SAGE-Hindawi Access to Research
Cardiology Research and Practice
Volume 2011, Article ID 267257, 9 pages
doi:10.4061/2011/267257

Review Article

Peripheral Vascular Dysfunction in Chronic Kidney Disease

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Received 24 December 2010; Accepted 15 March 2011

Academic Editor: Abarmard Maziar Zafari

There is an increased prevalence of cardiovascular disease- (CVD-) related mortality in patients with chronic kidney disease (CKD). Endothelial dysfunction is a primary event in the development of atherosclerosis and hypertension and likely contributes to the elevated cardiovascular risk in CKD. Endothelial dysfunction has been shown to occur in the peripheral vasculature of patients with both severe and moderate CKD. Mechanisms include oxidative stress, L-arginine deficiency, and elevated plasma levels of ADMA. Interventions designed to restore vascular function in patients with CKD have shown mixed results. Evidence from cell culture studies suggest that the accumulation of uremic toxins inhibits L-arginine transport and reduces nitric oxide production. The results of these studies suggest that endothelial dysfunction may become less reversible with advancing kidney disease. The purpose of this paper is to present the current literature pertaining to potential mechanisms of peripheral vascular dysfunction in chronic kidney disease and to identify possible targets for treatment.

1. Introduction

Chronic kidney disease (CKD) is a major public health concern affecting nearly 20 million people in the United States alone [1]. Patients with CKD are at greater risk of cardiovascular disease- (CVD-) related morbidity and mortality than individuals without CKD with similar cardiovascular risk factors and tend to die before reaching end-stage renal disease (ESRD) [2–5]. Treatments aimed solely at reducing traditional cardiovascular risk factors do not improve cardiovascular function in patients with late-stage CKD [6]. Therefore, traditional CVD risk factors alone cannot explain the high incidence of CVD in CKD.

Endothelial dysfunction is a precursor to the development of atherosclerosis [7, 8] and has been shown to be associated with increased cardiovascular risk in patients with left ventricular dysfunction and congestive heart failure [9–11]. The combination of traditional risk factors in CKD is not enough to explain the high incidence of CVD and endothelial dysfunction has been suggested to play a role in the increased CV risk in CKD [12, 13]. In support of this, a longitudinal study of patients with end-stage renal disease (ESRD) found all cause mortality to be independently associated with impaired endothelial function [14].

The majority of studies of endothelial function in renal disease have focused on ESRD and patients receiving dialysis; however, little is known about endothelial function in earlier stages of CKD. Guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI) place patients with CKD into one of five stages based on glomerular filtration rate (GFR) and are presented in Table 1 [1, 15]. The risk of developing CVD can be predicted from GFR and increases as GFR declines [3]. These guidelines make it easier to delineate differences in vascular function in CKD patients with low to moderate renal deficiency; however to date those data are limited. With the majority of patients dying of cardiovascular disease before needing dialysis, there is an urgent need for investigations into vascular function in earlier stages of CKD. A great deal of literature has described the role of vascular calcification and aortic stiffness in promoting atherosclerosis in CKD and have been reviewed elsewhere [16]. The purpose of this paper is to present a summary of the available research regarding mechanisms of peripheral vascular dysfunction throughout the progression of chronic kidney disease.

Table 1: Stages of CKD.

Stage	Description	GFR, mL·min^{-1} per 1.73 m^2
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

Adapted from National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease [15].

2. Vascular Function in CKD

The vascular endothelium consists of a single layer of cells lining the interior lumen of blood vessels. Aside from functioning as a barrier between the intravascular space and the interstitum, the vascular endothelium works as an important regulator of vascular homeostasis. Perhaps one of the most important functions of the endothelium is the synthesis and release of the vasodilator nitric oxide [17]. Nitric oxide is produced from the amino acid substrate L-arginine by the enzyme endothelial nitric oxide synthase (eNOS) [18]. Activation of eNOS requires the binding of the cofactor tetrahydrobiopterin (BH_4) as well as the presence of Ca^{2+}/Calmodulin for the synthesis of NO [19]. NO diffuses through the basal membrane of the endothelial cell into the smooth muscle where it activates the conversion of GTP to cyclic GMP by soluble guanylyl cyclase (sGC) signaling smooth muscle relaxation and vasodilation [20]. This pathway occurs in response to mechanical shear stress or the binding of bradykinin or acetylcholine to their receptors on endothelial cells and is vital for proper control and maintenance of blood pressure. Additionally, nitric oxide plays an important role by regulating vascular permeability, leukocyte adhesion [21], and smooth muscle proliferation [22], all of which play an important role in maintaining cardiovascular health [23]. Endothelial dysfunction is characterized by a reduced synthesis or bioavailability of NO and is a primary event in the development of atherosclerosis [24]. *In vivo* assessment of conduit artery and microvascular function through flow-mediated dilation (FMD) and venous occlusion plethysmography (VOP) have been used to assess vascular function in CKD (Table 2) and serve as measures of endothelial function.

Endothelial dysfunction is present in CKD and may explain the increased cardiovascular risk in these patients. Urinary nitrate and nitrite (NOx) excretion, an index of total body NO production, is lower in patients with ESRD and likely contributes to the hypertension observed in these patients [36]. Endothelial dysfunction has been shown to occur *in vitro* in human microvessels obtained via subcutaneous fat biopsies from patients receiving dialysis or renal replacement surgery [37] as well as *in vivo* in the forearm microvasculature of predialysis CKD patients using venous occlusion plethysmography [28]. Further, endothelial dysfunction has been shown to occur in conduit vessels upstream of the microvasculature [27, 34]. Thus, endothelial dysfunction appears to be characteristic of CKD.

The confounding effects of other risk factors in CKD make it difficult to differentiate whether the source of endothelial dysfunction is due to renal impairment or the combination of multiple risk factors. Studies using children with CKD have assessed endothelial function before atherosclerosis and other associated risk factors were believed to occur [38–40]. Endothelial-dependent dilation was shown to be impaired in children with chronic renal failure using flow-mediated dilation (FMD) suggesting that kidney disease alone leads to the development of endothelial dysfunction [38]. Additionally, nitric oxide plays an important role in attenuating renal impairment and may slow the progression of CKD in patients with mild renal impairment. Reduced NO bioavailability has been shown to contribute to glomerular hypertension and accelerate renal damage leading to more rapid progression of CKD [41]. While the presence of endothelial dysfunction is well documented in CKD, the mechanisms have not yet been fully explained.

3. Potential Mechanisms of Endothelial Dysfunction in CKD

3.1. Oxidative Stress. One of the most widely studied contributors to endothelial dysfunction is oxidative stress [42]. Oxidative stress is defined by a disruption in the balance between free radical production and removal by endogenous antioxidants [43]. Oxidative stress impairs NO signaling pathways in endothelial cells and contributes to endothelial dysfunction [43]. Oxidative stress is present in patients with moderate to severe CKD [32, 44] as well as patients with ESRD or receiving hemodialysis [32, 45]. Endothelial dysfunction worsens with progressive loss of renal function and is associated with a variety of markers of oxidative stress including lipid hydroperoxides, oxidized glutathione, protein carbonyls and F2-isoprostanes [29, 31, 44, 45] as well as reduced antioxidant capacity [46, 47].

Markers of oxidative stress are inversely correlated with endothelial function in patients with CKD. In one study, brachial-artery flow-mediated dilation was decreased in hemodialysis patients and correlated to increased levels of TBARS, a marker of lipid peroxidation [33]. Interestingly, these patients lacked overt symptoms of cardiovascular disease suggesting that oxidative stress may contribute to the early progression of endothelial dysfunction in CKD. Endothelial function and GFR have also been shown to be associated with increased levels of advanced glycation end products (AGEs) in different stages of predialysis, nondiabetic CKD, likely through increased abundance of AGE receptors (RAGE) on the surface of endothelial cells [48]. AGEs have been shown to increase inflammation and oxidative stress [48] and can also inhibit eNOS activity directly as well as reduce substrate bioavailability by reacting with L-arginine resulting in endothelial dysfunction [49].

The mechanisms behind the contribution of oxidative stress in endothelial dysfunction in CKD appear to occur primarily through eNOS and NO dependent pathways

Table 2: Summary of studies measuring *in vivo* endothelial function in adult patients with CKD.

Study	Reported degree of CKD	Method	Finding
Yilmaz et al. [25]	Stage 1	FMD	Improved following 12-week treatment with ramipril
Yilmaz et al. [26]	Stage 1–4	FMD	Improved following 3-month treatment with ramipril or valsartan
Nanayakkara et al. [27]	CCr = 38 ± 15	FMD	Improvement following 18-month stepwise treatment with pravastatin, vitamin E, and homocysteinie lowering therapy
Annuk et al. [28]	CCr = 29.4 ± 24.0	VOP	Impaired and related to degree of renal impairment
Annuk et al. [29]	CCr = 25.1 ± 16.2	VOP	Impairments correlated to markers of oxidative stress
Annuk et al. [30]	Serum Cr = 287 ± 143	VOP	Improved by acute COX inhibition or L-arginine treatment
Annuk et al. [31]	Stage 3–5	VOP	Negatively correlated to levels of lipid hydroperoxides (LOOH)
Ghiadoni et al. [32]	Stage 3–5, hemodialysis	FMD	Acute vitamin C infusion restored impaired function in hemodialysis but not in CKD
Costa-Hong et al. [33]	ESRD	FMD	Plasma TBARS levels associated with impaired endothelial-dependent dilation in patients without symptoms of CVD
Cross et al. [34]	Predialysis hemodialysis	VOP, FMD	Acute infusion of vitamin C improves endothelium-dependent dilation in forearm resistance vasculature but not in brachial artery
Cross et al. [35]	Predialysis, hemodialysis	VOP, FMD	Local or systemic L-arginine infusion did not improve resistance or endothelial-dependent dilation

FMD = flow-mediated dilation; VOP = venous occlusion plethysmography; CCr = creatinine clearance (mL/min/1.73 m^2); Serum Cr = serum creatinine (μmol/L).

(Figure 1). Cross et al. [34] observed a reduction in acetylcholine-induced forearm blood flow (venous occlusion plethysmography) in predialysis patients with ESRD (GFR <20 mLmin). This impairment was ameliorated when the antioxidant vitamin C was infused through the brachial artery suggesting that the source of endothelial dysfunction was oxidative stress. This improvement was abolished when vitamin C was infused with the NOS inhibitor L-NMMA suggesting that the effect of oxidative stress on forearm blood flow is NO dependent. Interestingly, vitamin C did not cause an improvement in endothelial function in larger upstream conduit vessels as assessed by brachial and radial artery flow-mediated dilation in both predialysis and dialysis patients with severe renal failure [34]. This finding suggests that some other mechanism contributes to endothelial dysfunction in late-stage kidney disease.

Although oxidative stress has been shown to be more severe in hemodialysis patients than in patients with stage 3–5 CKD [32], studies have shown oxidative stress to contribute to endothelial dysfunction earlier in CKD. Perfused mesenteric arteries from rats that underwent renal mass reduction have impaired vasodilation in response to acetylcholine within 3–10 days after surgery [50]. This impairment was restored by incubation with the antioxidant enzyme superoxide dismutase (SOD) [50] suggesting that oxidative stress also plays a role in endothelial dysfunction early in the progression of CKD. In human patients with moderate renal impairment, the forearm blood flow response to an arterial infusion of methacholine was attenuated [29]. These same patients also demonstrated increased levels of lipid hydroperoxides (LOOH) and an increased ratio of oxidized to reduced glutathione (GSSG/GSH). These markers of oxidative stress were correlated to both serum creatinine and forearm blood flow suggesting that oxidative stress contributes to endothelial dysfunction in humans with moderate CKD.

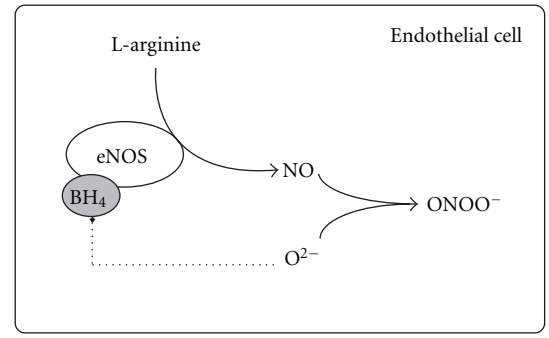

Figure 1: Simplified schematic depicting mechanisms by which reactive oxygen species can reduce nitric oxide (NO) availability. NO is synthesized from eNOS and can combine with excess superoxide (O^{2-}) from vascular oxidases to form peroxynitrite ($ONOO^-$) limiting NO availability. Superoxide can also oxidize the eNOS cofactor tetrahydrobiopterin (BH_4), uncoupling eNOS and reducing NO synthesis.

Supplementation with antioxidants has been shown to reduce cardiovascular events in CKD and hemodialysis [51]. In the Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial, hemodialysis patients receiving 800 IU/day of vitamin E had significantly fewer primary cardiovascular end-points than placebo-treated controls [52]. The benefits of antioxidant therapy have also been studied in earlier stages of CKD and have been shown to improve endothelial function. The Antioxidant Therapy in Chronic Renal Insufficiency (ATIC)

study demonstrated that antioxidant treatment in patients with mild to moderate renal impairment was effective at improving brachial artery flow-mediated dilation [27]. Patients underwent three stages of drug treatment consisting of treatment with pravastatin, vitamin E, and homocysteine-lowering therapy introduced consecutively at 6 month intervals. Additionally, this improvement in endothelial function occurred despite a progressive loss in renal function. Antioxidant treatment has not been effective at reducing cardiovascular risk in other diseases [53]; however, these studies suggest that the use of antioxidants in CKD may be an exception.

Another strategy for combating oxidative stress mediated endothelial dysfunction may be bolstering endogenous antioxidant defense mechanisms. Endogenous antioxidant enzymes play an important role in preventing oxidative stress and are impaired in CKD. Plasma and erythrocyte levels of glutathione peroxidase (GSH-px), superoxide dismutase (SOD), and catalase were shown to be significantly lower in predialysis patients with ESRD compared to healthy control subjects [46]. Endogenous antioxidants have also been shown to be lower in earlier stages of CKD with levels of erythrocytic GSH-px, and SOD impaired as early as stage 1 (GFR <90 mL/min) [45]. Treatments aimed at improving the endogenous antioxidant defense systems may be more effective than antioxidant therapy. Chronic exercise training was shown to reduce levels of ROS and improve endothelial-dependent relaxation in 5/6 nephrectomized rats [54]. Exercise has been shown to improve endothelial-dependent dilation in aging [55] and may help prevent the progression of endothelial dysfunction in CKD; however, further study is needed.

The role of oxidative stress on vascular function in CKD is well documented however more research is needed to uncover the sources and specific targets of free radicals. The production of the powerful radical superoxide from NADPH oxidases is a likely contributor oxidative stress in the endothelium [43] and can combine with NO to form reactive nitrogen species such as peroxynitrite ($ONOO^-$) (Figure 1). Peroxinitrite formation reduces the bioavailibilty of NO and contributes to nitrositive cellular damage. Vaziri et al. [56] measured increased nitrotyrosine abundance, a marker of nitrositive protein modification, in aorta, heart, liver, and plasma of 5/6 nephrectomized rats. Nitrotyrosine levels were decreased to normal levels in rats treated with the antioxidant vitamin E. Angiotensin II is elevated in CKD and has been shown to activate NADPH oxidases [57]. Few studies have examined the role of inhibition of the renin-angiotensin system on endothelial-dependent dilation in CKD. One study observed improved FMD following short-term ACE-inhibition in patients with stage 1 diabetic CKD [25]. Additional free radical production may occur from xanthine oxidase; however, the role of this enzyme in humans with CKD is not well known. Treatment with the xanthine oxidase inhibitor allopurinol slowed the progression of CKD, and reduced cardiovascular risk in patients with CKD (eGFR <60 mL/min) [58]; however, it is unclear if these beneficial effects were due to decreased oxidative stress or reduced serum uric acid levels.

Oxidation of the essential eNOS cofactor tetrahydrobiopterin (BH_4) has been shown to cause uncoupling of eNOS (Figure 1). Once uncoupled, eNOS itself becomes a source of superoxide contributing to further oxidative damage [59, 60]. Chronic treatment with BH_4 has been shown to lower systolic blood pressure and reduce proteinuria in 5/6 nephrectomized rats [61]. In another study, endothelial-dependent relaxation of aortic rings from 5/6 nephrectomized rats was restored in isolated vessels treated with BH_4 [62]. These vessels were also associated with increased superoxide production which was ameliorated by treatment with L-NAME suggesting that the source of oxidative stress was uncoupled eNOS. The presence of oxidative stress in CKD is well defined and is a contributing factor to the development of endothelial dysfunction. Treatments aimed at restoring vascular redox balance may be effective at reducing cardiovascular risk in CKD. In addition, supplementation with BH_4 in humans with CKD may prevent eNOS uncoupling and reduce oxidative stress.

3.2. L-Arginine Deficiency. Nitric oxide synthesis relies on the amino acid substrate L-arginine. L-arginine synthesis primarily occurs in the proximal tubules of the renal cortex and is impaired with loss of functional renal mass [41]. Despite reduced production, the plasma concentration of L-arginine in patients with CKD appears to be maintained at normal levels [63]. The maintenance of plasma L-arginine levels in CKD may be a consequence of increased amino acid release into the blood due to skeletal muscle wasting [64], and impaired L-arginine transport due to increased uremic toxins [65, 66]. Both mechanisms could potentially mask the decrease in L-arginine production by maintaining the plasma concentrations.

The intracellular concentration of L-arginine in endothelial cells is normally much higher than the Km of eNOS for L-arginine [67]. Despite the apparent cellular abundance of substrate, exogenous treatment with L-arginine has been effective at restoring endothelial function in other disease states including aging [68] and hypercholesterolemia [69, 70]. Cooke et al. [69] demonstrated that endothelial-dependent relaxation of aortic rings was restored in hypercholesterolemic rabbits pretreated with an intravenous infusion of L-arginine. In 5/6 nephrectomized rats, both chronic and acute treatment with L-arginine improved blood pressure and restored endothelial-dependent relaxation of aortic rings [62]. This phenomenon, referred to as the "arginine paradox" [67, 71], was not observed, however, in patients receiving dialysis or in predialysis patients with severe renal failure [35]. In another study, infusion of L-arginine into the forearm improved the endothelial-dependent dilatory response to methacholine in both patients with CKD and aged-matched controls [30]. Age may have been a confounding factor in this study, however, since subjects were between 50 and 80 years of age.

L-arginine transport has been shown to be impaired by uremic toxins and may potentially explain why L-arginine treatment has been ineffective in later stages of CKD (Figure 2). Endothelial cells cultured in uremic plasma had a reduced ability to transport L-arginine into the cells [65].

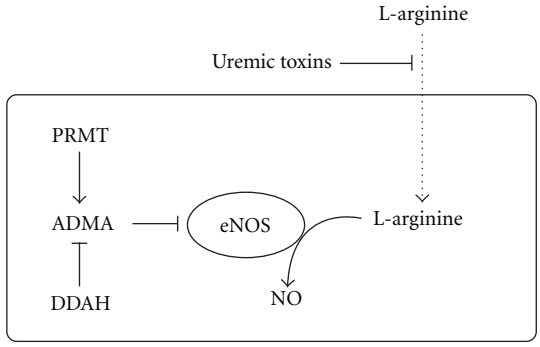

Figure 2: Potential mechanisms of L-arginine deficiency in chronic kidney disease (CKD). Asymmetric dimethylarginine (ADMA) is a competitive inhibitor of eNOS and ADMA levels are increased in CKD. Synthesis of ADMA occurs via protein arginine methyltransferase (PRMT) which may exhibit increased expression and activity in CKD. Expression of the enzyme dimethylarginine dimethylaminohydrolase (DDAH) may be decreased in CKD resulting in reduced degradation of ADMA. L-arginine transport into endothelial cells can be inhibited by increased levels of uremic toxins as disease progresses and result in reduced substrate availability for NO production.

When the same experiment was repeated with cells cultured in a synthetic solution containing uremic levels of urea, the same result was observed indicating that urea is an important inhibitor of L-arginine transport. The transport of L-arginine occurs through the cationic amino acid transporter CAT-1. Urea transport occurs through urea transporters (UT) that appear to be colocalized with CAT-1 in endothelial cells [66]. The movement of urea into the cell appears to be required in order to inhibit L-arginine transport. This mechanism may occur with the accumulation of uremic toxins as seen in CKD and lead to impaired L-arginine transport and reduced substrate available for NO synthesis.

The uremic inhibition of L-arginine transport appears to occur in an "all-or-nothing" fashion [41, 65]. Inhibition of L-arginine transport was only effective with a synthetic solution of urea at or above 15 mmol/L and not effective at lower concentrations [65]. Interestingly, when uremic plasma was diluted to achieve a lower urea concentration below this threshold, L-arginine transport was still inhibited. This suggests that other uremic toxins also contribute to transport inhibition and should be studied more extensively in order to elucidate their mechanisms.

Hyperhomocysteinemia reduced L-arginine uptake in cultured endothelial cells and impaired endothelial-dependent relaxation in homocysteine-treated vessels and was associated with oxidative stress and increased nitrotyrosine levels [72]. Treatment with vitamin C restored cellular uptake of L-arginine while L-arginine treatment improved endothelial-dependent relaxation of aortic rings. CAT-1 expression was also attenuated in homocysteine-treated cells and was related to impaired NO production with no change in eNOS expression or activity. Hyperhomocysteinemia is present in patients with CKD [4] and may contribute to the uremic inhibition of L-arginine transport in humans; however, this has not been studied.

The accumulation of uremic toxins in the plasma occurs progressively with loss of renal function. Increased levels of urea in humans has been correlated to decreased endothelial-dependent dilation [31] and may be related to reduced L-arginine transport. While L-arginine treatment has been ineffective at later stages of CKD and during hemodialysis, it is plausible that treatment in earlier stages, when the influence of uremic toxins is not as robust, may be effective at restoring endothelial function.

3.3. ADMA in CKD. Another potential contributor to endothelial dysfunction in CKD is the formation of the endogenous NOS inhibitors asymmetric dimethylarginine (ADMA) and *N*-monomethylarginine (L-NMMA) [73, 74]. ADMA and L-NMMA are the result of posttranscriptional methylation of L-arginine residues by protein arginine methyltransferases (PRMTs) and are released in their free form following protein hydrolysis. ADMA production is about 10-fold that of L-NMMA and is elevated in patients with chronic renal failure [75]. Plasma levels of ADMA predict progression to ESRD in patients with CKD [76] and ultimately predict adverse cardiovascular events in patients with mild to moderate CKD [77, 78]. ADMA is associated with impaired endothelial function in healthy adults [79], and has been shown to be inversely correlated to brachial artery FMD in patients with proteinuria and amyloidosis [26].

ADMA has been classified as a "uremic toxin" and exhibits adverse cardiovascular effects [4]. In healthy subjects infused with ADMA, heart rate and cardiac output were reduced while mean arterial pressure increased [80]. ADMA has also been linked to impaired endothelial function. Brachial artery FMD was impaired in healthy individuals treated with L-NMMA suggesting that a reduction in the ratio or L-arginine to methylated arginines competitively inhibits NO production *in vivo* [35]. The addition of L-arginine in these patients improved this balance and restored endothelial function. While L-arginine treatment is an effective strategy in restoring substrate balance and combating ADMA and L-NMMA in other disease models, its effectiveness in CKD is questionable due to the L-arginine transport issues discussed above. It is therefore important to explore alternative strategies for reducing circulating levels of ADMA in kidney disease.

Interventions designed to lower ADMA production or increase ADMA clearance may be effective at improving endothelial function in CKD. Clearance of ADMA in the urine is impaired with renal damage and contributes to elevated plasma concentrations [81]; however, this is not the primary reason for elevated ADMA in CKD. Urinary clearance of ADMA did not explain elevations in plasma ADMA in an animal model of CKD [82]. Instead, increased PRMT activity and expression and reduced degradation of ADMA by dimethylarginine dimethylaminohydrolase (DDAH) are likely the major causes of increased ADMA in CKD [41] (Figure 2). PRMT expression and activity is

increased in the presence of oxidized LDL cholesterol and results in increased production of ADMA in endothelial cells [83]. Antioxidant therapy with vitamin E has been shown to reduce ADMA levels in patients with CKD [84] and may be an effective treatment strategy to restore endothelial function. PRMT expression was increased in an animal model of CKD [82] and may be a potential therapeutic target to restore endothelial function.

DDAH converts ADMA to dimethylarginine and L-citrulline and has been shown to decrease expression in an animal model of CKD [82]. A useful method for studying the role of ADMA in disease states is through the modification of DDAH enzyme expression in animal models. In mice infected with recombinant DDAH, NO synthesis was significantly increased while plasma ADMA concentrations were reduced compared to wild-type animals [85]. Endothelial-dependent relaxation was impaired in streptozotocin-induced diabetic rats and restored by overexpression DDAH [86]. When isolated mouse carotid artery sections were transfected with recombinant DDAH in the presence of exogenous ADMA, endothelial-dependent relaxation was improved compared to uninfected vessels [87]. ACE inhibition may also reduce ADMA levels and contribute to improved endothelial function. One study showed that 3 months of treatment with the ACE inhibitor Ramipril (5 mg/day) or the angiotensin II receptor antagonist Valsartan (160 mg/day) reduced ADMA levels and restored FMD in patients with nondiabetic CKD [26].

4. Conclusion

The endothelium represents the largest organ in the human body and is vital for the maintenance of vascular homeostasis. There is an urgent need to understand the mechanisms by which the endothelium becomes impaired in CKD in order to design more effective strategies for reducing cardiovascular risk. Chronic kidney disease is a worldwide health concern and leads to an accelerated risk of cardiovascular death. Because there are a significantly lower number of patients with later stages of CKD likely due to CVD-related death [3], earlier stages of CKD should be more extensively studied in order to better predict and prevent cardiovascular mortality in CKD. There is limited but convincing data supporting the role of endothelial dysfunction in earlier stages of CKD. Future research should focus on better understanding the mechanisms of endothelial dysfunction as well as development of effective interventions in earlier stages of CKD where the risk of cardiovascular death is most evident.

Evidence suggests that oxidative stress, L-arginine deficiency, and ADMA inhibition of NO synthesis all play roles in the pathogenesis of endothelial dysfunction in CKD. Based upon differences between patients with ESRD and earlier stages of CKD, it appears that there may be a point at which endothelial dysfunction becomes less reversible with advancing kidney disease [27]. Evidence from cell culture studies linking the impaired transport of L-arginine to uremic toxins supports this hypothesis and may be applied to other mechanisms of endothelial dysfunction. The increased uremic burden that accompanies late-stage CKD may trigger a "uremic switch" resulting in endothelial dysfunction that is less reversible due to an inability to transport L-arginine into endothelial cells. Once triggered, conventional therapies for treating endothelial dysfunction may become less effective leading to the increased prevalence of CVD seen in late-stage CKD. It is therefore necessary to understand the pathogenesis of endothelial dysfunction in earlier stages of CKD in order to prevent the deterioration of vascular function.

Acknowledgment

This work was supported by National Institutes of Health Grants DK080469 and P20 RR016472-11.

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