Arterial Stiffness in the Heart Disease of CKD

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ABSTRACT

CKD frequently leads to chronic cardiac dysfunction. This complex relationship has been termed as cardiorenal syndrome type 4 or cardio-renal link. Despite numerous studies and reviews focused on the pathophysiology and therapy of this syndrome, the role of arterial stiffness has been frequently overlooked. In this regard, several pathogenic factors, including uremic toxins (i.e., uric acid, phosphates, endothelin-1, advanced glycation end-products, and asymmetric dimethylarginine), can be involved. Their effect on the arterial wall, direct or mediated by chronic inflammation and oxidative stress, results in arterial stiffening and decreased vascular compliance. The increase in aortic stiffness results in increased cardiac workload and reduced coronary artery perfusion pressure that, in turn, may lead to microvascular cardiac ischemia. Conversely, reduced arterial stiffness has been associated with increased survival. Several approaches can be considered to reduce vascular stiffness and improve vascular function in patients with CKD. This review primarily discusses current understanding of the mechanisms concerning uremic toxins, arterial stiffening, and impaired cardiac function, and the therapeutic options to reduce arterial stiffness in patients with CKD.

FROM CKD TO VASCULAR RISK

The link between CKD and cardiovascular (CV) events is well recognized.1–3 CV risk increases in a graded fashion with progressive decrease in kidney function and reaches a zenith in ESRD, but can be reduced by renal transplantation. It is widely accepted that only part of this excessive CV risk is explained by traditional risk factors. The relationship between CKD and chronic cardiac dysfunction is complex and has been named cardiorenal syndrome type 4 or cardio-renal link.1,2 Arterial stiffness is a vascular biomarker4 that is increased in patients with CKD,5–8 even in those with a mildly impaired renal function,5 and is associated with an independent increase in CV risk.7,8 Conversely, at least in patients with advanced CKD, the reduction in aortic stiffness is associated with an improved survival independent of BP changes.7 The increase of arterial stiffness in CKD is mostly caused by reduced renal excretion of vascular toxins, maladaptive metabolic and hormonal processes, and as a result, premature vascular aging. Also, in ESRD, RRT (dialysis) plays a role in the stiffening process and its consequences. Several therapeutic options have been proposed to reduce arterial stiffness, but most of them have been tested primarily in other settings (i.e., hypertension and diabetes).

Herein, we review the role of arterial stiffening as an independent mediator of myocardial dysfunction in CKD and the strategies to reduce arterial stiffness and, possibly, CV risk.
Chronic inflammation can lead to arterial stiffening through several mechanisms. Increased levels of TNF can interfere with the activity of endothelial nitric oxide synthase (eNOS) and induce the production of reactive oxidative species. Moreover, nitric oxide (NO) deficiency may itself cause oxidative stress. Oxidative stress can lead to endothelial dysfunction through the reduction of the endothelial production of NO, and to structural arterial stiffening through the phenotypic switching of vascular smooth muscle cells (VSMCs), the production of matrix metalloproteinases, and the inhibition of the tissue inhibitors of matrix metalloproteinases. In addition, TNF activates LDL receptor gene transcription, increases alkaline phosphatase protein expression, and reduces α-smooth muscle actin protein expression. All of these processes, together with the infiltration of white blood cells into blood vessels and the direct toxic action of several uremic toxins (such as inorganic phosphate, advanced glycation end-products, and indoxyl sulfate [IS]), lead to the proliferation and changes in phenotype of VSMCs and the consequent release of matrix metalloproteinases, elastin fragmentation, collagen degradation, vascular calcification, and structural arterial stiffening. The effect of TNF on the arterial wall is partially mediated by the release of IL-6 from VSMCs and endothelial cells. In other models of chronic severe inflammation (i.e., inflammatory bowel disease and rheumatoid arthritis), chronic inflammation is associated with increased arterial stiffness and early return of reflected waves. In these individuals, the inflammation-dependent aortic stiffening is at least in part reversible by anti-TNF therapy. Despite these promising results in other models of chronic inflammation, baseline low-grade inflammation did not predict changes in arterial stiffness over time in CKD, suggesting that, in parallel with chronic inflammation, other pathways can be involved in arterial stiffening in CKD. In this regard, the progressive accumulation of uremic toxins during CKD can also lead to arterial stiffening.

Figure 1. The vascular pathway in CKD. AGEs, advanced glycation end-products; BRS, baroreflex sensitivity; DBP, diastolic BP; LV, left ventricular; MMPs, matrix metalloproteinases; PP, pulse pressure; SBP, systolic BP; SMC, smooth muscle cell; TIMP, tissue inhibitor of matrix metalloproteinases. Modified from reference 14, with permission.
via a direct toxicity on the arterial wall (see above).

**Uremic Toxins Are Also Vascular Toxins**

Under normal conditions, several calcification inhibitors, including pyrophosphate, adenosine, matrix Gla protein, osteopontin, fetuin-A, osteoprotegerin, and bone morphogenetic protein-7, protect against abnormal mineral deposition in the vessel wall, whereas hypercalcemia, increased levels of parathyroid hormone, inflammatory cytokines, oxidative stress, uremic toxins, advanced glycation end-products, and, most importantly, phosphates induce vascular calcification. During CKD there is an imbalance between inhibitors and inducers of vascular calcification.\(^{24}\) Phosphates increase during CKD because of progressively reduced renal excretion. High phosphate levels may directly induce vascular calcification via the activation of Toll-like receptor 4/NF-κ light-chain enhancer of activated B cells (NF-κB) signaling in VSMCs.\(^{25}\) Moreover, in the presence of high phosphate levels, VSMCs can change their phenotype into osteoblast-like cells via the loss of smooth muscle markers (e.g., α-smooth muscle actin, SM22) and the expression of bone-forming genes (e.g., core-binding factor α-1 Runx2/Cbfα1, Osterix, and alkaline phosphatase).\(^{26}\) Phosphates could also directly modify mitochondrial function with high production of reactive oxygen species in parallel with activation of proinflammatory molecules and upregulation of TNF. These processes lead to vascular calcification and structural arterial stiffening. In this regard, calcium-phosphate mineral deposits are found in the subintimal and medial layer and represent the predominant vascular calcification in patients on dialysis. During CKD, several hormones that regulate serum phosphate levels by modulating intestinal phosphate absorption, renal phosphate reabsorption, and bone metabolism (i.e., vitamin D, fetuin, klotho, and fibroblast growth factor 23), can have a role in arterial stiffening. These hormones can affect the arterial wall by the increase of phosphates levels and/or the development of vascular inflammation, endothelial dysfunction, and proliferation of VSMCs.

Another vascular toxin increased in patients with CKD is uric acid. This molecule attenuates NO production by decreasing the activity of the eNOS,\(^{27}\) leads to the proliferation of VSMCs,\(^{28}\) increases the expression of cyclooxygenase 2, stimulates the production of angiotensin II, and increases angiotensin-1 receptor expression in cultured VSMCs. Taken together, these effects suggest that uric acid may contribute to arterial stiffening in CKD.

Advanced glycation end-products are partially responsible for uremic vasculopathy. Advanced glycation end-products can progressively accumulate during CKD even in the absence of diabetes, as a consequence of reduced renal clearance and increased production. Advanced glycation end-products affect the phosphorylation status and expression of eNOS,\(^{29}\) leading to endothelial dysfunction and functional arterial stiffening, and cause crosslinking of collagen molecules\(^ {30}\) and changes of the VSMCs phenotype,\(^ {17}\) leading to structural arterial stiffening. Moreover, as already mentioned for phosphates, advanced glycation end-products also activate NF-κB, which contributes to the development of vascular inflammation.

Asymmetric dimethylarginine (ADMA), an endogenous eNOS inhibitor, is another vascular toxin in CKD linked to arterial stiffening. Elevated levels of ADMA are reported during CKD likely related to reduced renal excretion and increased production caused by dysfunction of the endothelial L-arginine/NO pathway. ADMA is related to inflammation\(^ {31}\) and associated with left ventricular hypertrophy,\(^ {32}\) high sympathetic activity,\(^ {33}\) and increased CV risk.\(^ {31,33,34}\) ADMA can cause endothelial dysfunction through eNOS inhibition, and vascular remodeling through the amplification of oxidative stress. The inhibition of the NO production is enhanced in presence of eNOS polymorphisms.\(^ {35}\) Current data suggest that the blood flow in the forearm is reduced after the infusion of ADMA,\(^ {36}\) whereas systemic vascular resistance,\(^ {37}\) intima–media thickness,\(^ {38}\) and augmentation index are increased.\(^ {39}\)

Endothelin-1, a peptide with powerful vascular properties, increases during CKD, probably because of increased production and reduced clearance. The increased synthesis and release of endothelin-1 during CKD is regulated by angiotensin II, vasopressin, IL-1, oxidized LDL, cyclosporine, and a reduced extracellular pH.\(^ {40}\) Two receptor subtypes, ETA and ETB, with opposing actions, mediate the actions of endothelin.\(^ {40}\) ET\(_A\) receptors promote endothelial dysfunction, vascular inflammation, and vascular calcification via the induction of VSMCs differentiation into osteoblast-like cells, whereas ET\(_B\) receptors contribute to vasodilation, sodium excretion, and inhibition of inflammation.\(^ {40}\)

Cholesterol metabolism is altered in patients with CKD. Elevated triglycerides levels, frequently detected in patients with CKD, can lead to vascular inflammation, oxidative stress, oxidized LDL, foam cell production, VSMC proliferation, and endothelial dysfunction.\(^ {41}\) Recent evidence suggests that HDLs, frequently reduced in patients with CKD, may lose their CV protective properties and promote endothelial dysfunction and an abnormal vascular phenotype in patients with CKD.\(^ {42,43}\)

Recent experimental studies suggested that protein-bound uremic toxins, especially IS and p-cresyl sulfate, also contribute to the arterial phenotype observed in CKD. Acute in vitro exposure to IS increases VSMCs proliferation through a mechanism involving reactive oxygen species production and activation of mitogen-activated protein kinase P44/44 and P38, and aryl hydrocarbon receptor/NF-κB signaling pathways. In addition, IS has been shown to increase VSMC migration and senescence. p-Cresyl sulfate has pro-oxidative properties, but its effect on VSMC proliferation is still debated.\(^ {17}\)

**The Arterial Phenotype of Patients with CKD**

Several alterations of the arterial wall have been reported during CKD...
(Figure 2). Endothelial dysfunction can be detected starting from the early stages of CKD, and can cause functional arterial stiffening, whereas the structural alterations of the arterial wall, such as lipid deposition and atherosclerosis, result in an increased intima-media thickness and atherosclerotic plaque. Changes of the intrinsic characteristics of the biomaterial, including vascular calcification, are evident from moderate CKD and are associated with structural changes and arterial stiffening. In more advanced CKD, an enlargement of the carotid artery wall and outward remodeling are also reported. Interestingly, arterial remodeling during CKD seems to be different in elastic arteries (i.e., aorta and carotid artery) and muscular arteries (i.e., brachial, femoral, and renal artery), because aortic and carotid stiffness increases in patients with CKD whereas brachial and femoral stiffness does not increase and can be even reduced during CKD. Loss of elastic fibers in the wall of the aorta has been reported in forms of aortic disease and can account for the circumstance of having aortic dilation yet reduced compliance in the same patient. Finally, an inward remodeling (reduction of diameter) of the renal arteries has been reported in patients with CKD with a low prevalence of renal artery stenosis and a high CV risk. The inward remodeling was associated with an increased risk of CV events.

**From Vascular Impairment to Cardiac Dysfunction**

A well functioning arterial system is essential to receive pulsatile blood from the left ventricle and distribute it as a steady flow through the peripheral capillaries. Physiologically, during systole, approximately 50% of the stroke volume is momentarily stored within the aorta because of the elastic deformation of the arterial wall (cushioning function), whereas the remaining 50% is directly forwarded into the peripheral tissues (conduit function). During diastole, despite the blood flow from the left ventricle to the aorta being interrupted, a continuous blood flow from the aorta to the periphery is ensured by the discharge of the energy stored in the aortic wall. In individuals with elastic arteries, the forward wave originated by the contraction of the left ventricle propagates slowly from the aorta to the periphery; accordingly, the backward wave, originated by the reflection of the forward wave into the bifurcations and into the progressive reductions in the diameters of the arterial tree, propagates slowly from the periphery to the aorta. As a result of the slow propagation of the waves within the arterial tree, the backward wave meets the forward wave during diastole, thus contributing to the maintenance of a diastolic BP that is sufficient for tissue perfusion (Figure 3).

In the presence of increased arterial stiffness, the cushioning function of the aorta is altered and a larger part of the stroke volume is directly forwarded into the peripheral tissues during systole. Moreover, because the forward and backward waves propagate faster within the arterial tree, the reflected wave will meet the forward wave earlier (during systole), at the level of the aortic notch. The hemodynamic consequences of increased arterial stiffness and early return of reflected waves (i.e., in patients with CKD) are a rise in central systolic BP, a drop in diastolic BP, and an increase in pulse pressure (Figure 1). The increased central systolic BP leads in turn to an augmented left ventricular work, oxygen requirement, and left ventricular hypertrophy; the decreased central diastolic BP is responsible for the decreased coronary artery perfusion pressure observed during diastole, with a consequent increased risk of myocardial ischemia; and the increased central pulse pressure leads to an increased risk of stroke. Because elastic arteries are specifically altered in CKD, and not muscular arteries, the physiologic gradient of stiffness (from low to high) is reversed in CKD. The consequences of the reduced stiffness gradient are more transmission of pulsatility to the microcirculation. In this regard, increased aortic stiffness is associated with white matter hyperintensity and lower cognitive function, as well as CKD progression, for the penetration of the energy of the pulse wave into low-resistance tissues like brain and kidneys. Therefore, increased arterial stiffness not only mediates at least some of the effects of CKD on cardiac function, but also affects the worsening of cardiorenal syndrome type 4.

**Arterial Stiffening and Baroreflex Dysfunction**

Arterial stiffening and baroreflex dysfunction, two conditions associated with an increased CV risk, seem to be strictly linked. Interestingly, both of them are detectable during CKD and are reverted after renal transplantation. Given that baroreceptors are located in the carotid bulb and are sensitive to deformations of the arterial

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**Figure 2.** Carotid lesions in patients with CKD. CWS, circumferential wall stress; Einc, Young elastic modulus; IMT, intima-media thickness. Modified from reference 5, with permission.
Arterial stiffness and pulse-wave propagation. DBP, diastolic BP; SBP, systolic BP. Modified from reference 14, with permission.

THERAPEUTIC OPTIONS TO REDUCE ARTERIAL STIFFNESS

The therapeutic options available to reduce arterial stiffness are reported in Table 1.

Antihypertensive Drugs
Arterial stiffness can be passively reduced by all antihypertensive drugs through a BP-dependent mechanism involving reduced stretching of the arterial wall. Few classes of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors, could reduce arterial stiffness even independently from BP changes, whereas β-blockers seem to be inferior to other classes of antihypertensive drugs in reducing central BP and arterial stiffness. In this regard, a profibrotic effect of celiprolol, a β1-adrenoceptor antagonist with partial β2 agonist activity, on the arterial wall has been recently reported in patients with Ehlers–Danlos syndrome. In patients with ESRD, the insensitivity of aortic stiffness to decreased BP is an independent predictor of mortality, and the use of angiotensin-converting enzyme inhibitors has a favorable effect on survival that is independent of BP changes. At least two classes of diuretics could have a beneficial effect on the arterial wall. Spironolactone reduces vascular and soft tissue calcification in Klotho-hypomorphic mice. In this regard, aldosterone is associated with high levels of inactive matrix Gla protein, a vitamin K–dependent protein that inhibits arterial calcification. Spironolactone could also reduce aortic stiffness in stage 3 CKD through the reduction of vascular fibrosis. However, its use in more advanced stages of CKD should be carefully evaluated because of the risk of hyperkalaemia. Sodium-glucose cotransporter-2 inhibitors, a new class of oral hypoglycemic/diuretic for the treatment of diabetes, have shown additional diuretic properties that could be potentially helpful in the early stages of CKD. Moreover, sodium-glucose cotransporter-2 inhibitors can have a beneficial effect on the arterial wall through the reduction of circulatory levels of oxidants TNF and IL-6. Their use in more advanced CKD is questionable.

Destiffening Strategies
Advanced glycation end-product breakers can improve endothelial function in several populations, including patients...
Moreover, the use of alagebrium, an advanced glycation end-product breaker, is inversely correlated with plasma matrix metalloproteinase-9 and type 1 collagen, suggesting that this drug could also reduce the structural arterial stiffness. However, phase 2 trials have reported no changes in BP and aortic distensibility in the alagebrium group. Therefore, more clinical trials are necessary to further evaluate the potential benefit of advanced glycation end-product breakers in patients with CKD.

Anti-inflammatory drugs reduce chronic inflammation, which has a favorable effect on arterial stiffness in several populations. Only the most recent targeted drugs have proven efficacy. In other models of chronic inflammation and increased arterial stiffness, it has been reported that the long-term use of anti-TNF therapy can revert aortic stiffening to a level comparable with matched controls, whereas a high dose of salicylic acid had the opposite effect. In patients with CKD, although reducing chronic inflammation could be attempted with anti-inflammatory drugs and through the reduction of uremic toxins, the use of anti-inflammatory drugs cannot be recommended because of their detrimental effects on renal function and the lack of data on the effect of anti-inflammatory drugs on arterial stiffness in these patients. Promising results on endothelial function and CV events have been recently reported in patients treated with anti-IL-1 inhibitors. Antioxidant drugs are good candidates for destiffening arteries. The administration of ascorbic acid, a potent antioxidant, can be attempted to improve flow-mediated dilation and reduce central BP and ADMA in patients with CKD.

Table 1. Qualitative summary of the available evidence on the effect of drugs used in nephrology on arterial wall properties

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Effect on Arterial Wall Properties</th>
<th>Best Level of Evidence</th>
<th>Level of Evidence in CKD or Kidney Transplant Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGEs breakers</td>
<td>↑ EF</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>↓ AS</td>
<td>+ ++</td>
<td>+</td>
</tr>
<tr>
<td>ARBs</td>
<td>↓ AS</td>
<td>+ ++</td>
<td>+</td>
</tr>
<tr>
<td>DRi</td>
<td>↓ AS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Doubtful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>↓ AS</td>
<td>+ ++</td>
<td>+</td>
</tr>
<tr>
<td>Diuretics (spironolactone)</td>
<td>↓ AS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antioxidants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>↓ AS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Endothelin-1 antagonists</td>
<td>↓ AS, ↑ EF</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>↓ AS</td>
<td>+ ++</td>
<td>°</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>↑ AS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Doubtful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus or sirolimus</td>
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<td></td>
<td></td>
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<tr>
<td>Belatacept</td>
<td>Doubtful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>↓ AS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>↑ AS</td>
<td>+</td>
<td>°</td>
</tr>
<tr>
<td>Salicylates (low doses)</td>
<td>↓ AS</td>
<td>+ ++</td>
<td>°</td>
</tr>
<tr>
<td>Salicylates (high doses)</td>
<td>↑ AS</td>
<td>+</td>
<td>°</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td></td>
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<td></td>
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<tr>
<td>Statins</td>
<td>↑ EF</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Noncalcium-containing phosphate binders</td>
<td>↓ AS</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Doubtful</td>
<td></td>
<td></td>
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<tr>
<td>Xanthine oxidase inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>↑ EF</td>
<td>+ ++</td>
<td>+</td>
</tr>
<tr>
<td>Vitamin D analogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D$_2$</td>
<td>None</td>
<td>+ ++</td>
<td>+</td>
</tr>
<tr>
<td>Vitamin D$_3$</td>
<td>None</td>
<td>+ ++</td>
<td>+</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>↑ EF</td>
<td>+ ++</td>
<td>+</td>
</tr>
</tbody>
</table>

Arrows indicate increase or decrease. AGEs, advanced glycation end-products; EF, endothelial function; +, data derived from few single-center cohorts; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; DRi, direct renin inhibitors; °, lack of or scarce data.
proliferation of VSMCs. Magnesium levels rise during advanced CKD and ESRD because of the progressive reduction of renal excretion.\textsuperscript{83} However, several drugs currently used in patients with CKD, such as proton pump inhibitors, loop diuretics, and cyclosporine, can lead to hypomagnesaemia.\textsuperscript{84} The risk of hypomagnesaemia increases when these drugs are used in combination. Magnesium supplementation and the shift from proton pump inhibitors to H\textsubscript{2} antagonists is sufficient to restore magnesium levels in most patients with CKD. Long-term magnesium supplementation improves arterial stiffness in overweight and obese adults, whereas increasing dialysate magnesium decreases the propensity toward ectopic calcification in patients undergoing maintenance hemodialysis.\textsuperscript{85,86} Also, zinc may play a similar role in the arterial wall.\textsuperscript{87}

It has been reported that decreasing gastrointestinal phosphate absorption through the use of phosphate binders not containing calcium (\textit{i.e.}, sevelamer hydrochloride) reduces arterial stiffness in patients with ESRD.\textsuperscript{88} However, similar results have not been replicated in early stages of CKD.\textsuperscript{89} It is plausible that a long follow-up period (possibly years) is needed to revert the structural arterial stiffening caused by vascular calcification.

Statins prevent the development of endothelial dysfunction caused by acute inflammation in patients with hypercholesterolemia,\textsuperscript{90} and slow the rate of an increase in aortic stiffness in patients with CKD.\textsuperscript{91} They may also exert beneficial effects on kidney function and slow down the rate of decline in kidney function.\textsuperscript{92,93} Interestingly, the protective effect of statins on CV events seems to be reduced in patients undergoing hemodialysis,\textsuperscript{94} and improved by the coadministration of ezetimibe.\textsuperscript{95}

Vitamin D is a regulator of eNOS and arterial stiffness. The effect of vitamin D analog supplementation on vascular function has been evaluated in three meta-analyses that also included a minority of patients with CKD.\textsuperscript{96–98} In two meta-analyses, vitamin D analog supplementation was associated with improved endothelial function.\textsuperscript{97,98} In the third meta-analysis,\textsuperscript{96} paricalcitol, but not vitamin D\textsubscript{2} or vitamin D\textsubscript{3}, improved endothelial function. However, a high vitamin D level carries the risk of aggravating hyperphosphatemia, which could again be detrimental to endothelial function. All three meta-analyses were concordant regarding the lack of an effect on arterial stiffness and reflected waves.\textsuperscript{96–98}

There is evidence of a protective effect of allopurinol, a drug that reduces plasma uric acid levels, on endothelial function in patients with and without CKD.\textsuperscript{99} Allopurinol administration significantly reduced augmentation index, but not arterial stiffness.\textsuperscript{100}

**Specific Therapeutic Options to Reduce Arterial Stiffness in ESRD**

Several immunosuppressive drugs that are currently used in kidney transplant recipients may influence arterial function. Everolimus and sirolimus, two mammalian target of rapamycin inhibitors, could have beneficial effects on atherogenesis and fibrosis.\textsuperscript{101,102} However, whether these drugs are useful in reducing arterial stiffness is still matter of debate because arterial stiffness was reduced or remained stable in patients treated with sirolimus, and increased in those treated with cyclosporine, a calcineurin inhibitor.\textsuperscript{103} Conversely, in a cross-sectional study, endothelial dysfunction was more frequent in patients treated with everolimus plus a calcineurin inhibitor, compared with those treated with mycophenolate mofetil plus a calcineurin inhibitor.\textsuperscript{104} The immunosuppressant belatacept inhibits costimulatory signals that are essential for T lymphocyte activation \textit{via} the binding to CD80 and CD86 receptors on antigen-presenting cells. This drug could reduce vascular inflammation through the inhibition of the production of proinflammatory cytokines by activated T lymphocytes, as suggested by the reduction of antihypertensive medications at 1 year in patients treated with belatacept compared with those treated with cyclosporine.\textsuperscript{105} However, the results of two small, cross-sectional studies have not confirmed this hypothesis.\textsuperscript{106,107}

Therefore, further longitudinal studies are needed to better clarify the effect of belatacept on the arterial wall. Immunosuppressive drugs may also have a negative effect on the arterial wall. In particular, cyclosporine reduces NO production, leads to vasoconstriction and vascular fibrosis, and accelerates the stiffening process.\textsuperscript{108} In this regard, the switch to tacrolimus could potentially help to improve arterial stiffness. However, this hypothesis is still matter of debate. Finally, corticosteroids have a deleterious effect on the arterial wall, at least in part through the increase of BP (through salt retention and hyperactivation of the renin-angiotensin-aldosterone system) and LDL cholesterol levels.\textsuperscript{109}

Renal transplantation is an effective approach to reduce arterial stiffness in patients with ESRD.\textsuperscript{58} The improvement in arterial stiffness is better if kidneys come from young donors (living as opposed to deceased).\textsuperscript{110} Similar to the reduction of arterial stiffness, the baroreflex sensitivity is also improved after a renal transplant.\textsuperscript{57} However, the mechanism by which renal transplantation can improve baroreflex function, as well as the relationship between baroreflex function and arterial properties, needs to be clarified.\textsuperscript{111}

Dialysis modalities can influence the alteration in arterial stiffness. Arterial stiffness can be reduced through the use of convective dialysis techniques (such as a high-efficiency, on-line hemodiafiltration), rather than conventional hemodialysis, for the increased removal of middle molecular weight uremic toxins \textit{i.e.}, \(\beta_2\)-microglobulin, phosphate, and TNF) and protein kinase C\(\beta_2\), which is an eNOS inhibitor.\textsuperscript{112} The use of convective dialysis techniques also reduce chronic inflammation and mortality risk compared with conventional hemodialysis.\textsuperscript{113,114}

**PERSPECTIVES**

Reducing arterial stiffness can be attempted by several approaches, but few of them...
have been tested in patients with CKD. Moreover, we are far away from confirming that the treatment options discussed in this review independently reduce CV events or delay the progression of CKD. At the time of this review, only one trial has demonstrated that patients who improve their arterial stiffness during intervention have better outcomes. Therefore, large-scale, randomized trials that include long-term measures of vascular stiffness and recording cardiac and renal events are needed in patients with CKD.

In conclusion, vascular dysfunction is an important mediator between CKD and chronic impairment of cardiac function. Several therapeutic approaches can be attempted to reduce arterial stiffness in patients with CKD.

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DISCLOSURES

None.

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