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REVIEW | *2019 AJP Regu New Investigator Review Award Competition*

Nutraceuticals as a potential adjunct therapy toward improving vascular health in CKD

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Kruse NT. Nutraceuticals as a potential adjunct therapy toward improving vascular health in CKD. *Am J Physiol Regul Integr Comp Physiol* 317: R719–R732, 2019. First published October 2, 2019; doi:10.1152/ajpregu.00152.2019.— Chronic kidney disease (CKD) is a major public health epidemic and increases risk for developing cardiovascular disease (CVD). Vascular dysfunction is a major independent risk factor toward increased risk for CVD in CKD. Several mechanisms have been postulated to result in vascular dysfunction in CKD, including oxidative stress-mediated inflammation by redox imbalance and reduced nitric oxide (NO) bioavailability and synthesis. Therefore, strategies that decrease oxidative stress and/or increase NO bioactivity may have major clinical implications toward improving vascular health and reducing the burden of CVD in CKD. Nutraceutical therapy in the form of polyphenols, dietary nitrates, or selective mitochondria-targeting therapies has recently been shown to improve vascular function by reducing oxidative stress and/or increasing NO bioavailability and synthesis. This review, therefore, highlights these three emerging nutraceuticals recently implicated in pathophysiological improvement of vascular function in CKD. This review also describes those pathophysiological mechanisms thought to be responsible for the beneficial effects on the vasculature and possible experimental considerations that may exist within human CKD populations. It is clear throughout this review that human-based mechanistic preclinical and health-related clinical studies are lacking regarding whether nutraceuticals do indeed improve vascular function in patients with CKD. As such, a comprehensive, detailed, and fully integrated understanding of nutraceuticals and vasculature function is necessary in patients with CKD. Many opportunities exist for original mechanistic and therapeutic discoveries and investigations on select nutraceuticals and their impact on vascular outcomes in patients with CKD, and these will remain exciting avenues of research in the future.

chronic kidney disease; inflammation; nutraceuticals; oxidative stress; vascular function

INTRODUCTION

Chronic kidney disease (CKD) is a progressive disease that affects a significant proportion of the population (8–16%) worldwide (28, 75). In developed countries, patients with CKD have an exceptionally high risk of cardiovascular disease (CVD) and as such, are 10 times more likely to die from CVD before requiring dialysis or kidney transplantation when compared with age-matched controls (28, 75) (Fig. 1). Indeed, CVD affects 68.8% of individuals with CKD aged 66 years and older, which is nearly twofold greater than those of a similar age without CKD (142). Importantly, the increased prevalence of CVD in patients with CKD persists even when traditional risk factors of CVD are adjusted for, suggesting that other mechanisms may be involved in the etiology of CKD (13, 57, 107, 108, 165).

Patients with CKD exhibit functional and structural impairments within the vasculature (41, 44, 68, 88, 116, 149, 177). Specifically, stiffening of the large elastic arteries (i.e., the aorta), typically demonstrated by increased aortic pulse-wave velocity (aPWV) (Fig. 2) and a decline in microvessel and/or conduit endothelial function, generally examined via brachial artery flow-mediated dilation (baFMD) (Fig. 3), has been demonstrated in patients with CKD (16, 39, 54, 87, 135, 145, 164). Importantly these parameters predict future CVD risk in CKD and are considered "macroscale" physiological parameters that could facilitate other pathologies such as hypertension and atherosclerosis (16, 39, 54, 87, 135, 145, 164). Apart from these clinically accepted measures, several other methods have been used to assess vascular dysfunction in patients with CKD, as demonstrated by *1*) impaired cutaneous microvascular func-

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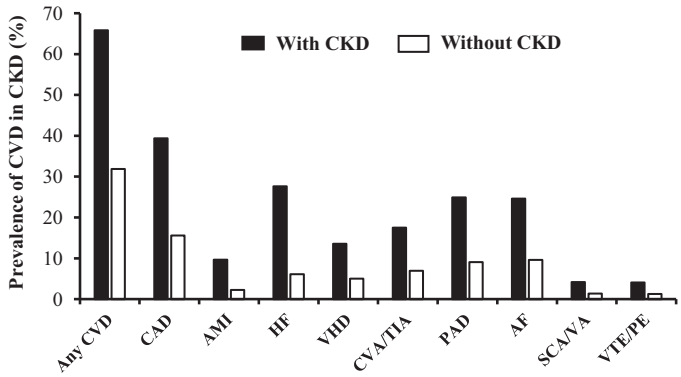

Fig. 1. Prevalence of several types of common cardiovascular diseases (CVD) in patients with (black bars) or without (white bars) chronic kidney disease (CKD). Overall, CVD affects 68.8% of individuals with CKD aged 66 and older. These associations increase exponentially with decreasing estimated glomerular filtration rate. AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral arterial disease; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; VHD, valvular heart disease; VTE/PE, venous thromboembolism and pulmonary embolism. Data are from Saran et al. (142).

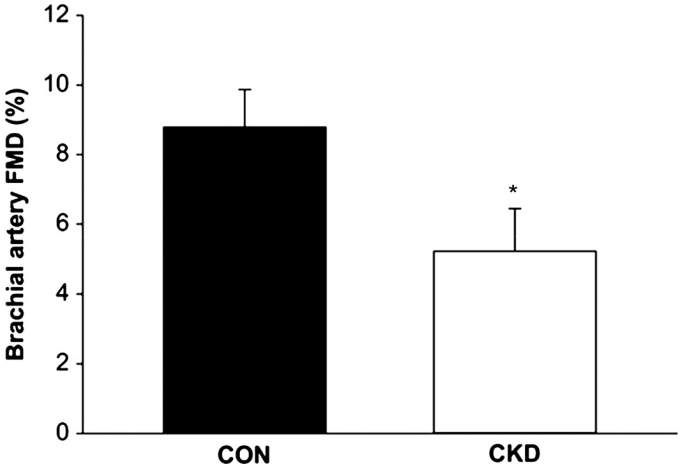

Fig. 3. Impaired vascular function as assessed by the percent change of brachial artery responsiveness to flow-mediated dilation (%FMD) in chronic kidney disease (CKD) compared with age-matched healthy control (CON) subjects. Brachial artery responsiveness is quantified by the maximal percent change in diameter from baseline (%FMD). *$P < 0.05$ vs. CON. Modified from Katulka et al. with permission (74).

tion (as measured by the red blood cell flux via laser Doppler flowmetry) (44); *2*) reduced peak leg blood flow assessed via passive leg movement (72); *3*) reduced blood flow and vasodilator response to intra-arterial infusion of pharmacological agents such as acetylcholine and sodium nitroprusside (32); *4*) impaired common carotid artery distensibility (15); and *5*) reduced brachial artery responsiveness to nitroglycerin-mediated vasodilation (83). Despite these well-established relationships, an effective treatment correcting vascular dysfunction and progression of renal disease in patients with CKD remain undiscovered (28, 78, 105).

The importance of nutrition in nephrology has been recognized as crucial in the management of patients with CKD and, potentially, with the concomitant use of pharmacological therapy, may slow the progression of renal disease (30, 52). Although there is evidence that nutraceuticals improve vascular-related outcomes in animal models and healthy human and aging populations, little evidence to date exists showing the beneficial effects on vascular health in patients with CKD (136). Therefore, understanding the mechanisms that contribute to vascular dysfunction and nutraceutical therapies that may counteract vascular dysregulation in CKD may hold clinical promise by facilitating the development of novel research strategies in the future.

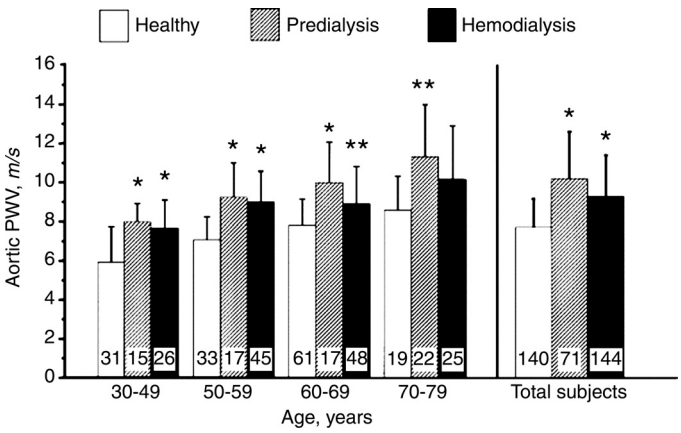

Fig. 2. Impaired (increased) aortic pulse-wave velocity (PWV) in predialysis chronic kidney disease (CKD) compared with healthy control and hemodialysis patients. Aortic PWV increased with age in patients with CKD. Aortic PWV is calculated as the ratio between the distance (in meters) from aortic-to-femoral arteries and the transit time (seconds) needed for the pressure or velocity wave to cover this distance (m/s). *$P < 0.05$ vs. healthy; **$P < 0.05$ vs. health and predialysis. Modified from Shinohara et al. with permission (148).

In this review, the physiology and underlying mechanisms of vascular dysregulation in CKD are briefly discussed, followed by a more comprehensive discussion of three emerging nutraceutical strategies that may show promise in preventing or reversing vascular dysregulation in CKD. Accordingly, these novel nutraceutical options include polyphenols, dietary nitrates, and selective mitochondria therapies. The mechanisms underlying the potential beneficial effects of these nutritional strategies whenever possible are examined. In most cases, there is limited direct evidence for the effects of nutritional factors on vascular function in patients with CKD. In those instances, the focus will be toward strategies for which there are compelling data from studies of at-risk human populations as well as other disease states and/or results of translational investigations using preclinical models.

MECHANISMS OF VASCULAR DYSFUNCTION IN CKD

Oxidative Stress/Inflammation

Increased oxidative stress is prevalent in patients with CKD, and this is believed to play an important role in vascular dysfunction and progression of kidney disease. Indeed, administration of the potent antioxidant vitamin C has been demonstrated to reduce oxidative stress leading to an improved nitric oxide (NO)-mediated vasodilation (i.e., increased the dilator response to acetylcholine in resistance vessels) in chronic renal failure patients (32). Oxidative stress is often characterized by biomolecular targets such as impaired ability to activate nu-

clear factor-like erythroid-related factor-2 (NRF-2) (138) and/or increased nitrotyrosine, ratio of oxidized to reduced glutathione (GSSG/GSH), lipid hydroperoxides, oxidized glutathione, protein carbonyls, and F2-isoprostanes as well as reduced antioxidant capacity [i.e., superoxide (peroxynitrite) (34)]. Chronic low-grade inflammation is also prevalent in patients with CKD (34). Specifically, central [nuclear factor-κB (NF-κB)] and circulating [interleukin-6 (IL-6)] inflammatory cytokines exacerbate these processes while interacting synergistically with oxidative stress pathways (110), although the exact order and relationship between these mechanisms are uncertain and may be interchangeable. Endothelial function and estimated glomerular filtration rate (eGFR), an index of renal function, have also been shown to be associated with increased levels of advanced glycation end products (AGEs) in different stages of predialysis, independent of diabetes (75). This is likely due, in part, to increased expression of AGE receptors on the surface of endothelial cells (98). In particular, AGEs have been shown to inhibit endothelial NO synthase (eNOS) activity directly as well as reduce substrate bioavailability by reacting with L-arginine resulting in endothelial dysfunction (51).

NO Bioavailability/Synthesis: Role of Asymmetric Dimethylarginine and L-Arginine

Enhancing NO bioavailability of the substrates for synthesis is a requisite for optimal human vascular health. Patients with CKD exhibit a reduction in NO bioavailability and/or inefficient synthesis of NO, leading to vascular dysfunction (105, 183). Another contributor to endothelial dysfunction in patients with CKD is the formation of the eNOS inhibitor asymmetric dimethylarginine (ADMA) (4, 10, 44, 77). ADMA has been classified as a "uremic toxin," leading to adverse cardiovascular effects (133, 161, 180), and is independently associated with CVD risk in patients with CKD (21). Moreover, ADMA prevents NO production through competitive eNOS uncoupling, manifesting as endothelial dysfunction and vascular disease in CKD (44, 105). ADMA is also elevated in patients with stage 3–4 CKD who exhibit endothelial dysfunction (8). Furthermore, elevated ADMA contributes to a reduction in the L-arginine-to-ADMA ratio (9).

L-Arginine deficiency may be another important mechanism involved in endothelial function in CKD, given its abilities as a reactive free radical scavenger and potent vasodilator (10, 11). NO bioactivity depends on the amino acid substrate L-arginine, which is synthesized in the proximal tubules of the renal cortex. L-Arginine transport has been shown to be impaired by the elevation of uremic toxins in patients with CKD (10, 11). Furthermore, increased levels of urea in humans, a common characteristic of CKD, have been correlated with decreased baFMD, and this has been implicated to reduced L-arginine transport (6). Finally, tetrahydrobiopterin (BH_4), an essential cofactor for NO synthase, has been shown to be significantly lower in humans with CKD when compared with age-matched controls (178), thus highlighting its role as a potential therapeutic vascular target in patients with CKD.

Sympathetic Nervous System Overactivation

Chronic overactivation of sympathetic nervous system activity (SNA) is also likely involved in the progression of vascular dysfunction in CKD (73). Multiple human and animal studies demonstrate that CKD is a state of heightened SNA (27, 60, 61, 80, 114, 123). Moreover, elevated SNA in the kidney increases renovascular tone, activates the renin-angiotensin-aldosterone system, and increases sodium reabsorption (38, 84). In doing so, it contributes to extracellular fluid volume expansion, increases blood pressure, and ultimately results in vascular remodeling (152). Outside the kidney, increased SNA leads to structural changes influencing the mechanical properties (i.e., vascular smooth muscle tone and stiffness) of peripheral and central arteries in young and older adults through mechanisms such as oxidative stress (48), although these processes are likely synergistic (Fig. 4). Similarly, sympathetic activation can impair NO function, and this may be attributed to reduction in NO synthase bioactivity through modulation of β- and/or α-adrenergic receptors (46, 53). Alternatively, NO has been shown to tonically suppress sympathetic tone (139, 179), again highlighting that these mechanisms are interactive.

NUTRACEUTICALS AS A NOVEL THERAPEUTIC OPTION IN CKD

Pharmaceutical therapy is the most common modality to reduce CVD burden in CKD (151, 155). Although some pharmaceuticals are aimed at treating oxidative stress, inflammation, and nephropathies in CKD, they have inherent limitations, as they exhibit negative side effects. Thus there is growing interest in nutraceutical interventions aimed at reducing vascular oxidative stress and/or inflammation without the underlying burden of negative side effects in patients with CKD. Recently, several dietary nutraceutical options have shown promise at reducing the risk for CVD by improving vascular phenotypes in healthy human and clinical populations such as, hypertension, diabetes, and congestive heart failure (5, 7, 25, 35). Nutraceuticals comprise a broad range of dietary supplements whose bioactive properties promote many important health benefits, including improved vascular function (147, 184). It is believed that the bioactive properties within some of these nutraceuticals play an integral role in suppressing macro-

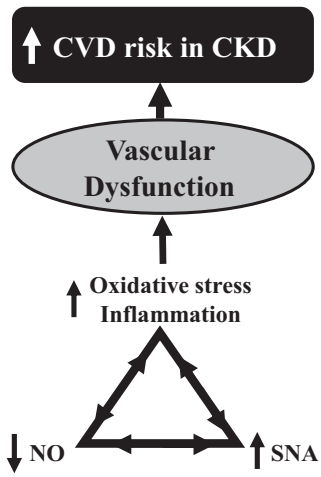

Fig. 4. Potential mechanisms leading to decreased vascular function and the increased risk for cardiovascular disease (CVD) in patients with chronic kidney disease (CKD). NO, nitric oxide; SNA, sympathetic nervous system activity.

mechanistic processes such as oxidative stress and inflammation, sympathetic overactivation, and upregulate antioxidant properties and NO bioavailability (30). As such, many nutraceuticals trigger a multitude of cellular signaling pathways, which, in part, may explain their beneficial effects on arterial/physiological function. However, some nutraceuticals target one specific pathway (i.e., cytosol of mitochondria). The following sections, therefore, highlight three emerging nutraceuticals that have recently been shown to either improve arterial health or modulate the mechanisms believed to be involved in vascular function in a variety of populations, including renal disease; specifically, these include *1*) polyphenols, *2*) inorganic nitrates, and *3*) selective mitochondria-targeting therapies.

POLYPHENOLS

There is substantial epidemiological evidence that a diet high in polyphenol-rich compounds found in fruits, vegetables, nuts, spices, red wine, tea, cocoa, etc. protect against the development of several chronic diseases, including CVD (29, 162, 167, 168). There is considerable data in healthy and clinical populations demonstrating that polyphenols improve several vascular/cardiovascular phenotypes including the following: *1*) reduced arterial stiffness (i.e., aPWV) (24, 112, 150); *2*) increased endothelial function by increasing baFMD and forearm blood flow responses to acetylcholine (3, 150, 169, 170, 182); *3*) reduced 24-h ambulatory blood pressure (42, 122); and *4*) inhibition of platelet aggregation (113, 119). Polyphenols are reported to alleviate vascular complications by attenuating oxidative stress in addition to acting on cellular signaling pathways including NO signaling, VEGF-mediated angiogenesis, endoplasmic reticulum stress, and the Nrf-2-antioxidant pathway (30, 50, 59, 134, 159). In particular, polyphenols activate the Nrf-2/antioxidant responsive element pathway, leading to induction of several antioxidant enzymes such as glutathione (GSH)-*S*-transferase (GST) and NADPH: quinone oxidoreductase 1 (134, 144). Polyphenols have also been shown to improve vasodilatory capacity through inhibiting the release of the potent vasoconstricting peptide endothelin-1 (90, 106). Lastly, polyphenols likely exert anti-inflammatory properties by modulating transcriptional networks and/or signaling cascades that regulate gene expression and inhibiting inflammatory mediators such as NF-κB, tumor nuclear factor-α (TNF-α), IL-6, and C-reactive protein in addition to adhesion molecules (VCAM-1 and ICAM-1) (59, 157, 158). Given that polyphenols exhibit potent ant-oxidant and anti-inflammatory properties, it could be speculated that these beneficial effects may extend to patients with CKD, leading to improved vascular function. Of the numerous polyphenol compounds shown to exhibit vascular protection, there is increasing evidence that the polyphenols resveratrol (RSV) and curcumin, in particular, promote cardiovascular health via reductions in endothelial dysfunction, arterial stiffness, and blood pressure regulation in several clinical and healthy populations (104, 109).

RESVERATROL

One of the most widely studied polyphenols in health and disease is RSV; a stilbene derivative found naturally in grapes and red wine, which exhibits potent antihyperglycemic, antioxidative, and anti-inflammatory properties (121). Translational works in humans have shown that supplementation with RSV results in a dose-dependent increase in baFMD in mildly hypertensive and overweight adults (169). These finding corroborate more recent studies showing improved endothelial function (via reactive hyperemia using peripheral arterial tonometry) after RSV treatment in older (129) and hypertensive adults (21). With regard to CKD, a recent meta-analysis revealed that light wine consumption (<1 but >0 glass/day) is associated with a significantly lower prevalence of CKD and lower rate of CVD in patients with CKD after adjusting for age, sex, race, waist circumference, diabetes mellitus, hypertension, and cholesterol levels (69) (Fig. 5). These data are consistent with the proposition that the protective role of phenols (predominantly RSV) within wine may extend to individuals with CKD and that RSV may reduce the risk of CVD within patients with CKD. Together, RSV appears to be a promising nutraceutical that may improve vascular function in patients with CKD. However, it remains unknown whether these beneficial effects can be directly applied to patients with CKD, as randomized, double blinded placebo-controlled trials are currently lacking.

Mechanisms of RSV

As shown in Fig. 6, the mechanisms by which RSV modulates vascular function are multifactorial and have been mainly demonstrated in cell/animal models (95). However, this topic remains largely unexplored in human clinical trials. Experimental studies have shown that RSV (at doses that can be

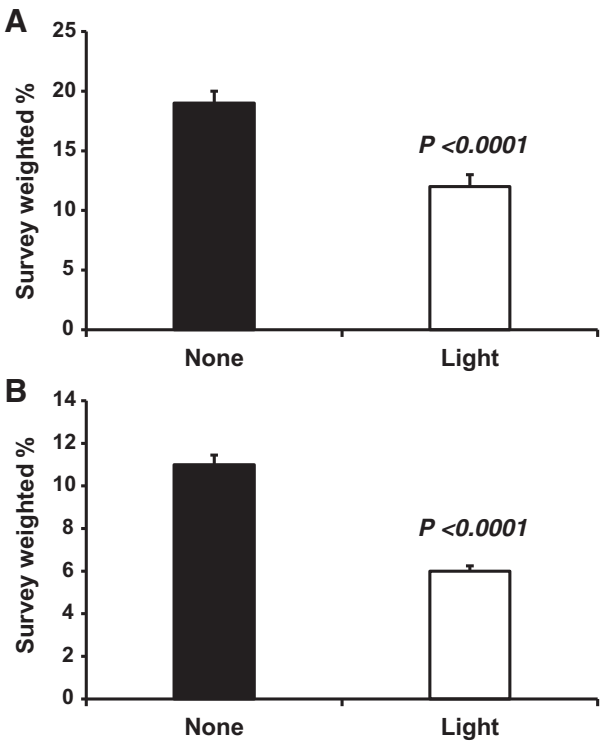

Fig. 5. Light wine intake is associated with a lower odds of prevalent CKD (*A*) and a lower prevalence of cardiovascular disease (*B*) in patients with chronic kidney disease. Variables are shown as a survey weighted percentage. None is defined as 0 glass/day, and light wine consumption is defined as <1 glass per day but >0 glass/day. Overall effect: $P < 0.05$. Values are means ± SD. Modified from Jespersen et al. with permission (69).

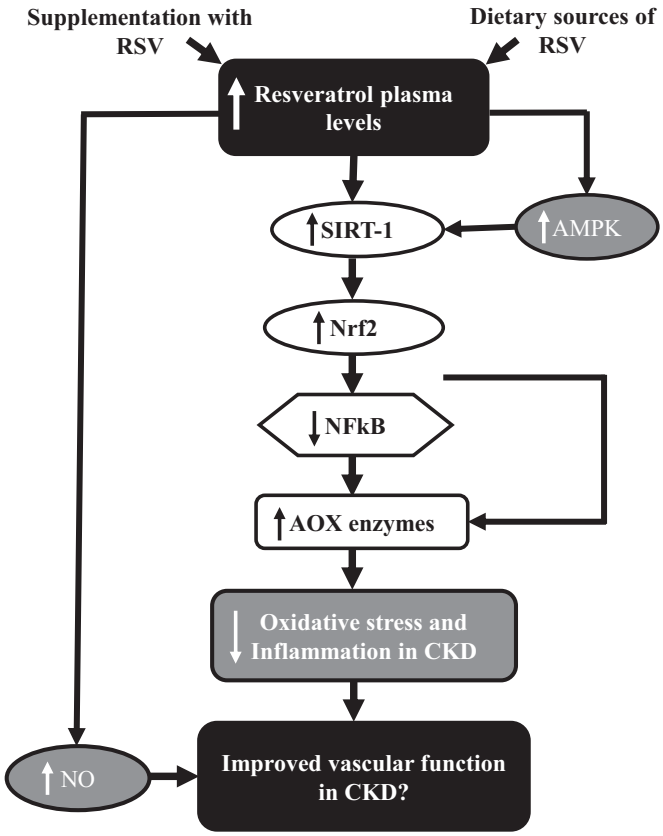

Fig. 6. Schematic of potential resveratrol (RSV) action mechanisms to reduce inflammation/oxidative stress and/or nitric oxide (NO) leading to improvements in vascular function in chronic kidney disease (CKD). AMPK, adenosine monophosphate-activated protein kinase; AOX, antioxidant; Nrf2, nuclear factor-like erythroid-related factor-2; NF-κB, nuclear factor-κB; SIRT-1, sirtuin 1.

achieved by light to moderate drinking of red wine) inhibits inflammation, restores NO production, and reduces oxidative stress in vitro (33, 96, 163) and in vivo (96, 143, 181). RSV activates the protein deacetylase enzyme silent information regulator 2/sirtuin 1 (SIRT1) (65, 160, 171), which may lead to improved endothelial function (173). Several other mechanisms may also be at play including the induction and activation of eNOS expression (92, 163, 174), inhibition of inflammatory mediators (33, 47), and modulation of oxidative stress (172). Furthermore, simultaneous activation of SIRT1-AMPK and endoplasmic reticulum pathways by RSV can indirectly increase eNOS expression and activity in addition to amplifying the L-arginine/NO/cGMP pathway by enhancing its expression and activity, resulting in increased NO bioavailability (51).

CURCUMIN

Translational evidence also supports a role of curcumin supplementation toward improving vascular health (18). Along these lines, supplementation with curcumin has been shown to restore endothelial function and reduce arterial stiffness in old mice to comparable levels seen in young controls (49). In humans, supplementation with curcumin has been demonstrated to be as effective as exercise at improving endothelial function (3, 141) and may synergistically improve vascular parameters related to arterial stiffness with age (156). Regarding CKD, it has been shown that supplementation with curcumin in a rat model (5/6 nephrectomy) of CKD-induced several beneficial effects that may reduce CVD risk, such as amelioration of cardiac function, decrease in blood pressure and oxidative stress, and improvement of mitochondrial integrity and functionality (62). Presently, it remains unknown whether the effects of curcumin on vascular function translate from animals and other human based populations to patients with CKD.

Mechanisms of Curcumin

Similar to RSV, curcumin is believed to improve vascular function through its multitargeting actions as an antioxidant and anti-inflammatory agent both in vitro and in vivo (67, 117, 125, 130). Specifically, the oxidative stress-lowering effects of curcumin are largely attributable to enhanced antioxidant defenses via activation of Nrf-2, which, in turn, induces expression of endogenous antioxidant enzymes such as superoxide dismutase and glutathione reductase (58). In addition, curcumin has been shown to inhibit NF-κB and its downstream targets such as IL-6, monocyte chemoattractant protein-1, and TNF-α in a variety of animal models of CVD (125, 176). Furthermore, curcumin supplementation has been demonstrated to reverse arterial aging by reducing oxidative stress and inflammation in mice (49).

EXPERIMENTAL CONSIDERATIONS TOWARD THE USE OF POLYPHENOLS (RSV AND CURCUMIN) IN PATIENTS WITH CKD

It has been suggested that, rather than acting as a chemical antioxidant in vivo, the chemical properties of polyphenol compounds generate signals for the induction of several protective detoxifying enzymes, potentially through a second messenger (i.e., SIRT-1, Nrf-2 activators, and NF-κB) within the vasculature (30, 64, 86). Thus an alternative hypothesis is that the chemically important "antioxidant" properties of polyphenols in vivo are either pro-oxidant (generating reactive species) and/or electrophilic (having the capacity to form adducts to proteins) and stimulate a general xenobiotic and/or antioxidant response in the target cells, activating many defense genes (30, 91, 144). Therefore, induction of these potent antioxidants through this phenomenon may rationalize the improvement in vascular function seen in several studies.

It has also been hypothesized that after polyphenols are ingested, the plasma concentration may not be sufficiently elevated in vivo to remove a significant portion of free radicals within the circulation (22, 30, 121). This could be due to extensive conjugation that occurs on first pass through the liver, as a metabolic detoxification process; this is followed by urinary elimination because of the increased hydrophilicity of the conjugates (59, 121). However, several lines of evidence have shown that the bioavailability of polyphenols, including RSV and curcumin, in the blood after consumption is significantly increased, especially when using techniques to enhance its bioavailability (94). Furthermore, CKD patients are unique compared with other clinical populations, in that plasma levels of polyphenol metabolites likely remain elevated for a longer period due to impairment in the ability of the kidney to adequately excrete these metabolites (reflected as reduced

eGFR). Consequently, this sustained bioavailability of polyphenols in the blood may allow for greater time for the bioactive agents to have greater effect on the vasculature in CKD.

In summary, observations from studies demonstrate that polyphenols in the form of RSV and curcumin supplementation exhibit a multitude of biologically active properties that can have therapeutic effects on vascular structure and function. Therefore, RSV and curcumin could represent a promising multitargeting treatment approach to reduced oxidative stress/inflammation and/or increase NO bioavailability, leading to improved vascular function in patients with CKD. More research is needed to warrant this possibility.

DIETARY NITRATES

The importance of dietary nitrates for vascular health has recently been investigated in several observational and intervention studies involving humans (101). It is now well recognized that the body can use exogenous nitrate (via direct exposure through a diet) to produce the important messenger molecule NO (2), a fundamental modulator of endothelial function, vasodilatation, and blood pressure regulation (93). Moreover, evidence suggests that a diet naturally rich in fruits and vegetables may confer cardiovascular benefits, largely due to its high nitrate content, and subsequent increased NO production (2, 101). After ingestion of a nitrate rich meal or supplement, circulating nitrate is excreted by the kidneys. Nitrate is then actively taken up by the salivary glands, concentrated, and secreted in saliva (153). In the mouth, much of the nitrate is reduced to nitrite by commensal bacteria (43, 103). Nitrite is subsequently swallowed and enters circulation after absorption (102). Once in circulation, nitrite can be reduced to NO during physiological and pathological stressors, such as hypoxia. Collectively, this phenomenon is referred to as the nitrate-nitrite-NO pathway (Fig. 7) and involves a series of oxygen-independent and NO synthase-independent single-electron transfer reactions that promote vasodilation and modulation of cellular respiration (82).

Several lines of evidence suggest that the decline in endothelial function in patients with CKD is likely due in part, to an impaired ability of endothelial cells to release/produce NO (11, 20, 105, 166). A diet high in inorganic nitrates substantially increases NO bioavailability, which, consequently, has been shown to reduce blood pressure, inhibit platelet aggregation, protect against ischemia-reperfusion, and improve mitochondrial efficiency and exercise performance in several observational and intervention studies involving healthy humans and clinical populations (36, 63, 81 85, 89, 101, 118, 131, 136). With regard to CKD, in a recent clinical trial with a crossover design, Kemmer et al. (76) found that a single dose of dietary nitrate (200 mL ~6 mmol/300 mg NO_3) significantly reduced renal resistive index in older adults with CKD. A high renal resistive index is a marker of vascular dysfunction (100) and is associated with an increased risk of cardiovascular dysfunction in humans (100, 126). Therefore, as older adults are at a greater risk of kidney dysfunction, a reduced renal resistive index following supplementation with dietary nitrate may result in reduced risk for CVD in patients with CKD, and this could be reflected by improvements in vascular function.

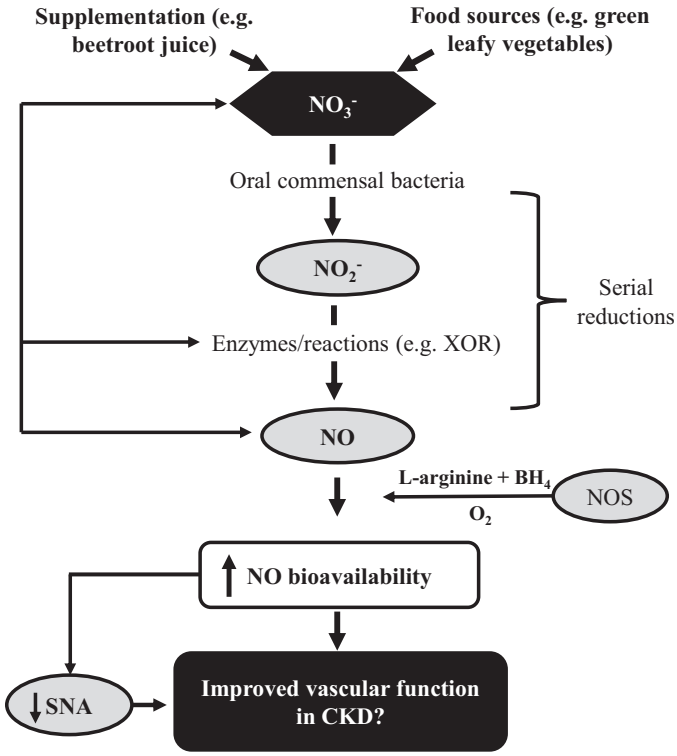

Fig. 7. The nitrate-nitrite-nitric oxide pathway as a potential therapeutic target toward increasing nitric oxide bioavailability and improve vascular function in chronic kidney disease (CKD). NO, nitric oxide; NOS, nitric oxide synthase; SNA, sympathetic nervous system activation.

Mechanistically, apart from its well-known capacity to increase NO bioavailability, chronic consumption of dietary nitrates in the form of beetroot juice has recently been shown to reduce muscle SNA in young healthy adults (115), attenuate elevated sympathetic vasoconstriction during exercise in peripheral arterial disease (85), and alleviate peripheral chemoreflex sensitivity in older adults (12). Moreover, these data suggest that tonic elevation of NO bioavailability via dietary nitrates inhibits central sympathetic outflow (139, 179), and this is attributed to the decline in sympathetic overactivation in humans. Given that patients with CKD exhibit a greater level of SNA compared with age-matched controls (73), supplementation with dietary nitrates may be one way to improve neurovascular tone by modulating NO bioavailability (Fig. 7). However, this hypothesis remains untested in patients with CKD, and thus studies are required to warrant this possibility.

Although not a direct form of dietary nitrate, BH_4 has shown promise as an important therapy that might improve vascular function in patients CKD. Supplementation with BH_4 has been shown to increase NO bioavailability and improve blood pressure and endothelial function in animal models (5/6 nephrectomized rats) of chronic renal failure (128, 175). Recent translational evidence has shown that a 12-wk treatment with sapropterin dihydrochloride (6R-BH_4), the synthetic form of the naturally occurring enzyme BH_4, significantly lowered resting muscle SNA (124) and ameliorated the exaggerated exercise pressor response (97) in patients with CKD. It was also demonstrated that 6R-BH_4 concomitantly and significantly improved arterial wave reflection and the vasodilatory response to nitroglycerin. These findings demonstrated that a novel form

of BH_4 supplementation (6R-BH_4) may be one important strategy for improving some aspects of vascular function, which is likely attributed to its lowering effect on SNA in patients with CKD.

EXPERIMENTAL CONSIDERATIONS TOWARD THE USE OF DIETARY NITRATES IN PATIENTS WITH CKD

Consumption of dietary nitrates in the form of certain vegetables can be detrimental to kidney function (assessed via eGFR, albumin, creatinine, and albumin/creatinine ratio) (8), and it is therefore, recommended that patients with CKD avoid some of these nitrate-containing vegetables. However, it remains unknown whether nitrates, either in the form of a dietary supplement or some other agent in certain vegetables containing high concentrations of nitrates are mainly responsible for the independent and detrimental effects on kidney function.

An avenue of research worth mentioning, in relation to dietary nitrates, is the use of nitrite supplementation to ameliorate kidney and vascular dysfunction. The nitrite anion (inorganic nitrite) is a cytoprotective molecule with antioxidant properties that are directly reduced to bioactive NO in the circulation and tissues (55). Importantly, nitrite is only a one-step reduction to NO (as opposed to multiple steps via nitrate), and it is considered an ideal candidate for restoring NO bioavailability and signaling in states of chronic NO insufficiency, such as CKD (17, 36). Preclinical data have demonstrated that sodium nitrite supplementation improves vascular function and oxidative stress in healthy older adults (36, 71). Moreover, infusions of nitrite have been shown to significantly increase NO and directly vasodilate both veins and arteries of the forearm and reduce vascular resistance during hypoxia (19, 56, 127). Although no studies to date have explored this option in human clinical trials, nitrite supplementation appears to represent a novel and safe alternative strategy for increasing systemic NO bioavailability and improving vascular function in patients with CKD.

SELECTIVE MITOCHONDRIAL-TARGETED THERAPIES

There is now increasing evidence that mitochondrial damage and dysfunction are implicated in the pathogenesis of several types of renal disease (45) and may therefore, contribute to multiple underlying pathological processes (23) including vascular dysfunction, hypertension, and diabetes (45). Endogenous antioxidant enzymes within the mitochondria play an important role in preventing oxidative stress and are impaired in CKD (132). Furthermore, in vivo evidence recently demonstrated that mitochondria-derived reactive oxygen species contribute to microvascular dysfunction in patients with CKD, thus suggesting that the mitochondria may be a potential therapeutic target to ameliorate CKD-related vascular dysfunction (79). As such, there is growing interest in more targeted compounds to combat vascular oxidative stress (111), aimed at improving the endogenous antioxidant defense systems (i.e., ubiquinol or a-tocopherol) of the mitochondria with lipophilic cations such as mitoquinone (MitoQ) or MitoE2 (111). These selective mitochondria targeting therapies may combat oxidative stress by correcting the redox imbalance in diseases and thus may be good candidates for targeting endothelial mitochondria of CKD (89, 146, 184). There is very limited evidence to date, however, examining selective mitochondrial targeting therapies on vascular function in human populations. Recently, MitoQ supplementation has been shown to restore endothelial function and reduce aortic arterial stiffness in aging humans (137). This improvement was mediated, at least in part, by suppression of plasma oxidized low-density lipoprotein, a biomarker thought to play a key role in the inflammatory response of the arterial vessel wall (66). Although there is no direct experimental evidence to date within patients with CKD, these findings in aging humans provide foundational experimental support for the concept that MitoQ, and perhaps other selective mitochondrial targeting therapies, may serve as novel therapeutic options for improving vascular function and reducing the risk of CVD in CKD.

EXPERIMENTAL CONSIDERATIONS TOWARD THE USE OF SELECTIVE MITOCHONDRIAL TARGETING THERAPIES IN PATIENTS WITH CKD

It has been suggested that certain selective mitochondrial targeting therapies, such as MitoQ, may be pro-oxidant and proapoptotic as its quinone group can participate in redox cycling and superoxide production (40), resulting in a level of "toxicity" within the vasculature. Although MitoQ has been shown to be safe in preclinical studies, using MitoQ as an antioxidant should be interpreted with caution (40). Thus future work is needed comprehensively examining MitoQ in clinical populations (i.e., CKD) to determine its efficacy. In addition, future works may need to consider other selective mitochondrial targeting therapies (i.e., GC4401, MitoCP, MitoTEMPO, MitoE, etc.), which have been shown to be more efficacious in preclinical studies. Nevertheless, the direct actions of such alternative selective mitochondrial targeting therapies remain deficient in the literature involving patients with CKD.

CLINICAL APPLICATIONS, CONSIDERATIONS AND FUTURE RESEARCH QUESTIONS

Disease Type/Severity and the Uremic Switch

The severity of CKD (as categorized by stages 1–5 of disease progression) should be considered in the context of nutraceutical efficacy. eGFR is used to stage CKD progression/severity and is directly related to the ability of the kidney to filter and reabsorb substrates (140). Therefore, it is possible that individuals with a greater impairment in kidney function (i.e., later stages 4–5) may not benefit from nutraceuticals, as there may be a point in which the elevated uremic toxins (due to a decline in kidney function) contributing to endothelial dysfunction become irreversible. This "uremic switch" could confound the influence of nutraceutical therapies aimed at targeting the endothelium and improving endothelial function in CKD (105). However, it remains undetermined whether treatment in earlier stages of CKD, when the influence of uremic toxins is less, may be effective at restoring endothelial function. Future works are needed to address these experimental concerns in patients with CKD.

Pathophysiological Phenotypes Contributing to Vascular Function in CKD

The risk for CVD is substantially higher in people with CKD compared with the general population, leading to uncertainty

around pathophysiological mechanisms and the validity of generalizations from the general population (70, 99). Published reports of subgroup analyses from clinical trials have identified that a variety of interventions may have different effects in patients with kidney disease compared with those with normal kidney function (70). For example, patients with end-stage renal disease exhibit an impaired vasculature, as evidenced by greater impairment in baFMD to a greater extent than earlier stages in patients with CKD (105). Furthermore, within CKD, arterial stiffness (i.e., aPWV) increases with increasing CKD stage, and this can be attributed, in part, to the inverse correlation seen between eGFR and aPWV (Fig. 8). It is also possible that those patients with CKD who have diabetes mellitus, hypertension, or the combination of both may exhibit a greater impairment in vascular function compared with patients who have CKD alone. Indeed, patients with diabetic kidney disease have a disproportionally higher risk for CVD when compared with patients with diabetes who do not have CKD (74, 120), suggesting that the etiology of diabetes within CKD patients appears to exacerbate the condition more so than CKD alone. However, a recent study demonstrated that the presence of diabetes with CKD did not result in a greater decline in vascular function (via baFMD and aPWV) when compared with patients with CKD alone (without diabetes) (31). Nevertheless, the study has inherent limitations due to the relatively small sample size, the absence of a healthy age-matched control group, and the cross-sectional design.

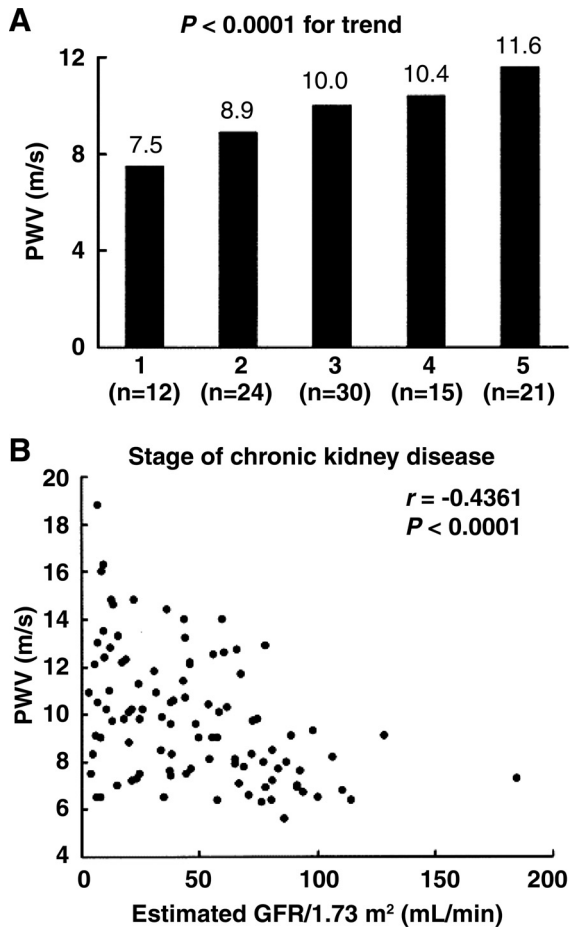

Fig. 8. Increased aortic pulse-wave velocity (aPWV) with increasing chronic kidney disease (CKD) stage (*A*) and the correlation between estimated glomerular filtration rate (eGFR) per 1.73 m^2 and aPWV in patients with CKD (*B*). There was a trend ($P < 0.0001$) for PWV as the stage of CKD progresses. Additionally, eGFR, a marker for kidney dysfunction was inversely correlated with aPWV. Modified from Wang et al. with permission (164).

Hypertension is also a common complication in patients with CKD, and its prevalence increases with progression of the disease (26). Endothelial dysfunction is a primary event in the development of hypertension and as such may contribute to the elevated cardiovascular risk in CKD. Because hypertension alone alters vascular morphology and behavior (37), it might be uncertain whether CKD is the primary cause of endothelial function. However, hypertension alone, although important and highly prevalent, has been suggested to not justify the tremendous cardiovascular burden in CKD (154). Nevertheless, future work that aims to target vascular function using different nutraceutical therapies should consider the many different pathophysiological phenotypes within CKD that may contribute to vascular outcomes.

Pharmaceutical Agents and Vascular Function

The standard care for therapy in CKD requires the use of drugs to attenuate disease progression in addition to alleviating the cardiometabolic risks associated with the disease (14). It has been hypothesized that some pharmaceuticals in which patients with CKD are taking to reduce blood pressure (i.e., ACE/ARB inhibitors) and clotting and/or alleviate diabetic complications (i.e., metformin) already exhibit a sufficient antioxidant response that improves vascular function (1). Thus any further improvements with concomitant use of nutraceuticals may be negligible toward improving vascular function in patients with CKD. However, it remains unclear if these beneficial effects could be due to decreased oxidative stress or reduced serum uric acid levels in CKD. Conversely, it is possible that some nutraceuticals may interfere with certain pharmacological agents taken by patients with CKD. For example, allopurinol, a commonly prescribed drug in CKD, interferes with pharmacological dietary nitrates in the form of beet root juice, by blocking its blood pressure-lowering effects in animals (101). In addition, coadministration of allopurinol with dietary nitrates significantly reduced right ventricular pressure and reduced left ventricular hypertrophy and vascular remodeling in mice with pulmonary arterial hypertension (9). Nevertheless, it has been suggested that there may be a synergistic effect when combining certain pharmaceuticals with nutraceuticals (30), thus resulting in an overall beneficial effect on vascular/cardiovascular function.

SUMMARY

CKD is a progressive disease characterized by an increased risk for CVD. Vascular dysfunction is an important mediator and "nontraditional" risk factor in the development of CVD within patients CKD and thus serves as an attractive target for many therapeutic interventions. Nutraceutical therapy has emerged as a plausible new therapeutic strategy to improve vascular function in patients with CKD. The present review, therefore, provides supporting evidence that the use of several recent and emerging nutraceuticals (i.e., polyphenols, dietary nitrates, and selective mitochondrial therapies) may be implicated toward improving vasculature function in patients with

CKD. It is clear throughout this review that human-based mechanistic preclinical and health-related clinical studies are lacking regarding whether nutraceuticals do indeed improve vascular function in patients with CKD. As such, a comprehensive, detailed, and fully integrated understanding of nutraceuticals and vasculature function is necessary in patients with CKD. Many opportunities exist for original mechanistic and therapeutic discoveries and investigations on select nutraceuticals and their impact on vascular outcomes in patients with CKD and these will remain exciting avenues of research in the future.

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AUTHOR CONTRIBUTIONS

N.T.K. prepared figures; N.T.K. drafted manuscript; N.T.K. edited and revised manuscript; N.T.K. approved final version of manuscript.

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