Benefits of Exercise in Chronic Kidney Disease Progression

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Chronic Kidney Disease (CKD) is a progressive condition characterised by declining estimated glomerular filtration rate (eGFR) and associated, particularly in advanced stages, with increased morbidity and cardiovascular mortality. Current treatment options for delaying disease progression are limited to a small number of pharmacological agents. Considering that rates of kidney function decline are greater in patients with lower levels of habitual physical activity, there is interest in the potential benefits of structured exercise training in delaying CKD progression.

Keywords: aerobic ; Chronic Kidney Disease ; disease progression ; eGFR ; exercise ; kidney function

1. Introduction

Chronic Kidney Disease (CKD) is a progressive condition characterised by variable, but usually inevitable, annual rates of estimated glomerular filtration rate (eGFR) decline [1]. Even before progressing to end-stage kidney disease (ESKD), CKD is associated with increased mortality, particularly cardiovascular death [2]. Furthermore, CKD is an independent risk factor for cardiovascular disease with an increased risk of death, cardiovascular events and hospitalisation as eGFR falls [3]. Current treatment options for delaying the progression of CKD are limited to a small handful of therapeutic options, namely renin-angiotensin-aldosterone (RAS) system inhibitors, sodium bicarbonate supplementation and sodium-glucose transporter 2 (SGLT-2) inhibitors [4][5]. In the hunt for additional strategies, exercise training has been considered a possible therapy for delaying disease progression.

Despite evidence of exercise-induced acute kidney injury (AKI) in endurance athletes and increased proteinuria post-exercise, concerns that exercise may have a detrimental effect on kidney function have been allayed by a wealth of studies showing exercise training to be safe [6][7][8][9]. Indeed, structured exercise training has been shown to have multiple beneficial effects in the non-dialysis-dependent CKD (ND-CKD) population, including improved aerobic capacity [10][11][12][13], physical function [9][14][15], muscle strength [14][15][16] and health-related quality of life (HRQoL) [9][17]. Increased habitual physical activity is associated with better survival in both ESKD [18] and ND-CKD patients [19][20] (though there is a possible influence of selection bias and other factors not adjusted for in these observational studies).

2. Exercise Training to Delay CKD Progression

Exercise training in CKD patients produces physiological adaptations that produce improved cardiorespiratory fitness and muscle strength. It is reasonable to consider whether similar training may induce adaptations in the kidney.

Whilst the precise mechanisms have not been elucidated, the stimulants for exercise-induced physiological adaptations occur primarily due to muscle stretching. Muscle activity results in changes including intra-muscular energy consumption, intracellular pH and Ca^{2+} concentration, as well as the generation of mechanical forces by muscle contraction [21]. These stimulants have all been linked to changes in protein and enzyme transcription, which result in metabolic, hormonal and vascular changes, which then produce beneficial adaptations to exercise training. There are also stimulants that occur outside of the contracting muscles, including increased shear stress driven by increased cardiac output and blood flow and altered sympathetic nervous activity [22]. Clearly, physical stretching is not relevant to kidney tissue. Furthermore, during exercise, renal blood flow diminishes rather than increases. Hence, mechanisms specific to muscles (related to mechanical stretching and increased shear stress) are not replicated in the kidney. However, whilst these stimulants derive from active muscle tissue, the downstream effectors are not necessarily limited to muscles, and some are of relevance to renal pathophysiology. For example, skeletal muscle capillary growth is stimulated by mechanical influences, such as shear stress induced by increased blood flow, and stretching of the muscle tissue, with VEGF mediating the effect [23][24]. VEGF may have systemic and beneficial effects on maintaining the renal vasculature, particularly the glomerular and tubular capillaries, which are so relevant to the pathogenesis of CKD progression. There are a number of lines of

evidence to suggest that the physiological changes that occur during exercise not only occur in the active skeletal muscle but also take place elsewhere in the body. Examples include an improvement in endothelial-dependent dilation in the brachial artery as a result of leg cycling training [25]. Distal vascular changes have also been demonstrated in studies where there is no increased cardiac load: in a four-week passive leg movement programme, there was an increased capillary density and VEGF concentration in the muscle of the untrained leg [26].

Another key adaptation to exercise training is mitochondrial biogenesis [27]. This is an important development, in response to Ca^{2+} cycling and ROS production etc., for improving the energy supply to active muscle. It would also be a useful adaptation in metabolically active kidney tissue, helping to optimise the use of oxygen to produce energy, potentially alleviating the effects of hypoxia in CKD pathophysiology. In animal models of diabetic and hypertensive nephropathy, aerobic exercise training produced beneficial effects on renal mitochondria, including inducing key enzymes and transcription factors for mitochondrial biogenesis, increasing mitochondrial ATP and reducing mitochondrial ROS production. These changes were associated with reduced renal disease progression compared with untrained animals [28][29][30].

Studies in humans have demonstrated reduced concentrations of some of the key molecules implicated in renal pathophysiology (discussed above) in response to exercise. These include MCP-1 [31][32], RANTES [33], NF-κB [34] and TNFα [35]. Exercise also increases anti-oxidants and decreases pro-oxidants in a variety of healthy and chronic disease populations [36]. Alterations to levels of myokines, i.e., cytokines produced by active skeletal muscle tissue, may also be relevant because of their anti-inflammatory and metabolic effects. These include the effects of IL-6 on increasing fatty acid oxidation, thus increasing energy availability, and reducing TNFα production from macrophages, amongst other anti-inflammatory effects [37]. Another example is the myokine irisin, serum levels of which are decreased in patients with CKD [38][39] and can be increased with exercise training, e.g., in older adults [40]. Interestingly, a mouse model of CKD (interstitial fibrosis) demonstrated improved kidney mitochondrial energy metabolism and reduced fibrosis after irisin induction [41]. Whilst some of these changes have not yet been demonstrated in patients with CKD, exercise may help readjust the imbalance of these important mediators in this population.

Benefits on other inflammatory and oxidative stress molecules have been seen in patients with CKD: 12 weeks of exercise in CKD 3–4 ameliorated cutaneous microvascular endothelial dysfunction by reducing oxidative stress. This suggests systemic anti-oxidant and endothelial function benefits of exercise [42]. Similarly, exercise training in CKD has been shown to reduce serum markers of oxidative stress, including F_2-isoprostane [12] and reduce lipid peroxidation and glutathione oxidation after 12 weeks of aquatic exercise in participants with mild-to-moderate CKD [43]. There is reduced (sodium oxide dismutase) SOD and Nrf2, important anti-oxidant/anti-inflammatory molecules in moderate CKD, compared with healthy controls; this was improved after acute exercise [44]. Likewise, resistance exercise in haemodialysis patients increases Nrf2 [45]. These are systemic anti-oxidant effects that may benefit ROS imbalance present in the diseased kidney.

Finally, whilst a bout of exercise leads to increased SNS activity [46], exercise training is known to dampen this response and may even reduce resting sympathetic tone [47]. Indeed, exercise training in healthy adults has been shown to result in reduced resting renal sympathetic activity, specifically [48]. As discussed, CKD patients have SNS overactivity, which may contribute to the pathophysiology of the disease. Thus, reduced SNS activity may be another way in which exercise training may affect CKD progression.

In summary, there are a number of potential ways in which exercise may reduce CKD progression. Prominent risk factors for CKD—BP and BMI—are improved by exercise, both in CKD patients and other populations. It is also plausible that exercise may affect the mediators of kidney disease pathophysiology themselves, with human exercise studies showing modification of many of the relevant molecules and pathways.

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