Accepted Article

Journal of Research and Practice on the Musculoskeletal System JRPMS

Review Article

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

Konstantina Kanellopoulou[1,2]

[1]Nephrology department of General Hospital of Athens G. Gennimatas, Athens, Greece;
[2]Postgraduate Program "Metabolic Bone Diseases", National and Kapodistrian University of Athens, Medical School, Athens, Greece

Abstract

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 months[1]. 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 CKD[2], 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 individuals[3], and is believed to be the major cause of mortality[4]. In fact, CVD related mortality is responsible for more than 50% of the deaths among patients with CKD[5] meaning that a patient is more likely to die from CVD rather than progress to ESRD[6]. 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 patterns[7]). 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.

Corresponding author: *Konstantina Kanellopoulou, Asprogeraka 5, 11744, Athens, Greece*

E-mail: *kanellopoulou.konst@gmail.com*

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 metanalyses 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 outcomes[10] constituting a major therapeutic target to reduce CVD risk. Studies on the impact of aerobic exercise on this issue come to inconclusive results. More spefically Petchter et al concluded that mild aquatic exercise, twice a week, among CKD stage 2 patients decreased both systolic and diastolic BP[11] 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 pressure[13] 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 pressure[14]. 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 group[15]. 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% VO2[16] 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 patients[17] and Toyama et al. concluded that a daily aerobic intervention for 12 weeks had no changes in BP[18]. 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 pressure[19]. The most recent collective data, to clear the topic, come from 3 major reviews and metanalyses 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 therapy[20] and thus it is not fully related to our current investigation. In 2018 the metanalysis of Wyngaert 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 analysis[21], while one year later the metanalysis 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 patients[22].

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 capacity[23]. Peak VO2 is considered an independent predictor of mortality in CKD patients[7] and it is well established that it is significantly decreased in pre-dialysis patients with levels ranging from 50-80% in healthy individuals[24]. 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 metanalysis of Wyngaert 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 metanalysis 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 population[25]. 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<OO.1)[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 loss[15]. The metanalysis of Zhang et al. revealed that BMI of non-dialysis patient decreased by 2.27 kg/m^2) 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 period[22] 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/m^2 [-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 patients[33]. 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 therapy[2] and the metanalysis 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 unchanged[22]. These results may reflect a pathogenic lipid profile resistant to exercise training due to conditions of renal disease's microenvironment itself, such as inflammation[34], deficiency in the primary apolipoproteins AI and AII[35], and accompanied proteinuria[36].

Vascular dysfunction

Vascular dysfunction is emerging as a major mediator for the development and progress of cardiovascular disease in patients with CKD[37] 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 thrombosis[3] 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 CKD[28] 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 risk[38]. It can be attributed to intrinsic microenvironment's alterations observed in CKD such as high aldosterone levels[39], subclinical inflammation[39], excessive oxidative stress, and NO dysregulation[3], 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 cells[40]. Unfortunately there are only two trials meeting our inclusion criteria. van Craenenbroeck et al observed that 3 months of interminent home-based aerobic exercise did not alter significantly peripheral endothelial vasodilation[40], 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 function[41].

Similar results are extracted for the arterial stiffness, with the exception of one RCT supporting improvement in arterial elasticity[42].

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 (TNFa), 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 patients[17] and similar results are extracted by the trials of Leehey et al. in obese diabetic population[19] and Miele et al. who studied the impact of a 16 week aerobic intervention in 46 patients with CKD stage 3[27]. 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 inCRP which remained unchanged[43].

Discussion

The impact of physical exercise on CKD patients in prediallysis 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.

References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Official Journal Of The International Society Of Nephrology 2013;3(1). http://www.kidney-international.org
2. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. In: Advances in Experimental Medicine and Biology. Vol 1165. Springer New York LLC; 2019:3-15.
3. Bronas UG. Exercise Training and Reduction of Cardiovascular Disease Risk Factors in Patients With Chronic Kidney Disease. Advances in Chronic Kidney Disease 2009;16(6):449-458.
4. Howden EJ, Leano R, Petchey W, Coombes JS, Isbel NM, Marwick TH. Effects of exercise and lifestyle intervention on cardiovascular function in CKD. Clinical Journal of the American Society of Nephrology 2013;8(9):1494-1501.
5. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: A systematic review. Journal of the American Society of Nephrology 2006;17(7):2034-2047.
6. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. American Journal of Kidney Diseases 2017;69(3):A7-A8.
7. Gould DW, Graham-Brown MPM, Watson EL, Viana JL, Smith AC. Physiological benefits of exercise in pre-dialysis chronic kidney disease. Nephrology 2014;19(9):519-527.
8. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45(4 Suppl 3):S1-S153.
9. Cheung AK, Chang TI, Cushman WC, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney International 2021;99(3):S1-S87.
10. Flint AC, Conell C, Ren X, et al. Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. New England Journal of Medicine 2019;381(3):243-251.
11. Pechter Ü, Ots M, Mesikepp S, et al. Beneficial effects of water-based exercise in patients with chronic kidney disease. International Journal of Rehabilitation Research 2003;26(2):153-156.
12. Headley SA, Germain MJ, Milch CM, Buchholz MP, Coughlin MA, Pescatello LS. Immediate blood pressure-lowering effects of aerobic exercise among patients with chronic kidney disease. Nephrology 2008;13(7):601-606.
13. Baria F, Kamimura MA, Aoike DT, et al. Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients. Nephrology Dialysis Transplantation 2014;29(4):857-864.
14. Aoike DT, Baria F, Kamimura MA, Ammirati A, de Mello MT, Cuppari L. Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease. International Urology and Nephrology 2015;47(2):359-367.
15. Kosmadakis GC, John SG, Clapp EL, et al. Benefits of regular walking exercise in advanced pre-dialysis chronic kidney disease. Nephrology Dialysis Transplantation 2012;27(3):997-1004.
16. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: A pilot study. International Urology and Nephrology 2011;43(4):1133-1141.
17. Headley S, Germain M, Milch C, et al. Exercise training improves HR responses and VO2 peak in predialysis kidney patients. Med Sci Sports Exerc 2012;44(12):2392-2399.
18. Toyama K, Sugiyama S, Oka H, Sumida H, Ogawa H. Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. Journal of Cardiology 2010;56(2):142-146.
19. Leehey DJ, Moinuddin I, Bast JP, et al. Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study. Cardiovasc Diabetol 2009;8:62.
20. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev 2011;(10):CD003236.
21. Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W, et al. The effects of aerobic exercise on eGFR, blood pressure and VO2peak in patients with chronic kidney disease stages 3-4: A systematic review and meta-analysis. PLoS One 2018;13(9):e0203662.
22. Zhang L, Wang Y, Xiong L, Luo Y, Huang Z, Yi B. Exercise therapy improves eGFR, and reduces blood pressure and BMI in non-dialysis CKD patients: Evidence from a meta-analysis. BMC Nephrology 2019;20(1).
23. Lim K, McGregor G, Coggan AR, Lewis GD, Moe SM. Cardiovascular Functional Changes in Chronic Kidney Disease: Integrative Physiology, Pathophysiology and Applications of Cardiopulmonary Exercise Testing. Front Physiol 2020;11:572355.
24. Johansen KL, Painter P. Exercise in individuals with CKD. American Journal of Kidney Diseases 2012;59(1):126-134.
25. Yang H, Wu X, Wang M. Exercise Affects Cardiopulmonary Function in Patients with Chronic Kidney Disease: A Meta-Analysis. Biomed Res Int 2017;2017:6405797.
26. Headley S, Germain M, Wood R, et al. Short-term aerobic exercise and vascular function in CKD stage 3: A randomized controlled trial. American Journal of Kidney Diseases 2014;64(2):222-229.
27. Miele EM, Headley SAE, Germain M, et al. High-density lipoprotein particle pattern and overall lipid responses to a short-term moderate-intensity aerobic exercise training intervention in patients with chronic kidney disease. Clinical Kidney Journal 2017;10(4):524-531.
28. van Craenenbroeck AH, van Craenenbroeck EM, Kouidi E, Vrints CJ, Couttenye MM, Conraads VM. Vascular effects of exercise training in CKD: Current evidence and pathophysiological mechanisms. Clinical Journal of the American Society of Nephrology 2014;9(7):1305-1318.
29. Kamimura MA, Carrero JJ, Canziani MEF, Watanabe R, Lemos MM, Cuppari L. Visceral obesity assessed by computed tomography predicts cardiovascular events in chronic kidney disease patients. Nutrition, Metabolism and Cardiovascular Diseases 2013;23(9):891-897.

30. Elsayed EF, Tighiouart H, Weiner DE, et al. Waist-to-Hip Ratio and Body Mass Index as Risk Factors for Cardiovascular Events in CKD. American Journal of Kidney Diseases 2008;52(1):49-57.
31. Greenwood SA, Koufaki P, Mercer TH, et al. Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: A pilot randomized controlled trial. American Journal of Kidney Diseases 2015;65(3):425-434.
32. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: A pilot study. International Urology and Nephrology 2011;43(4):1133-1141.
33. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42(5):1050-1065.
34. Vaziri ND. Role of dyslipidemia in impairment of energy metabolism, oxidative stress, inflammation and cardiovascular disease in chronic kidney disease. Clinical and Experimental Nephrology 2014;18(2):265-268.
35. Vaziri ND. Causes of dysregulation of lipid metabolism in chronic renal failure. Seminars in Dialysis 2009;22(6):644-651.
36. Trevisan R, Dodesini AR, Lepore G. Lipids and renal disease. Journal of the American Society of Nephrology 2006;17:S145-S147.
37. Martens CR, Kirkman DL, Edwards DG. The Vascular Endothelium in Chronic Kidney Disease: A Novel Target for Aerobic Exercise. Exercise and Sport Sciences Reviews 2016;44(1):12-19.
38. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. Hypertension 2005;45(6):1042-1049.
39. Oliveira E Silva VR, Stringuetta Belik F, Hueb JC, et al. Aerobic Exercise Training and Nontraditional Cardiovascular Risk Factors in Hemodialysis Patients: Results from a Prospective Randomized Trial. CardioRenal Medicine 2019;9(6):391-399.
40. van Craenenbroeck AH, van Craenenbroeck EM, van Ackeren K, et al. Effect of Moderate Aerobic Exercise Training on Endothelial Function and Arterial Stiffness in CKD Stages 3-4: A Randomized Controlled Trial. American Journal of Kidney Diseases 2015;66(2):285-296.
41. Kirkman DL, Ramick MG, Muth BJ, et al. Effects of aerobic exercise on vascular function in nondialysis chronic kidney disease: a randomized controlled trial. Am J Physiol Renal Physiol 2019;316(5):F898-F905.
42. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: A pilot study. International Urology and Nephrology. 2011;43(4):1133-1141.
43. Viana JL, Kosmadakis GC, Watson EL, et al. Evidence for anti-inflammatory effects of exercise in CKD. Journal of the American Society of Nephrology 2014;25(9):2121-2130.