophysiology. The dominant one is endothelial function disorder resulting from the existence of risk factors such as dyslipidemia, diabetes, smoking, and high blood pressure and hyperhomocysteinemia bacterial and viral infections. The inflammation is an important parameter for CKD appearance and evolution too. In this review we will summarize the most recent evidence that inflammation and endothelial dysfunction are implicated in the enhanced cardiovascular risk experienced by individuals with CKD, we will not discuss the role of dialysis or transplantation in the propagation of cardiovascular risk.
Literature Review: Electronic medical databases were searched using as key - words

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the terms: "atherosclerosis", "hemodialysis patient", "end stage renal disease", "Chronic Inflammation", "Endothelial Dysfunction". The search was conducted in English language. All studies referred to the correlation of the key terms were included and highlight the Inflammation and Endothelial Dysfunction in the Initiation and Propagation of Cardiovascular Disease in patients with Chronic Kidney Disease.

Conclusions: The presence of enhanced CV risk in patients with CKD is well known but the mechanisms by which it occurs are less clear. The endothelium is a complex, multi-functional organ with a variety of vascular homeostatic functions and ED has been shown to result in the initiation and propagation of atherosclerosis. Causes of ED are numerous but inflammation and oxidative stress are clearly highly implicated; albuminuria (even at levels thought to be well below previous definitions of abnormal) may contribute to the inflammatory process, as might dyslipidemia (though a combination of traditional and no-traditional pathways).

1. INTRODUCTION

Cardiovascular disease (CVD) results from the formation of occlusive atherosclerotic plaques in the circulation. While it was previously thought that such plaques were inert collections of lipids and fibrous tissue it is now accepted that the atherosclerotic process is one in which inflammation is implicated [1]. It has also been observed that individuals with Chronic Kidney Disease (CKD) are at increased risk of cardiovascular events and share traditional risk factors such as diabetes and hypertension which explain only in part the increased cardiovascular risk. It has been proposed that the inflammatory response, through the initiation and propagation of endothelial dysfunction, may be a cause and consequence of both CVD and CKD. In this review we will summarize the most recent evidences that inflammation and endothelial dysfunction are implicated in the enhanced cardiovascular risk experienced by individuals with CKD. However, we will not discuss the role of dialysis or transplantation in the propagation of cardiovascular risk.

2. INFLAMMATION AS A PROMOTER OF ENDOTHELIAL DYSFUNCTION

The endothelium is a single layer of cells that separates the vessel wall from the blood stream. It is now accepted that far from being an inert barrier the endothelium has a number of vital homeostatic roles. In response to potential damage the endothelium is frequently activated as a protective response, the result of this activation is reduced vessel dilation and increased adhesion of leukocytes and platelets. Prolonged activation of the endothelium can be described as endothelial dysfunction (ED), as the normal homeostatic functions of the endothelium are disrupted [2].

The relationship between ED and inflammation is complex. In the 'response to injury' hypothesis, inflammation is one of several factors which can contribute to ED, and in turn ED results in atherosclerosis and inflammation. As a result inflammation is an important factor that not only initiates ED but also propagates and is a consequence of ED [3-5]. In a number of animal models signs of inflammation are seen in tandem with lipid accumulation in the vessel wall, leukocytes have been found to localize in early plaques and while the healthy endothelium does not usually support the binding of these cells, experimental models have

shown that they can be encouraged to do so in the context of an atherogenic diet [6]. When leukocytes have bound to the endothelium they have then been shown to invade the intima via a number of chemo attractant molecules, such as Monocyte Chemo attractant protein-1 (MCP-1). The leucocytes are then able to participate in and perpetuate a local inflammatory response [7-9]. Because of its location measurement of endothelial function was traditionally complex and involved invasive methodology, however, recent advances have led to a number of different methods of assessing endothelial function, these have been described in a recent detailed review by Lekakis et al. [10] and are summarized in Table 1. They include, flow mediated dilatation (FMD), pulse wave analysis, arterial tonometry and a variety of biomarkers.

Table 1. Methods of measuring endothelial function in the clinic

Technique	Description	Shortcomings
Direct coronary measurement	Coronary angiography with pharmacological stimuli to assess vasodilation [11]	Invasive
MRI/PET coronary imaging	Allows quantification of myocardial function and micro vascular function[12] PET is the method of choice for myocardial blood flow assessment	Expensive
Venous occlusion plethysmography	Measurement of muscular blood flow by assessment of tissue volume change induced by the inflation of a cuff proximally [13]	Invasive
Flow mediated dilation	Vessels are imaged after induced hyperaemia and diameter measured before and after removal of hyperaemia [14]	Significant inter and intra operator variability
Pulse wave analysis	Non-invasive arterial waveform imaging to measure the augmentation index (the difference between the 1st and 2nd systolic peak)	Little data available yet on relationship with treatment and clinical outcomes
Peripheral artery tonometry	After induced hyperaemia the digital pulse wave amplitude is measured [15]	Yet to be validated in large cohorts

3. CHRONIC KIDNEY DISEASE AND ENDOTHELIAL DYSFUNCTION

It is well described that individuals with CKD are at enhanced cardiovascular risk [16]. While a number of traditional cardiovascular risk factors may co-exist in individuals with CKD (for example diabetes, hypertension and hyperlipidemia) it is clear that not all the cardiovascular risk experienced by these individuals can be attributed to these risk factors [17,18]. An explanation for this is that there are non-traditional or novel risk factors, for the development of CVD in CKD that have not previously been considered. These proposed novel risk factors include albuminuria, anemia, inflammation, abnormal calcium/phosphate metabolism, oxidative stress, malnutrition and ED (which may be the consequence as well as the cause of a number of the other novel risk factors). We will now focus on several significant putative risk factors for ED in CKD; albuminuria decreased nitric oxide activation, dyslipidemia and oxidative stress.

4. ALBUMINURIA AND ENDOTHELIAL DYSFUNCTION IN CKD

Albuminuria has been associated with cardiovascular diseases in both diabetic and non-diabetic patients; the association has been shown to be independent of traditional risk factors such as smoking and hypertension [19-21].

This association has been seen when micro albuminuria is present and the pathophysiological basis of the association is not clearly understood. It has been suggested that rather than being a causative association albuminuria reflects generalized ED, itself a cardiovascular risk factor [22]. As the renal endothelium influences the glomerular capillary barrier it is plausible that renal ED may be involved in the development of albuminuria [23].

A defect in the endothelial surface layer (ESL) has been suggested as a mechanistic link between widespread vascular dysfunction and albuminuria in CKD. Albuminuria in the glomerulus could show damage in the endothelial glycocalyx that alters the micro vascular permeability of the multiple capillary beds. Similar phenomenon has been observed not only in diabetes but also in ischemia-reperfusion injury and infectious disease [24].

During glomerular injury filtration of low-molecular-weight proteins increases and larger proteins start to penetrate the glomerular filtration barrier leading to proteinuria causing overload of the proximal tubule, chronic hypoxia and inflammation induced by a glomerulotubular feedback loop.- Production of cytokines, chemo attractants and matrix proteins by tubular epithelial cells may stimulate interstitial inflammation and scarring [25].

To explore the associations a number of studies have been conducted. In two different cohorts of renal patients (one with nephropathy caused by type-2 diabetes but normal renal function and one with advanced CKD), higher degree of albuminuria was strongly associated with increased levels of PTX3, an inflammatory mediator structurally linked to CRP and serum amyloid P. PTX3 has been shown to be elevated in prevalent HD patients as compared with healthy individuals and has been identified as a novel mortality risk factor in incident dialysis patients, independent of traditional risk factors and CRP [26].

The Framingham Offspring cohort study enrolled 3294 participants (53% women) with mean age 61 demonstrate that TNFR2 (TNFα receptor) was   associated with measures of kidney function and albuminuria, suggesting that TNF-alpha pathway may potentially be a key player in the mediation of inflammation in kidney disease [27].

Stehouwer et al. [23] hypothesized that ED and chronic inflammation explained the association between microalbuminuria and mortality; to address this they followed 328 type 2 diabetics for a mean of 9 years (using von Willebrand factor (vWF), soluble E selectin and soluble vascular cell adhesion to assess ED and C-reactive protein and fibrinogen as markers of inflammation). They found that individuals with markers of both ED and inflammation were at increased risk of death, the presence of such markers were also strongly associated with the development of increases in, urinary albumin excretion during follow up; traditional risk factors were also associated with increases in markers of both ED and inflammation. As a result of their findings they concluded that traditional risk factors may contribute to ED and inflammation and microalbuminuria and consequently increase cardiovascular risk.

Another study to explore the relationship between ED and albuminuria involved 94 diabetic subjects, again with vWF being used as a measure of ED; patients were divided into groups

dependent upon their baseline urinary albumin excretion and were followed up for 9 up to 53 months. Outcomes related to urinary albumin excretion, cardiovascular event rates and death were collected. The results demonstrated that there was a relationship between increased urinary albumin excretion, cardiovascular events and ED in patients with type 2 diabetes, ED was strongly related to the development of microalbuminuria and the occurrence of cardiovascular events [28].

Albuminuria is also connected with CKD without diabetic etiology. A prospective study performed in 1375 non diabetic and 1056 diabetic type I subjects during the 7-year follow-up, shown that clinical proteinuria predicts the incidence of stroke, as well as serious CHD events (CHD death or nonfatal MI), both in nondiabetic and NIDDM subjects. CVD mortality and atherosclerotic vascular disease events were higher in nondiabetic and NIDDM subjects with clinical albuminuria (>300 mg/L) than in those without proteinuria. The implication of these findings in the studied subjects   is that increased urinary protein excretion rate may be the reflection of widespread vascular damage. Albuminuria is not only the complication of some serious disease but could be the reflection of underlying disorder itself. In this study were found statistically significant associations between albuminuria and history of hypertension and elevated levels of triglycerides and total and decreased levels of HDL cholesterol [29].

These studies suggest that albuminuria and ED are intimately related and that the relationship is complex, ED being both a potential initiator and propagator of albuminuria but in addition that albuminuria also serves as a marker of ED.

5. NITRIC OXIDE AND ED IN CKD

Oxidative stress is the imbalance between the production of reactive oxygen species and their clearance, such imbalance results in free radical and peroxide production which result in cellular damage [30]. In combination with these reactive oxygen species and free radicals, nitric oxide (NO) contributes to the atherosclerotic process involving the endothelium with reduced NO bioavailability being associated with increased cardiovascular risk [31-33].

It is not clear by what mechanism this effect takes places, it is possible that reduced NO production (via decreased NO synthase (NOS), itself a consequence of the NOS inhibitor asymmetric Dimethylarginine (ADMA), decreased availability of the NOS substrate L-arginine or increased concentration of oxygen radical species that inactivate NO may explain the reduced bioavailability of NO [34-38].

Wever et al. [39] hypothesized that NO production was reduced in individuals with CKD, in a group of 33 patients (7 of whom had CKD, 7 had familial hypercholesterolemia, 14 healthy controls and 5 healthy smokers) they measured whole body NO production by giving an infusion of (15N2)-arginine and then measured isotopic plasma enrichment of (15N)-citrulline. They found that whole body NO production was significantly lower in patients with CKD than healthy controls, it was also lower in those with familial hypercholesterolemia than healthy controls though this did not reach significance.

The formation of advanced glycation end products (AGEs) in response to oxidative stress have been implicated as inhibitors of NOS, as AGEs are known to accumulate in CKD Weiss et al. hypothesized that AGE excess in CKD resulted in ED via reduced NOS [40]. In a cross-sectional study of patients with various stages of CKD and a group of matched healthy controls AGEs were measured in serum and Laser Doppler was used to measure

microcirculatory blood flow in hyperemia. They found that individuals with CKD had increased circulating AGEs and decreased endothelial reactivity; they also found that AGE-rich sera from individuals with CKD inhibited NOS expression; from these findings they concluded that AGEs are influential in the pathogenesis of CVD in patients with CKD [41]. In animal work Vaziri et al. [42] tested the hypothesis that CKD results in oxidative stress via NO inactivation which could be ameliorated by anti-oxidant treatment. By performing either sham nephrectomy or nephrectomy on male rats and feeding them either an anti-oxidant rich diet or a normal diet and then measuring a variety of markers of NOS activity. They found that CKD (in the rats who had undergone 5/6 nephrectomy) was associated with decreased tissue NO production and reduced NOS proteins in the renal and cardiac tissues, the anti-oxidant therapy resulted in improved tissue NO production in the CKD subjects. From these findings it is suggested that CKD might result in oxidative stress which in turn results in NO inactivation and that anti-oxidant therapy might increase NO availability, however, these findings have not been reproduced in human.

6. DYSLIPIDAEMIA AND OXIDATIVE STRESS AND ED IN CKD

Dyslipidemia is a traditional risk factor for CVD but is increasingly considered as also being a non-traditional risk factor that results in ED, it has been reported that ED was independently related to dyslipidemia in type 2 diabetics [43]. The size of lipid particles and their susceptibility to oxidation has been proposed as a mechanism for ED, in a study of patients with type 2 diabetes and a control group, the diabetic patients had a greater concentration of smaller, dense particles and the rate of oxidation was also greater [44]. When endothelial function was measured using a brachial artery vasodilation method these changes were associated with ED.

In a study to investigate the role of chronic versus acute hyperlipidemia in ED de Man et al. gave a group of patients with dyslipidemia treatment with high dose Atorvastatin and a group with normolipidemia a high dose infusion of artificial triglycerides and then measured endothelial function using forearm blood flow response [45]. They found that in the patients with chronic dyslipidemia had evidence of ED that was normalized after 6 weeks of high dose statin treatment; artificially induced dyslipidemia did not alter the endothelial function of the control subjects, from these findings the authors concluded that only chronic dyslipidemia results in ED.

Very interesting was the randomized trial "Study of Heart and Renal Protection" (SHARP) [46]. The aims of these studies were to determine the benefits of lowering LDL cholesterol in the prevention of vascular events (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke or any arterial revascularization procedure) among patients with advanced CKD and to test the hypothesis that lowering LDL cholesterol might reduce the rate of loss of renal function. The study was performed on a total of 9,438 CKD patients, of whom 3,056 were on dialysis. Mean age was 61 years, two thirds were male, one fifth had diabetes mellitus and one sixth had vascular disease. In order to achieve a safety average absolute reduction in LDL cholesterol of 1 mmol/L low dose of statin (simvastatin 20 mg daily) combined with the cholesterol-absorption inhibitor ezetimibe or placebo was used for an average of about 4.4 years. This study suggests that use of LDL-cholesterol-lowering therapy in patients with chronic kidney disease would safely reduce the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.

Other studies to investigate the potential benefits of the treatment of dyslipidemia in the setting of ED have been carried out; in a study of Fenofibtrate versus Atorvastatin it was

found that both drugs improved endothelial function, with no significant difference between them, the beneficial effects were independent of lipid lowering [47]. Another study by Hamasaki et al. [48] considered the effect of cholesterol lowering therapy on vascular re-modelling and endothelial function in patients with normal or mildly diseased coronary arteries. They found that patients who had successful treatment of dyslipidemia had an increase in the vessel lumen area which was related to both reduction in atherosclerotic plaque size but also to increase in vessel lumen related to vascular re-modelling, the authors suggested that this re-modelling may arise as a result of improved endothelial function.

Lipid oxidation has been implicated in ED via a mechanism of the release of soluble cell adhesion molecules (CAMs) and vWF. In order to evaluate the relationship between lipid oxidation and the inflammatory state in CKD Bolton et al. conducted a cross-sectional study of individuals with CKD and angina and a group of healthy controls [49]. They measured a variety of adhesion molecules, vWF, circulating levels of cytokines and CRP; endothelial function was assessed using a forearm FMD technique. In contrast to other research they found that ED was not related to lipid oxidation and concluded that the role of lipid oxidation in the development of ED had been previously overstated. In fact ED was more severe in patients with CKD than angina and was associated with increased acute phase proteins and cytokines.

Other work has considered the role that inflammation plays in the initiation and propagation of ED, in CKD there is an increased plasma concentration of cytokines and chemokines (resulting from increased production and decreased clearance). Oberg, et al. [50] measured a number of biomarkers of inflammation and oxidative stress (CRP, IL-6, plasma protein free carbonyl group content and plasma free F2-isoprostane content) in a group of patients with CKD 3-5 and a group of matched healthy controls. They found that there was evidence of oxidative stress and inflammation in patients with CKD but that this did not correlate with degree of renal impairment, there was a correlation between CVD and inflammation in patients with CKD and that there was an inverse correlation with angiotensin blocker and statin use in this group, oxidative stress was present in those individuals with diabetes and dyslipidemia as has previously been shown.

7. STRATEGIES FOR INTERVENTION IN RELATION TO REDUCTION OF INFLAMMATION/ED IN CKD

Given that inflammation and ED appear to have a significant role in the initiation and propagation of CV disease, strategies to reduce inflammation and ED would be potentially very beneficial. However, apart from the management of traditional risk factors (control of hypertension, diabetes, smoking cessation and lipid lowering) there is little evidence for other interventions (though as we have seen there is overlap between traditional and novel risk factors with many traditional risk factors having their effect via an inflammatory pathway). Table 2 summarizes some potential targets for intervention; however, much of the evidence for these targets comes from dialysis populations which are not analogous to CKD populations.

Table 2. Targets for intervention to reduce inflammation in CKD

Intervention	Example	Proposed mechanism of action
Renal Angiotensin Aldosterone blockade	ACEi/ARB	By reducing proteinuria these agents have been shown to improve both cardiovascular and renal outcomes beyond the blood pressure lowering effect [51-53].
Anti-oxidants	Vitamin E, Acetylcysteine	Vitamin E is a potent anti-oxidant with anti-inflammatory properties and has been shown in patients on dialysis to improve cardiovascular outcomes [54-55]. Acetylcysteine is another anti-oxidant that may reduce pro-inflammatory cytokine release (IL-6) and CRP levels [56].
Treatment of periodontal disease		Periodontal disease is prevalent in patients with CKD and has been postulated as a driver of chronic inflammation and endothelial dysfunction though no large randomised control trials have been conducted in patients with CKD [57].
Vitamin D receptor activation	Paricalcitol	Vitamin D deficiency thought to have haemodynamic and pro-inflammatory effects, paricalcitol has been shown to reduce inflammation and improve cardiovascular end point in patients on dialysis (thought there was no improvement in endothelial function) [58].
Statines		Reduce CRP levels, are connected with reduced mortality levels in CKD patients that are due to cardiovascular complications [59].
The blockade of aldosterone	Spironolactone or eplerenone together with and ACEI or ARB	Have beneficial effects in patients with proteinuria, although the potential risk of hyperkalemia is increased [60].
Monocyte chemotactic protein-1 and endothelin antagonists		Drugs that may lower proteinuria independent of the RAAS action emerge as potential alternatives [25].

8. CONCLUSIONS

The presence of enhanced CV risk in patients with CKD is well known but the mechanisms by which it occurs are less clear. The endothelium is a complex, multi-functional organ with a variety of vascular homeostatic functions and ED has been shown to result in the initiation and propagation of atherosclerosis. Causes of ED are numerous but inflammation and oxidative stress are clearly highly implicated; albuminuria (even at levels thought to be well below previous definitions of abnormal) may contribute to the inflammatory process, as might dyslipidemia (though a combination of traditional and no-traditional pathways).

There are a number of limitations to many of the studies described here, many of the measures of endothelial function are putative, invasive or suffer from poor reproducibility, and many biomarkers of inflammation such as cytokines are unstable and difficult to

measure in routine clinical practice. While statin use and angiotensin blockade has been shown to improve endothelial function in some studies no randomized controlled trials have been conducted with the specific aim of trying to demonstrate an improvement in endothelial function resulting from one treatment intervention or another. An additional limitation is that many of these interventions have known and well understood effects on traditional risk factors as well as on some non-traditional inflammatory risk factors. Thus documenting would be challenging. The future direction of research in this area is likely to require such studies to take place to result in patient benefit from what is currently a very interesting and promising area.

Atherosclerosis is a progressive disease characterized by the deposition of lipids and fibrous elements and is a common complication of the uremic syndrome because of the coexistence of a wide range of risk factors. Inflammatory process is also involved in the development of CKD. The inflammation under uremic conditions could be produced by oxidative stress, coexistent pathological conditions as well as factors that are due to renal clearance techniques.

The treatment of chronic inflammation in CKD is of high importance for the development of the disease as well as for the treatment of the endothelial dysfunction. The treatment factors focus on to prevention of the action of inflammatory cytokines that have the ability to activate the mechanisms of inflammation [61].

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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