Vascular Effects of Exercise Training in CKD: Current Evidence and Pathophysiological Mechanisms

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Abstract

Cardiovascular disease remains the main cause of morbidity and mortality in patients with CKD, an observation that cannot be explained by the coexistence of traditional risk factors alone. Recently, other mechanisms, such as alterations in nitric oxide bioavailability, impaired endothelial repair mechanisms, inflammation, and oxidative stress (all characteristic in CKD), have gained much attention as mediators for the increased cardiovascular risk. Regular physical training is a valuable nonpharmacological intervention for primary and secondary prevention of cardiovascular disease. Likewise, the benefits of exercise training on exercise capacity and quality of life are increasingly recognized in patients with CKD. Furthermore, exercise training could also influence potential reversible mechanisms involved in atherosclerosis and arteriosclerosis. After discussing briefly the general concepts of vascular disease in CKD, this review provides an overview of the current evidence for the effects of exercise training at both clinical and preclinical levels. It concludes with some practical considerations on exercise training in this specific patient group.

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Introduction

The growing prevalence of CKD poses a major challenge to health care, mainly because of cardiovascular (CV) complications. The risk for CV morbidity and mortality increases with the progression of renal disease, which is evident from numerous epidemiologic observations (1,2). In ESRD, CV mortality rates are approximately 15 times higher compared with the general population (3). In moderate to severe CKD, CV death is more frequent than the progression to kidney failure and the need for RRT (4). Therefore, as reviewed by Sarnak (5), the presence of CKD is considered an independent CV risk factor and a coronary artery disease equivalent for all-cause mortality (6,7). Apart from traditional CV risk factors, overarching mechanisms acting on both intimal and medial layers of the vessel wall, such as inflammation, oxidative stress (OS), decreased nitric oxide (NO) bioavailability, and disturbances in mineral metabolism, add to this high CV burden in CKD (reviewed by Stenvinkel et al. [8]). The interplay between these mechanisms is complex, which partly explains the disappointing results of interventions directed at single traditional risk factors and favors a multifactorial approach for effective preventive strategies.

Exercise training (ET) is such an intervention, with well known effects on the heart and skeletal muscle as well as the vascular wall. Other than traditional risk factor modification, ET improves vascular health through increased NO bioavailability and generalized antioxidative and anti-inflammatory effects (9). As such, regular physical activity as well as formal ET are strongly recommended in both European (class I,

level of recommendation A) (6) and American (class IIa, level of recommendation A) (10) clinical practice guidelines for CV disease (CVD) prevention. Although they are general recommendations, it is clear that they also could be of value in the high-risk population of CKD. For additional reading on the epidemiology, etiology, prevention, and management of CV risk in CKD, which is beyond the scope of this review, the reader is referred to the recent comprehensive overview by Gansevoort et al. (11). Here, we first discuss briefly the general concepts of vascular disease in CKD. Next, we provide an overview of the current clinical evidence for the effects of ET as well as known effects on mediators of vascular disease in CKD. For the exercise intervention studies, we searched PubMed for full-text articles in English published until November 12, 2013. The search terms used were CKD and ET, and all articles that evaluated the discussed mediators of the vascular wall were included. We conclude with practical considerations.

Vascular Disease in CKD

Vascular disease in CKD involves both the intimal and medial layers of the vascular wall. Distinction between both histopathological entities is relevant, because each type has different clinical consequences (12).

Intimal Layer: Endothelial Dysfunction and Atherosclerosis

The high prevalence of coronary and noncoronary atherosclerotic lesions as well as the high incidence of acute coronary syndromes in patients with CKD are

well documented (11). It is generally accepted that the structural changes of atherosclerosis, possibly with (sub-) occlusive lesions, are preceded by a functional and yet reversible impairment of endothelial function (13). Indeed, clinical data show that endothelial dysfunction occurs early in the course of renal failure and predisposes to accelerated atherosclerosis in patients with CKD, which is clinically translated in poor CV outcome (14).

Medial Layer: Arteriosclerosis and Arterial Stiffness

The damage of the medial layer that typically involves calcification and results in arteriosclerosis (Monckeberg sclerosis) is a well known entity in CKD. Vascular calcification alters arterial elasticity and induces arterial stiffness. Aortic stiffness is strongly and independently associated with increased CV mortality in patients with CKD (15). The carotid–femoral pulse wave velocity (CF-PWV), a noninvasive measure of regional large-artery stiffness, increases early in the development of CKD and shows progression as renal impairment evolves. Clinical manifestations of arterial stiffness include systolic hypertension, increased myocardial afterload with left ventricular hypertrophy, decreased subendocardial perfusion, diastolic dysfunction, and eventually, heart failure. Other than an increase of CF-PWV, the central augmentation index (AIx), a composite marker of systemic arterial stiffness and left ventricular systolic loading, will rise with progressive decline in arterial elasticity. Similar to CF-PWV, the AIx has been shown to predict all-cause and CV mortality in ESRD patients (15).

Interplay between Endothelial Dysfunction and Arterial Stiffness

Although affecting two different layers of the vascular wall, endothelial dysfunction and arterial stiffness share common pathophysiological mechanisms. Low-grade inflammation, uremic toxins, mineral metabolism disturbances (i.e., hyperphosphatemia), and OS cause permanent endothelial insults superimposed on the detrimental effects of traditional risk factors (8). At the level of the medial layer, growing insight into the nature of the calcification process reveals the involvement of processes, such as inflammation and OS, in addition to disturbances of mineral metabolism (12). Moreover, there is reciprocity between endothelial dysfunction and arterial stiffness. By exposing the endothelial cells to increased biomechanical stress, arterial stiffness can aggravate endothelial dysfunction, whereas in endothelial dysfunction, impaired bioavailability of the relaxing factor NO adds to arterial stiffness (12,16).

In this work, we will provide more mechanistic insight into the vascular adaptations that are characteristic in CKD, with a special emphasis on the potential beneficial effects of ET, on the basis of clinical and preclinical evidence in predialysis CKD and ESRD requiring dialysis. Table 1 summarizes the exercise intervention studies in both CKD groups.

ET in CKD: Current Clinical Evidence
Exercise Capacity and Mortality

Data from numerous observational and longitudinal studies unequivocally confirm that regular physical activity or formal ET reduces CV risk in primary and secondary prevention (17,18). Despite these clear benefits, the implementation of ET in patients with CKD is limited, and physical performance remains poor. As recently shown, low levels of physical activity are strongly associated with all-cause mortality in both predialysis and ESRD patients (18–20). In line with this finding, peak oxygen consumption (VO$_2$peak), a parameter for exercise capacity (physical fitness), seems to be a very strong predictor of survival in ESRD (21). Interestingly, both VO$_2$peak and activity level are closely interrelated. In the general population, several studies have shown that physical fitness is more strongly correlated with better outcomes and health benefits than physical activity (22,23). Whether genetics may partly explain the more favorable effect of physical fitness compared with physical activity in terms of CV prevention remains to be elucidated. Although a prospectively randomized controlled trial (RCT) on the effect of ET on CV outcome in CKD patients is currently lacking, ET has proven to ameliorate physical performance, VO$_2$peak, and several nontraditional mediators of vascular disease in CKD (24).

Arterial Stiffness

Considering its strong prognostic relevance, improving arterial stiffness in CKD patients by ET could beneficially impact their CV outcome. Blacher et al. (25) showed that each 1-m/s increase in PWV increases all-cause mortality by 39% in ESRD. In a prospective study of 150 dialysis patients, the absent decrease in PWV in response to effective BP lowering emerged as a predictor for mortality in this patient population (26).

In patients with renal disease, four studies with a rather small sample size (Table 1) examined the effect of aerobic exercise on arterial stiffness. In hemodialysis patients, an uncontrolled study by Mustata et al. (27) showed that a two times per week outpatient aerobic exercise program for 3 months significantly improved the central AIx, which returned to baseline levels within 1 month after detraining. The beneficial effect on CF-PWV of an intradialytic bicycling program for 3 months was shown in a randomized crossover study, allowing comparison with usual care (28). The sole RCT so far in hemodialysis patients, however, failed to confirm these beneficial effects on arterial stiffness after a 6-month intradialytic or home-based aerobic training program compared with usual care. As suggested by Koh et al. (29), these results could be attributed, in part, to the relatively low exercise intensity prescribed compared with the aforementioned studies. This finding implies that exercise volume (intensity, duration, and frequency) is an important determinant in the training-induced benefits on arterial stiffness.

Studies in predialysis CKD patients are limited to one RCT that reported that long-term (12 months) aerobic ET of moderate intensity, combining supervised and home-based training, significantly reduces AIx compared with usual care (30).

Endothelial Dysfunction

Despite the extensive evidence that ET improves endothelial function in young prehypertensive patients and patients with established CVD (31), clinical studies in the setting of CKD are still lacking. Only one experimental study in rats undergoing 5/6 nephrectomy showed that

Table 1.   Exercise intervention studies in hemodialysis patients and predialysis patients

Study	Design	No. of Patients (Mean Age [yr]± SD or Median)	Type of Training	Intensity	Sessions Duration (min)	Frequency (times/wk)	Duration (mo)	Outcome Within Group	Outcome Between Group	%
Hemodialysis Arterial stiffness										
Mustata et al. (27)	Uncontrolled	11 EX (55±4)	Aerobic	60%–80% heart rate peak	60	2	3	AIx 17±3 to 12.2±3[a]	N/A	−28
Toussaint et al. (28)	Randomized crossover Bias risk: B	Group A n=10 (median age=70) Group B n=9 (median age=67)[c]	ID cycling	No target	30	3	3 EX versus 3 non-EX	PWV (m/s) Group A: baseline versus EX 10.4±3.1 versus 8.7±2.7 (NS) Group B: EX versus non-EX 9.33±2.3 versus 10.5±3.6 (NS)	9.04±0.59 versus 10.16±0.74[b]	−11
Koh et al. (29)	RCT	15 ID EX (52±11)	ID EX: ID cycling	RPE=12–13	120	3	6	ID EX: 9.1±2.8 to 8.8±2.9 (P=NR)	NS	
	Bias risk: A	15 HB EX (52±14)	HB EX: interdialytic walking	RPE=12–13	45	3		HB EX: 9.7±3.2 to 9.5±3.4 (P=NR)		

Table 1. (Continued)

Study	Design	No. of Patients (Mean Age [yr]± SD or Median)	Type of Training	Intensity	Sessions Duration (min)	Frequency (times/wk)	Duration (mo)	Outcome Within Group	Outcome Between Group	%
Oxidative stress Wilund et al. (56)	RCT	16 untrained CON (51±14) 8 EX (61±3) 9 CON (59±5)	CON: no specific intervention ID cycling	RPE=12–14	45	3	4	CON:8.7±2.5 to 9.2±3.5 (P=NR) EX: 9.5±1.55 to 5.9±1.05[a] CON: 7.2±0.7 to 6.9±1.31 (NS) EX: 6.2±0.22 to 6.0±0.67 (NS) CON:5.2±0.78 to 4.9±0.69 (NS) EX: 2.2±0.71 to 1.8±0.6 (NS) CON: 2.9±0.93 to 2.5±0.44 (NS)	TBARS (μmol/L) [a] CRP (mg/L) NS IL-6 (pg/ml) NS	−38
Inflammation Afshar et al. (64)	RCT	14 EX (51±21) 14 CON (53±19)	ID cycling	RPE=12–14	10–30	3	2	EX: 5.5±2.5 to 0.9±0.7[b] CON: 4.05±3.97 to 4.10±3.90 (NS)	CRP (mg/L) NR	−83
Cheema et al. (66)	RCT	24 EX (60±15) 25 CON (65±13)	ID resistance	RPE=15–17		3	3	EX: −0.08 ±0.37 (P=NR) CON: +0.24 ±0.37 (P=NR)	Log CRP (effect size) [a]	N/A

Table 1. (Continued)

Study	Design	No. of Patients (Mean Age [yr]± SD or Median)	Type of Training	Intensity	Sessions Duration (min)	Frequency (times/wk)	Duration (mo)	Outcome Within Group	Outcome Between Group	%
Kopple et al. (65)	RCT Bias risk: C	10 END EX (46±4) 15 STR EX (46±3) 12 COM EX (43±4) 14 CON (41±3) 20 healthy CON (42±3)	END EX: ID cycling STR EX: NDT resistance COM EX: combined END/STR	50% VO$_2$peak 80% 5 RM	40	3	4.5	CRP (mg/L) END EX: 4.5±1.5 to 2.5±0.6 (NS) STR EX: 3.5±0.8 to 4.2±1.3 (NS) COM EX: 4.6±1.4 to 5.8±2.1 (NS) CON: 2.1±0.4 to 2.8±0.8 (NS) Healthy CON: 2.5±0.7 to 3.6±1.4 (NS) IL-6 (pg/ml) END EX: 6.6±1.7 to 3.9±0.7 (NS) STR EX: 5.7±1.3 to 4.7±1.2 (NS) COM EX: 4.5±0.9 to 4.3±0.5 (NS) CON: 3.8±0.8 to 3.6±0.8 (NS)	CRP (mg/L) NS IL-6 (pg/ml) NS	

Table 1. (Continued)

Study	Design	No. of Patients (Mean Age [yr]± SD or Median)	Type of Training	Intensity	Sessions Duration (min)	Frequency (times/wk)	Duration (mo)	Outcome Within Group	Outcome Between Group	%
EPC										
Manfredini et al. (50)	Nonrandomized control group	14 EX (62±9) 8 CON (66±15)	Walking two times per day	50% maximum treadmill speed	10	7	6	e-CFU (colonies/ml)[d] EX: 0.14±0.36 to 1.93±3.52[a] CON: 0.75±1.75 to 0.0±0.0 (NS)	NS	+1278
								EPC (cells/µl) EX: 0.05±0.10 to 0.06±0.21 (NS) CON: 0.0±0.0 to 0.04±0.08 (NS)	NS	
Predialysis **Arterial stiffness**										
Mustata et al. (30) *Stages 3–4*	RCT	10 EX (median age=64) 10 CON (median age=73)	Aerobic training	40%–60% of VO$_2$peak; RPE=12–15	5–60	2	12	AIx (%)[b] EX: 29 to 27.5 (NR) CON: 28.5 to 28 (NR)		−11
Oxidative stress										
Pechter et al. (55) *Stages 2–3*	Nonrandomized, self-selecting control group	17 EX (52; range=31–72) 9 CON (48; range=35–65)	Vertical aerobic aquatic exercise		30	2	3	LPO (ng/ml) EX: 1.51±0.23 to 0.99±0.11[a] CON: 0.99±0.06 to 1.35±0.15 (NS)	NR	−34
								Reduced glutathione (µM) EX: 751.2±46.8 to 864.2 ±44.5[a] CON: 869.1±44.3 to 607.9 ±123.6 (NS)	NR	+15

Table 1. (Continued)

Study	Design	No. of Patients (Mean Age [yr]± SD or Median)	Type of Training	Intensity	Sessions Duration (min)	Frequency (times/wk)	Duration (mo)	Outcome Within Group	Outcome Between Group	%
Inflammation										
Leehey et al. (63) Stages 2–4	RCT Bias risk: B	7 EX 4 CON (all subjects: mean age=66)	Aerobic training	Guided by VO2peak	30–40	3	6	CRP (mg/L) EX: 5.5±7.2 to 8.9±9.2 (NS) CON: 17±24 to 11.7±7.1 (NS)	NS	
Castaneda et al. (61) Stages 3–4	RCT Bias risk: A	14 EX (65±9) 12 CON (64±12)	Resistance training	80% 1 RM	45	3	3	EX: 7.8 to 6.1 (NR) CON: 6.2 to 7.7 (NR)	a	−21
								IL-6 (pg/ml) EX: 11.3 to 6.9 CON: 7.7 to 10.0	a	−39
Headly et al. (62) Stages 2–4	RCT	10 EX (58±12) 11 CON (53±11)	Combined aerobic and resistance	50%–60% VO2peak	45	3	12	EX: 4.93±1.4 to 4.40±2.01 (NS) CON: 5.05±2.1 to 5.42±1.84 (NS)	NS	
								hs-CRP (mg/L) EX: 1.74±1.61 to 1.58±1.85 (NS) CON: 3.35±2.82 to 3.17±3.69 (NS)	NS	

Outcome is presented as within-group (pre- to postintervention unless stated otherwise) or between-group differences (EX versus CON, P value for interaction). Significant changes are presented as percentage changes versus baseline or control. For RCTs, estimations of total bias risk are presented as published in the meta-analysis by the Cochrane Collaboration (34): A, low risk; B, moderate/unclear risk; C, high risk. AIx, augmentation index; EX, exercise; N/A, not applicable; PWV, pulse wave velocity; ID, intradialytic; NS, not significant; RCT, randomized controlled trial; RPE, rating of perceived exertion; NR, not reported; HB, home based; CON, control; TBARS, thiobarbituric acid reactive substances; CRP, C-reactive protein; END, endurance; VO2peak, peak oxygen consumption; STR, strength; NDT, nondialysis time; RM, repetition maximum; COM, combined; EPC, endothelial progenitor cell; e-CFU, endothelial colony-forming unit; LPO, lipid peroxidation; hs-CRP, high-sensitivity CRP.
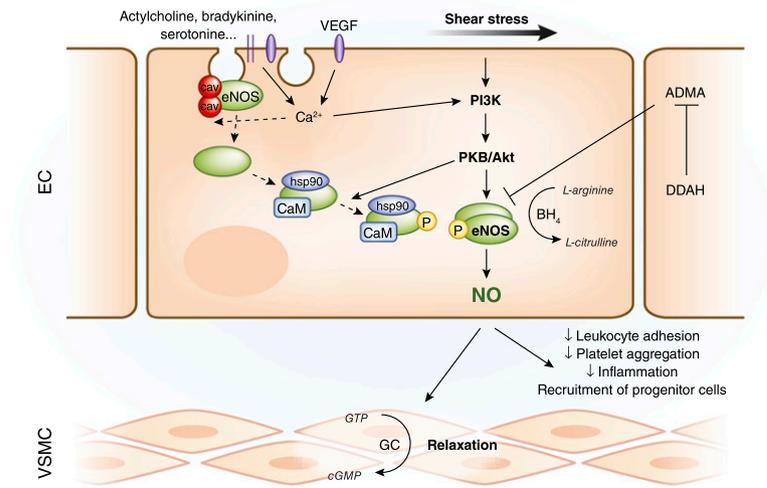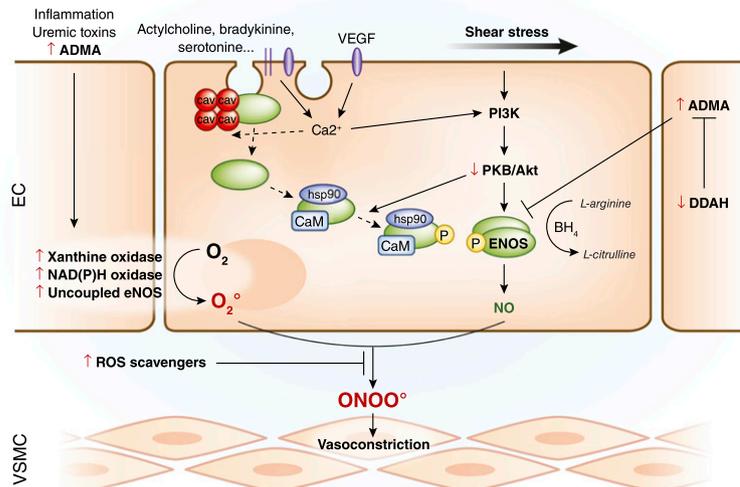[a] $P<0.05$.
[b] $P<0.01$.
[c] Group A: exercise for 3 months, 1-month washout, and then no exercise for 3 months. Group B: no exercise for 3 months, 1-month washout, and then exercise for 3 months.
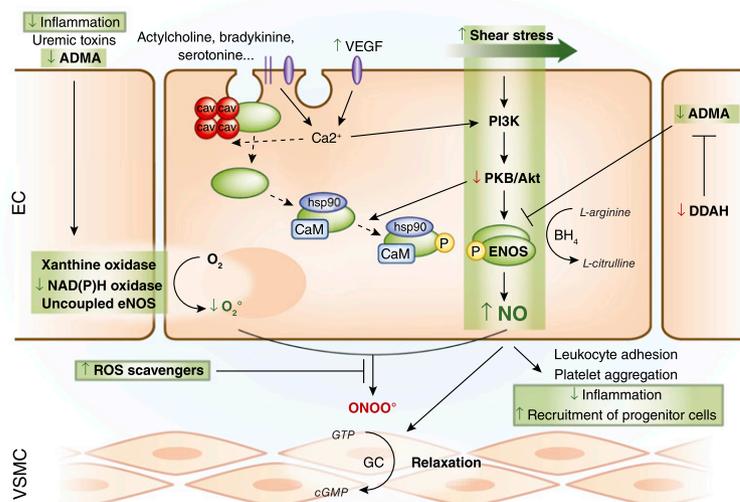[d] $P<0.001$.

A NO bioavailability in physiological conditions

B NO bioavailability in CKD

C Training-induced increase in NO bioavailability in CKD: plausible mechanisms

regular exercise for 4 weeks improved endothelium-dependent relaxation of the thoracic aorta (32).

BP

ET effectively lowers systolic BP (SBP) and diastolic BP (DBP) in (pre-)hypertensive subjects (33). In patients with CKD, the benefit of ET on both DBP and SBP was unequivocally shown in a meta-analysis of the Cochrane Collaboration that included 11 RCTs and 419 participants (34); 9 of 11 RCTs were conducted in hemodialysis patients (4 RCTs used aerobic training, and 5 RCTs used combined aerobic and resistance training). The two remaining RCTs studied the effect of aerobic exercise in patients with CKD stages 2–4 and kidney transplant recipients. Overall, ET resulted in a mean decrease in DBP of 2.32 mmHg (95% confidence interval, 0.59 to 4.5, $P<0.01$) and a mean decrease in SBP of 6.08 mmHg (95% confidence interval, 2.15 to 10.12, $P=0.002$) compared with the control group. Subanalyses revealed that long-term combined aerobic/resistance training and high-intensity aerobic training have a superior effect on lowering BP.

ET in CKD: Effects on Key Mechanisms in Vascular Disease

NO Bioavailability

Decreased NO bioavailability is one of the most important factors involved in endothelial dysfunction. NO is a critical endothelium-derived vasoactive factor with vasodilatory and antiatherosclerotic properties produced by endothelial NO synthase (eNOS) (Figure 1A). Other than its role as a relaxing factor of the vascular smooth muscle cells, NO inhibits leukocyte adhesion, platelet aggregation, and inflammation and acts as an important liberator of stem and progenitor cells in the vascular zone of the bone marrow (35). eNOS is predominantly present in intracytoplasmatic caveolae, flask-shaped invaginations of the luminal endothelial plasma membrane (36). Herein, the protein caveolin-1 is bound to calmodulin, thereby inhibiting eNOS activity in basal conditions. Increase in intracellular calcium in response to agonist stimulation (e.g., acetylcholine and vascular endothelial growth factor) leads to the disruption of the caveolin–eNOS interaction by calcium-bound calmodulin. Heat shock protein 90 consecutively binds eNOS and favors the recruitment of protein kinase B (PKB or Akt), which in turn, phosphorylates eNOS. However, the effect of physiologic shear stress, which is the most potent stimulus for continuous eNOS activity, is a calcium independent process driven by shear mechano-sensing, a joint action of multiple mechanotransducers. Shear stress on the endothelial cell results in activation of phosphatidylinositol 3-kinase, which eventually leads to an upregulation of eNOS at the transcriptional level as well as calcium-independent phosphorylation at the post-transcriptional level (37).

In CKD, different stressors, such as low-grade inflammation, uremic toxins, hyperphosphatemia, and OS, cause permanent endothelial insults superimposed on the detrimental effects of traditional risk factors. At the molecular level, several mechanisms contribute to a decrease in NO bioavailability in this particular patient population (Figure 1B). An increased caveolin-1 expression and decreased Akt expression in vascular tissue were found in an animal experimental model of chronic renal failure (38). In patients, a growing body of evidence points to retention products such as asymmetric dimethylarginine (ADMA), which has prognostic value in predicting CV events and mortality (39,40). ADMA is a competitive inhibitor of eNOS. Other than its direct inhibitory effect on NO production, ADMA reduces NO bioavailability through several mechanisms, including

Figure 1. | Training-induced increase in NO bioavailability in CKD. (A) NO is synthesized from L-arginine by eNOS after agonist occupation (merely calcium-dependent) or shear stress (merely calcium-independent). Other than its role as a relaxing factor, NO inhibits leukocyte adhesion, platelet aggregation, and inflammation and acts as an important liberator of stem and progenitor cells in the vascular zone of the bone marrow (35). eNOS is predominantly present in caveolae, which are flask-shape invaginations of the luminal endothelial plasma membrane (36). In basal conditions, eNOS is maintained in an inactive state in caveolae by interaction with caveolins. Increase in intracellular calcium in response to agonist stimulation leads to the disruption of the caveolin–eNOS interaction by calcium-bound calmodulin; hsp90 consecutively binds eNOS and favors the recruitment of PKB/Akt, leading to eNOS phosphorylation. Activation of Akt results from the activation of signaling pathways, including the stimulation of PI3K in response to a variety of agonists and shear stress (mechanotransducers), the latter being the most potent stimulus for continuous eNOS activity (37). (B) NO bioavailability in CKD is reduced because of a number of mechanisms. First, eNOS activity can be reduced as a result of increased inhibition (increased ADMA levels) and decreased activation (less PKB/Akt expression and increase in caveolin-1 expression) (38–41). Second, there is an increase in ROS-mediated breakdown of NO as a result of increased oxidative stress. The latter results from increased activation of ROS-generating enzymes, such as xanthine oxidase, NAD(P)H-oxidase, and eNOS uncoupling, for example, as a result of BH4 deficiency or increased ADMA levels as well as a lack of efficient antioxidative defense mechanisms. After interaction with NO, superoxide anion forms highly toxic nitrogen derivatives, such as peroxynitrite (which is cytotoxic) and increases platelet aggregation and vasoconstriction. (C) Green-shaded areas represent evidence from animal and human studies in cardiovascular disease. When framed, evidence is available for patients in CKD. As we know from studies in patients with stable coronary artery disease, most ET effects on the vascular endothelium are mediated by increases in shear stress, which results in higher NO production. An increase in eNOS activity occurs within seconds and implicates cytosolic calcium and eNOS phosphorylation. Later increases in transcription and eNOS mRNA stability allow maintenance of an increased NO production when the stimulus is prolonged. In addition to eNOS activation, ET results in more efficient antioxidative defense mechanisms (e.g., by reducing ROS production [reduction in NAD(P)H expression, less eNOS uncoupling, etc.] and increasing the expression of antioxidative enzymes and ROS scavengers [e.g., glutathione]) (9,55,56). As such, ROS-mediated breakdown of NO is prevented. A decrease in ADMA levels could contribute to both an increase in eNOS activity and prevention of eNOS uncoupling (44). ADMA, asymmetric dimethylarginine; BH4, (6R)-5,6,7,8-tetrahydro-L-biopterin; CaM, calmodulin; cav, caveolin; cGMP, cyclic guanosine monophosphate; DDAH, dimethylarginine dimethylaminohydrolase; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; GC, guanylyl cyclase; GTP, guanosine triphosphate; hsp90, heat shock protein 90; NO, nitric oxide; O2˚, superoxide anion; ONOO˚, peroxynitrite; P, phosphorus; PI3K, phosphatidylinositol 3-kinase; PKB/Akt, protein kinase B; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells.

activation of NAD(P)H oxidase, eNOS uncoupling, and subsequent production of reactive oxygen species (ROS). Elevated ADMA levels in CKD result mainly from decreased activity of the enzyme responsible for its degradation, dimethylarginine dimethylaminohydrolase (reviewed by Schwedhelm *et al.* [41]).

ET. An overview of potential relevant mechanisms in increasing NO bioavailability by exercise interventions and possible consequences is given in Figure 1C. Of note, most data derive from studies in CVD, and the CKD population, characterized by its specific internal milieu, has not been formally addressed yet. As we know from studies in patients with stable coronary artery disease (42), chronic intermittent increases in shear stress affect several signaling pathways through direct (glycocalyx deformation) and vascular endothelial growth factor receptor 2-mediated mechanisms, resulting in an upregulation and increase in eNOS activity (reviewed by Gielen *et al.* [9]). Second, ET-associated reduction in OS, which has been confirmed in CKD patients, prevents ROS-mediated breakdown of NO (see OS below). Third, data from animal experiments suggest that ET can increase levels of the essential cofactor (6*R*)-5,6,7,8-tetrahydro-L-biopterin (BH4) (43), thereby preventing eNOS uncoupling and production of superoxide. In addition, ET in patients at CV risk has been shown to result in a significant decrease in circulating ADMA levels after 3 months (44), thus contributing to both an increase in eNOS activity and prevention of eNOS uncoupling.

Endothelial Repair

Sustained dysfunction of endothelial cells can eventually lead to their apoptosis with subsequent structural disintegration of the endothelial cell layer. Next, leukocyte and thrombocyte adhesion and activation cause microinflammation of the endothelial wall, which initiates a vicious circle, thereby maintaining and accelerating vessel wall damage (13). As such, insufficient endothelial repair mechanisms further contribute to endothelial dysfunction. With the identification of bone marrow-derived endothelial progenitor cells (EPCs) 15 years ago, the paradigm that endothelial repair solely depends on the limited migration and proliferation of local endothelial cells was abandoned (45). EPCs are mobilized on stimulation by growth factors and chemokines triggered by vascular injury or ischemia. In the circulation, EPCs follow chemokine gradients homing to sites of endothelial injury, where they proliferate, differentiate, and integrate into the endothelial layer or exert a paracrine function by producing angiogenic growth factors. As a consequence, a decline in the number or function of circulating EPCs is considered to be a significant contributor to the onset and progression of vascular disease in many conditions. Indeed, low EPC number and/or impaired EPC function are predictive for CVD in individuals with normal renal function and patients with ESRD (46). Of note, other than the technical challenges inherent to EPC quantification (additional information in ref. 47), considerable heterogeneity is present in EPC nomenclature, which calls for caution in the interpretation and comparison of results. In a broad sense, the term EPC covers two different cell types: circulating cells characterized by flow cytometric analysis as well as plated PBMCs giving rise to EPC colonies (for example,

endothelial cell colony-forming unit [e-CFU]) (48). Moreover, the unresolved issue of proper and unambiguous phenotypical characterization of circulating EPCs and the use of different membrane markers further impede the comparison of flow cytometrical results.

ET. The recruitment of EPCs after exercise has been linked to improved endothelial function in various populations (reviewed in ref. 49). In ESRD, one intervention study examined the effects of a moderate-intensity aerobic training scheme for 6 months on the number of EPCs. Despite the high dropout rate in the study and, consequently, small study numbers (14 exercise patients and 8 controls), a significant rise in e-CFUs was found in the exercise group. This rise in e-CFU seemed to be directly and significantly correlated to the patient-reported training load (*i.e.*, total training time and speed) (50). Although no changes were found in flow cytometrically enumerated EPCs, levels of these cells have been shown to be significantly associated with physical performance, which was determined by the 6-minute walking distance test (51). Until now, no studies have addressed the mobilization of EPCs after ET in patients with moderate to severe (stages 3 and 4) CKD. For CKD stages 1 and 2, which are defined as the existence of kidney damage for at least 3 months with normal or mild decreased eGFR, there are also no formal studies. However, we can expect a certain overlap with studies conducted in particular patient groups, such as patients with diabetes, hypertension, and coronary artery disease, where beneficial effects of ET on EPC number and functionality are supported with evidence (49).

OS

OS, the result from either an excess in production of free radicals or insufficient antioxidative defense mechanisms, has been pathophysiologically implicated in the processes of atherosclerosis as well as arteriosclerosis in CKD (52). OS increases with declining renal function, and several mechanisms underlying this finding have been described. Levels of the antioxidants serum gluthatione and plasma vitamin E are reduced, and there is an increased generation of ROS and reactive nitrogen species (52). Moreover, present inflammation acts as a trigger and amplifier of OS. Various uremic toxins, including homocystein, advanced glycation end products, p-cresyl sulfate, and indoxyl sulfate, directly contribute to OS through their pro-oxidant and proinflammatory actions (53).

Another mechanism that leads to excessive generation of ROS in CKD is eNOS uncoupling. The normal function of eNOS requires dimerization of the enzyme, the presence of the substrate L-arginine, and the essential cofactor BH4, one of the most potent naturally occurring reducing agents. Under a number of pathologic conditions, such as BH4 deficiency, shortage of L-arginine, or elevated ADMA levels, the enzymatic reduction of molecular oxygen by eNOS is no longer coupled to L-arginine oxidation, resulting in the production of superoxide rather than NO (eNOS uncoupling) (37). ROS scavenges NO, which reduces its bioavailability. After interaction with NO, superoxide anion forms highly active toxic nitrogen derivatives, such as peroxynitrite, which are cytotoxic for endothelial cells. Moreover, it increases platelet aggregation and induces vasoconstriction.

ET. In animal and human studies, the expression of various antioxidative enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, has been shown to increase after ET. In addition, ET reduces protein expression and activity of ROS-generating enzymes, such as NAD(P)H oxidase (9) (Figure 1C).

Results of animal experiments (5/6-nephrectomized Wistar rats) are suggestive of reduced OS at the level of the kidney after a 2-month training program with running wheels (54), but to date, only two small studies in CKD patients evaluated the effect of ET (aerobic training) on OS and are supportive of a beneficial effect. In 17 patients with mild-to-moderate CKD, aerobic water-based exercise significantly reduced lipid peroxidation products (malondialdehyde and 4-hydroxyalkenals) and increased levels of the antioxidant glutathione compared with a sedentary control group (55). Similarly, intradialytic aerobic training for 4 months reduced thiobarbituric acid reactive substance, a product of lipid peroxidation, by 38% in hemodialysis patients compared with usual care (56). No data currently exist on the effects of resistance ET or combined aerobic/resistance regimens.

Systemic Inflammation

Atherosclerosis is a chronic inflammatory disease of the vessel wall that results from the interactions between modified lipoproteins and various components of the immune system, including monocyte-derived macrophages, T lymphocytes, and a variety of cytokines secreted by immune cells and resident cells (13). Several proinflammatory cytokines, including serum IL-6 and the acute-phase reactant C-reactive protein (CRP), have emerged as particularly strong independent risk factors for atherosclerotic disease and CV mortality in not only the general population but especially, patients with CKD (57). Recent intriguing insights in the different subpopulations of monocytes, the protagonists of inflammation, shed more light on their key role in increasing CV risk in CKD. Circumstantial and epidemiologic data suggest a substantial role of intermediate ($CD14^{++}CD16^{+}$) monocytes in the development of atherosclerosis in this particular patient group (13,58).

Of note, the low-grade inflammation in CKD, which is enhanced by OS, also takes part in the process of arteriosclerosis. For example, the bone morphogenetic proteins (BMPs) BMP-2 and BMP-4, which are key factors in the initiation of arterial calcification, are released by endothelial cells and adventitial microvasculature in response to inflammatory cytokines or ROS (59).

ET. Whereas the general anti-inflammatory effects of ET are well documented (additional information in ref. 60), there are limited data available in CKD patients, and evidence is conflicting, mainly because of a lack of large-scale RCTs. Indeed, although most studies on the effects of ET on inflammatory parameters are RCTs, inflammation was frequently analyzed as a secondary outcome, which made them possibly underpowered for this end point. In patients with moderate CKD, the proinflammatory state, as evidenced by high levels of CRP and IL-6, can be improved by a resistance training program of 12 weeks (61). However, in another study involving a comparable population of moderate CKD, a program of 12 months of supervised combined aerobic and resistance training failed

to influence levels of IL-6 and CRP (62). Small sample size (10 exercise patients versus 11 controls) could have underpowered this study. Indeed, in the exercise group, a trend toward a decrease of both IL-6 and high-sensitivity CRP was seen, but it did not reach statistical significance (Table 1). In a small RCT in obese patients with CKD stages 2–4, no changes in CRP were seen after 6 months of aerobic training with progressive intensity versus control (63). Again, sample size was very small (seven exercise patients versus four controls). Also, in the dialysis population, data are inconsistent. After aerobic ET, some RCTs are clearly supportive of a favorable effect on circulating markers of inflammation (64), whereas others are not (28,56,65). In one of the largest RCTs (49 patients), a 12-week program of progressive intradialytic resistance training significantly reduced CRP levels compared with the levels in a sedentary control group (66). It is clear that more well designed RCTs are warranted to determine the optimal exercise type, intensity, and duration to lower inflammation.

Quantitative and qualitative changes in monocyte subsets could contribute, at least in part, to the global anti-inflammatory effect of ET. ET is known to selectively deplete circulating $CD16^{+}$ monocytes, inclusive of the ($CD14^{++}CD16^{+}$) intermediate monocytes, possibly through exercise-induced transient spikes in endogenous glucocorticoids (67). Moreover, physical activity seems to be associated with reduced cell surface expression of Toll-like receptor 4 and a subsequent blunted inflammatory response to LPS (68). In conclusion, ET results in a favorable shift of monocytes in terms of both numbers and expression profile.

ET in CKD: Practical Considerations

The most recent Kidney Disease Outcomes Quality Initiative clinical practice guidelines for dialysis patients dedicate an entire paragraph to the importance of improving physical activity (69). It is stated that "all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" (level of recommendation B) (69). Patients should exercise at a moderate intensity for 30 minutes on most, if not all, days per week, and attention has to be paid to regular follow-up. Patients who are not currently physically active should start at very low-intensity levels and durations and gradually progress to this recommended level.

Specific exercise guidelines for the predialysis CKD population were not available for many years, and physicians were referred to the recommendations for adults with chronic conditions published by the American College of Sports Medicine and the American Heart Association in 2007 (70). Using these recommendations, CKD patients for whom exercise is not contraindicated should be instructed to start a routine of physical activity (aiming for 30 minutes at least 5 days a week) that is appropriate to their individual level of fitness and safe for their clinical condition. This regimen is now incorporated in the section on prevention of CKD progression (level of recommendation D) in the latest Kidney Disease Improving Global Outcomes guidelines (2013).

Conclusion and Future Directions

ET increases exercise capacity and physical function in patients with kidney disease, and both are predictive

factors for mortality in this population. Vascular disease is a major contributor to the CV burden of patients with CKD. Over the past decades, evidence on the pathophysiology of vascular disease in CKD and the possible vasculoprotective effects of ET in the context of CKD has been accumulated. Although there has been a paucity of well designed large RCTs in CKD investigating specifically the vascular effects of ET, clinical evidence is clearly in favor of a beneficial effect. Accordingly, patient counseling to emphasize the importance of regular physical activity has been incorporated in clinical practice guidelines.

Many studies investigating the physiology of vascular adaptations to ET are conducted in patients with established CVD and need formal confirmation in the particular context of CKD. Furthermore, assessing whether changes in the mediators of vascular disease translate into improved vascular function and even better outcomes is important before implementation on a large scale can be expected. Hence, long-term follow-up studies have to be undertaken.

These preliminary data have set the stage to test and formally establish from which type of ET and at what intensity and dose patients derive the largest benefit in well designed RCTs with sufficient power.

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