

Review Article

The effect of exercise on cardiovascular function of patients with chronic kidney disease

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Chronic kidney disease is a growing syndrome of high prevalence, characterized by alterations in water, mineral and acid-base balance. It is strongly associated with other comorbidities, one of which being cardiovascular disease which not only is a causative factor but most importantly the result of the progression of renal disease. Sedentary life, dysregulation of blood pressure and lipid metabolism, inflammation, oxidative stress and endothelial dysfunction are considered to be the principal factors leading to cardiovascular deterioration in these patients. Aerobic exercise is a main therapeutic strategy targeting better cardiovascular outcomes in the general population with proven benefits on physical fitness status, visceral fat reduction and blood pressure control. In our review, we assessed the effects of aerobic exercise on cardiovascular function of renal disease patients and confirmed its beneficial effects on traditional risk factors of cardiovascular disease such as physical fitness status, body mass index and visceral fat reduction. However, no significant alterations in non-traditional aspects of cardiovascular disease such as inflammation, vascular function, and lipid metabolism were found because chronic kidney disease patients are rarely encouraged to exercise and there is a lack in adequate evidence from big trials to clarify the potency of aerobic exercise on these factors.

Keywords: Aerobic exercise, Cardiovascular disease, Cardiovascular function, Chronic kidney disease, Renal disease**Introduction**

Chronic kidney disease (CKD) is defined by an impairment of the kidney's structure or function, present for at least three months¹. It is divided in 5 stages based on estimated glomerular filtration rate (eGFR) and albuminuria, with stage 5 known to be the end stage of renal disease (ESRD) (eGFR <15 ml/min), leading patients to dialysis. Worldwide, it is estimated that approximately 1 out of 7 people have CKD², a percentage that will keep rising as life expectancy and comorbidities increase. At the same time, this population is in an increased risk of cardiovascular disease (CVD), ranging from 15 to 30 times that of healthy individuals³, and is believed to be the major cause of mortality⁴. In fact, CVD related mortality is responsible for more than 50% of the deaths among patients with CKD⁵ meaning that a patient is more likely to die from CVD rather than progress to ESRD⁶. This strong correlation is multifactorial and can be attributed to both traditional risk factors (i.e. hypertension, diabetes, physical inactivity, and obesity) and to characteristics

related to kidney disease itself (i.e. endothelial dysfunction, chronic inflammation, oxidative stress, and disturbances in lipid patterns⁷). One well known modifiable factor to prevent CVD is physical inactivity which could be a therapeutic target to decelerate the ongoing cardiovascular damage. Exercise is incorporated in official guidelines and is included in the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines that recommend increased level of physical activity for patients under renal replacement

The author has no conflict of interest.

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Edited by: Konstantinos Stathopoulos

Accepted 2 May 2022

therapy (level of evidence C)⁸ and as for the rest CKD population with coexistent high blood pressure, the latest KDIGO 2021 guidelines recommend moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week or at a level compatible with their cardiovascular and physical tolerance (level of evidence 2C)⁹. Although, there is a large pool of evidence demonstrating the benefits of regular exercise on primary and secondary prevention of cardiovascular disease, there are not strong recommendations referring to CKD patients and little is known on the impact and safety of exercise training on this population, especially those on the predialysis stage. In the present review we studied the recent bibliography data about the impact of aerobic exercise on cardiovascular parameters of CKD population in predialysis stage.

Material and methods

We searched PubMed with the keywords: chronic kidney disease (CKD), renal disease, aerobic exercise, cardiovascular disease. Our inclusion criteria were: articles, reviews, randomized control trials, systematic reviews and meta-analyses published from 2000 to 2021, all concerning aerobic exercise training and CKD stages 1 to 5. Our exclusion criteria were patients in dialysis and a combination of aerobic and resistance training, or resistance training alone.

Results

From our research we initially retrieved 58 articles and after implementing our inclusion and exclusion criteria, we eventually studied 25 articles.

On the next paragraphs, we appose our findings regarding the effects of aerobic exercise on each component known to relate to CVD, making the separation between traditional risk factors and non-traditional risk factors in the context of CKD's special pathophysiology.

Traditional risk factors

Blood pressure

Both systolic and diastolic hypertension is independently associated with poor cardiovascular outcomes¹⁰ constituting a major therapeutic target to reduce CVD risk. Studies on the impact of aerobic exercise on this issue come to inconclusive results. More specifically Petchter et al. concluded that mild aquatic exercise, twice a week, among CKD stage 2 patients decreased both systolic and diastolic BP¹¹ and Headley et al. studying the effects of 40 mins of moderate aerobic exercise (50-60%VO₂) in predialysis patients found a reduction in BP the first 60 min after the exercise training (ET)¹², but the longer term impact produced mixed results. Positive results were extracted too by two RCTs including obese CKD patients. Baria et al. showed that 12 weeks of aerobic exercise three times per week reduced mean arterial blood pressure¹³ and in another RCT of Aoike et al. 29 overweight

(BMI>29)CKD stages 3-4 patients, who underwent moderate intensity home-based ET, presented a significant reduction in both systolic (p<0.001) and diastolic (p=0.007) blood pressure¹⁴. Another study performed by Kosmadadkis et al., in a population of 32 CKD patients who participated in a 6 month aerobic exercise plus bicarbonate administration, did not show a significant reduction in blood pressure, though there was an increase in BP medication for the usual care group implying better BP control for the exercise group¹⁵. On the other hand, no improvement in BP control was found in several RCTs, mentioned below. Mustata et al. studying the outcomes of 1 year of aerobic exercise in 18 patients at a performance level of 40-60% VO₂¹⁶ found no significant effect, Headley et al., 4 years after his previous study, also showed no significant effect upon either resting or ambulatory BP after a 48-week intervention of ET 3 times per week in a group of 21 patients¹⁷ and Toyama et al. concluded that a daily aerobic intervention for 12 weeks had no changes in BP¹⁸. Finally in the same direction the study of Leehey et al. in obese CKD patients that observed only a slight but not statistically significant decrease in systolic blood pressure¹⁹. The most recent collective data, to clear the topic, come from 3 major reviews and meta-analyses with conflicting results. The systematic review of Heiwe et al. pointed against reduction of resting diastolic pressure, though it examined mostly patients under renal replacement therapy²⁰ and thus it is not fully related to our current investigation. In 2018 the meta-analysis of Wynngaert et al, which included 11 RCTs with primary outcome BP in CKD 3-4 patients under an average of 32 weeks of aerobic training, observed no change in blood pressure in the between-group analysis²¹, while one year later the meta-analysis of Zhang et al. indicated that exercise training could significantly reduce both systolic and diastolic blood pressure by 5.61 mmHg (P=0.001) and 2.87 mmHg (P<0.00001) respectively, in non-dialysis CKD patients²².

Physical fitness

The fundamental role of the cardiovascular system is to distribute oxygen throughout tissues. Thus, an objective index of physical fitness is the assessment of oxygen uptake at peak exercise (peak VO₂), which defines the maximal ability of an individual to transport and use oxygen reflecting his functional capacity²³. Peak VO₂ is considered an independent predictor of mortality in CKD patients⁷ and it is well established that it is significantly decreased in pre-dialysis patients with levels ranging from 50-80% in healthy individuals²⁴. Bibliography on this issue reports unanimously positive results regarding aerobic exercise in CKD population^{4,11,14,17,20,25-28}. Specifically, all RCTs that were reviewed reported an increase in peak VO₂, some of them ranging from 8,2%²⁶ to 11%⁴ whereas the most recent meta-analysis of Wynngaert et al. observed an absolute within-group increase of VO₂ peak by 1.7 ml/kg/min [0.65; 2.74] (I²=6%) and when compared to the usual care group, exercise training improved VO₂ peak by 2.39 ml/kg/min

[0.99; 3.79] (I²=90%)²¹ over an intervention period of average 32 weeks. Same outcomes were reported from the meta-analysis of Yang et al., which included 178 eligible CKD patients in total, who found improved peak VO₂ values in the intervention group, indicating that exercise ameliorated cardiopulmonary function in this population²⁵. Finally, it is worth mentioning that this improvement in physical fitness was the same regardless of intensity, duration, supervision or type of aerobic exercise.

Body mass index

The predictive power of increased abdominal fat in cardiovascular events has been demonstrated in the early stages of CKD^{29,30}. Most evidence indicates the beneficial effect of ET on visceral fat and Body Mass Index (BMI)^{14,15,21,22,31}, with only a few studies containing small population sizes observing no additional effect^{11,19,32}. RCTs with the biggest sample under investigation include Baria et al. who reported a significant reduction in visceral fat and waist circumference after a 12 week training program in 27 obese CKD stages 3 and 4 (P<0.001)¹³, as well as Kosmadakis et al. who studied 32 CKD stages 3 and 4 patients and proved a significant reduction in BMI after 1 month of aerobic exercise plus bicarbonate supplementation that was depicted in DEXA assessment mainly as fat loss¹⁵. The meta-analysis of Zhang et al. revealed that BMI of non-dialysis patient decreased by 2.27 kg/m² in those who received 6–12 months of exercise intervention (MD= -2.27, 95% CI: - 3.84 to - 0.70, P=0.005) with no benefit for a lesser period²² and similar results were produced in the systematic review of Wyngaert et al. in which an average of 32 weeks of aerobic exercise diminished BMI by 0.73 kg/m² [-1.38; -0.09] (I²=54%)²¹.

Non traditional risk factors

Lipid profile

Among other mediators of CVD, dyslipidemia has a high prevalence in CKD patients³³. Abnormal lipid profile consists of high levels of triglycerides (TG), low levels of high-density lipoprotein (HDL) and usually normal low-density lipoprotein (LDL) levels. There are a few studies on this field with converging outcomes. Most of them observed no change in the lipid profile^{11,19,27,31,32}, except Toyama et al. who showed a reduction in LDL and TG and an increase in HDL after a 12-week daily aerobic exercise intervention therapy² and the meta-analysis of Zhang et al. that found only a significant decrease in TG levels (P=0.0006) for the first 3 months of intervention and worse long term outcomes, while total cholesterol, HDL and LDL remained unchanged²². These results may reflect a pathogenic lipid profile resistant to exercise training due to conditions of renal disease's microenvironment itself, such as inflammation³⁴, deficiency in the primary apolipoproteins AI and AII³⁵, and accompanied proteinuria³⁶.

Vascular dysfunction

Vascular dysfunction is emerging as a major mediator for the development and progress of cardiovascular disease in patients with CKD³⁷ and thus it is an attractive target for intervention. With the term vascular dysfunction we include both endothelial dysfunction, which is a dysregulation of the vascular homeostasis favoring inflammation and thrombosis³ and its consequent arterial stiffness, the result of progressive endothelial dysfunction which leads to atherosclerosis and calcification.

Endothelial dysfunction appears in the early stages of CKD²⁸ and can be evaluated noninvasively by flow mediated vasodilation (fmv), which is an important predictor of coronary events in patients with CKD, further increasing the correlation between endothelial dysfunction and CVD risk³⁸. It can be attributed to intrinsic microenvironment's alterations observed in CKD such as high aldosterone levels³⁹, subclinical inflammation³⁹, excessive oxidative stress, and NO dysregulation³, as well as defective endothelial repair mechanisms due to reduced levels of bone marrow-derived endothelial progenitor cells and impaired migratory function of circulating angiogenic cells⁴⁰. Unfortunately there are only two trials meeting our inclusion criteria. van Craenenbroeck et al observed that 3 months of interminant home-based aerobic exercise did not alter significantly peripheral endothelial vasodilation⁴⁰, while Kirkman et al proved that the same duration of exercise training may not have improve endothelial function but it did not reduce FMV as was noticed in the control group through time, indicating a possible protective effect of aerobic exercise on endothelial function⁴¹.

Similar results are extracted for the arterial stiffness, with the exception of one RCT supporting improvement in arterial elasticity⁴².

Inflammation

CKD is characterized by a state of chronic inflammation, as evidenced by increased levels of acute phase proteins (C-reactive protein-CRP) and pro-inflammatory cytokines (such as tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), interleukin-6 (IL-6))⁷. The majority of RCTs on this field, though, show no improvement in inflammation following aerobic exercise training in predialysis patients. Specifically, Headley et al. report no statistically significant alterations in IL-6 and CRP after a 48 week intervention in 21 patients¹⁷ and similar results are extracted by the trials of Leehey et al. in obese diabetic population¹⁹ and Miele et al. who studied the impact of a 16 week aerobic intervention in 46 patients with CKD stage 3²⁷. Only the study of Viana et al. observed an anti-inflammatory effect after six months of regular exercise in a group of 15 predialysis patients as evidenced by a reduction in the ratio of IL-6 to IL-10, but not in CRP which remained unchanged⁴³.

Discussion

The impact of physical exercise on CKD patients in predialysis stage is unresolved and there is only few data in the recent literature that has produced conflicting results regarding cardiovascular events. From the review we conducted, there is an indisputable beneficial role of aerobic exercise in physical fitness and also most evidence converge in favor of visceral fat and body mass index reduction. Mixing results come from several studies in the field of blood pressure control with promising overall evidence from the latest metanalysis of Zhang et al. The above findings are in line with the protective role of aerobic exercise in cardiovascular function concerning traditional risk factors. However, when it comes to non-traditional risk factors and CKD most studies do not provide compelling evidence in either direction and more trials are necessary in order to broaden our knowledge in the complex state of CKD.

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