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The Role of Physical Exercise in Chronic Kidney Disease

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- CA: Contributed to the study concept, data collection, interpretation and writing the paper.
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ABSTRACT

Chronic kidney disease (CKD) affects more than 10% of the general population worldwide, amounting to more than 800 million individuals. Some important conditions associated with CKD are hypertension, diabetes, dyslipidemia, sedentary lifestyle, and smoking. According to World Health Organization (WHO), regular physical activity helps to prevent and manage non-communicable diseases such as diabetes and hypertension, associated with weight reduction. It is known that a decrease in systolic blood pressure is associated with significant reduction in all causes of mortality and major cardiovascular events. As far as diabetes concerned, beyond first-line medication, healthy lifestyle behaviours should be considered, in which physical activity is included. Training leads to improved skeletal muscle response with increased expression and activity of proteins involved in glucose metabolism and insulin sensitivity. Concerning dyslipidemia, one of the recommended interventions encompasses lifestyle, noting that in patients with low, moderate, or high cardiovascular risk, depending on the LDL value, the treatment involves physical activity and weight loss or its association with pharmacotherapy. CKD patients have some particularities that condition the exercise prescription and the interpretation of its benefits. This review is intended to systematize the importance of exercise in CKD and its determinants.

Keywords: Diabetes Mellitus/therapy; Dyslipidemia/therapy; Exercise; Exercise Therapy; Hypertension/therapy; Physical Fitness; Renal Insufficiency, Chronic/therapy

INTRODUCTION

CKD is a progressive condition that affects more than 10% of the general population worldwide, amounting to more than 800 million individuals.[1] The main risk factors associated with CKD and its progression, such as hypertension, diabetes mellitus and dyslipidemia, are highly preventable.[2,3]

A sedentary lifestyle is also related to CKD and a decrease in glomerular filtration rate,[4] just like smoking.[5,6] In all of them, a behavioural change is necessary and the paradigm that diseases are treated only with drugs must change. The evidence suggests that exercise does not lead to a worsening of renal function[1] and that clinicians should recommend exercise as part of the treatment of patients with CKD.[2,3] Although not trained in exercise prescription, all doctors should encourage the practice of exercise, provide material on the subject and refer patients to professionals trained in prescribing exercise to special populations. According to World Health organization (WHO), is proven that regular physical activity help prevent and manage non-communicable diseases such as heart disease, stroke, diabetes, and several cancers. It also helps to prevent hypertension, contributes to a healthy body weight, and improve mental health, quality of life, and well-being.[7] Exercise is an important therapeutic weapon, cost-effective, and it is underutilized, so it is crucial to understand the impact of the integration of exercise on the treatment of the main pathologies associated with chronic kidney disease and chronic kidney disease by itself.

An analysis of the most recent guidelines of CKD (KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease) and its main risk factors, as hypertension (2018 ESC/ESH Guidelines for the Management of Arterial Hypertension), diabetes (Standards of Medical Care in Diabetes 2023) and the role of exercise in CKD (Clinical Practice Guideline Exercise and Lifestyle in Chronic Kidney Disease) was conducted. Considering the high prevalence of dyslipidemia in CKD, the 2019 ESC/EAS Guidelines for the Management of Dyslipidemias were also integrated.

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A systematic literature search was undertaken to identify relevant clinical evidence and understand the role of physical exercise prescription. This information was associated with the recommendations from the American College of Sports Medicine (ACSM) to patients with CKD.

HYPERTENSION

In general population, arterial hypertension is defined as a systolic blood pressure (SBP) value > = 140 mmHg and/or diastolic blood pressure (DBP) > = 90 mmHg.[8] However, these targets changes in CKD: the optimal value in patients not receiving dialysis is SBP <120 mmHg, but in kidney transplant recipients the target SBP is <130 mmHg and DBP <80 mmHg.[9] Lifestyle changes are recommended as an initial approach for all degrees of hypertension.[8] These effective changes, like diet and exercise, may delay or prevent the need for pharmacological therapy in patients with Grade 1 hypertension.[8] In addition, despite they should not delay the introduction of drugs, these changes may increase the effects of antihypertensive therapy. It is noteworthy that the use of beta-blockers is not associated with exercise limitation.[10]

Aerobic exercise (e.g., walking, running, cycling), dynamic resistance (e.g., squats, bench presses, biceps curls) and isometric exercise (e.g., plank, wall sit, glute bridge) leads to a reduction in SBP and DBP in the general population.[8] Endurance training (aerobic) was associated to a reduction in BP in hypertensive patients.[8] It is also known that the reduction is more effective in moderate to high-intensity training.[8] CKD patients should also perform exercise regularly, even if not always capable of achieving the levels recommended to the general population.[9] The post-exercise hypotensive response lasts about 22 hours and is associated with decreased levels of norepinephrine and inhibition of the sympathetic system, reduction of circulating angiotensin II, adenosine, endothelin and its response in the central nervous system.[11] In addition, there is a vasodilatory effect mediated by prostaglandins and nitric oxide.[11] In a systematic review and meta-analysis of the effect of exercise on blood pressure, there was a decrease in SBP with dynamic aerobic exercise and in DBP with the same type of exercise, but also with resistance dynamic training. The most significant reduction in both SBP and DBP was seen with isometric training.[12] It is known that a reduction of 10 mmHg in SBP or 5 mmHg in DBP, which is attainable only with weight loss (for every 10 kg lost) and exercise, is associated with reductions of about 10% to 15% in all causes of mortality, 20% in major cardiovascular events, 35% in strokes, 20% of coronary events and 40% in heart failure decompensation.[13] In addition, these reductions are independent of comorbidities such as diabetes mellitus and CKD.[8]

Taking into account the growing evidence about the effects of exercise, the European Society of Cardiology recommends regular aerobic exercise, at least 30 minutes, moderate, dynamic, for 5 to 7 days a week for hypertensive patients (Class of Recommendation I, level of evidence A),[8] which is in line with CKD recommendations. In addition, CKD patients should perform activities to enhance muscle strength, balance, and flexibility, at least 2 days a week, to improve blood pressure.[14] Hemodialysis patients should aim for the same time of activity as non-dialysis patients (150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity, or both combined).[14]

DIABETES

Glycemia reductions are related to the intensity and duration of exercise and the patient's previous physical condition.[15] Aerobic exercise, even just after a week, can improve insulin sensitivity.[15] Training leads to improved skeletal muscle response with increased expression and activity of proteins involved in glucose metabolism and insulin sensitivity. Mechanisms include increased glucose transporter GLUT4, mRNA, increased hexokinase synthesis, decreased fatty acid release, and increased glucose transport to the muscle (increased capillarization and blood flow).[11] All individuals, including diabetics, should reduce the time of sedentary lifestyle since there is evidence of reduced HbA1c with resistance training in elderly diabetic patients and a cumulative effect with combined exercise (aerobic and resistance).[16] The 2023 American Diabetes Association recommendations for patients with type 2 diabetes include aerobic exercise with moderate to vigorous-intensity activity, at least 150 minutes per week (no more than 2 consecutive days without activity) and resistance exercise, two to three times a week. The plans must include daily exercise, with a progressive increase in intensity, frequency, and/or duration.[16]

Besides first-line medication, healthy lifestyle behaviours, in which physical activity is included, should be considered in the treatment of diabetes.[16] It should be noted that despite the benefits that come from physical exercise, there are some situations, namely in patients with uncontrolled proliferative retinopathy, in which activities that increase intraocular pressure and hemorrhagic risk should be avoided.[15] Despite the documented acute increase in albuminuria during exercise, there is no evidence that exercise (even at a high intensity) leads to the progression of CKD, thus not constituting a restriction on its practice.[17]

The current research is not strong enough to specifically recommend the practice of exercise in non-dialysis CKD patients to improve glycemic control, however, except in patients with contraindications, physical activity should be considered in this population.[14]

DYSLIPIDEMIA

Among the factors that modify the coronary risk are obesity, mostly central, and inactivity. In fact, exercise practice, regardless of diet, improves lipid profile, namely low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.[18]

In untreated patients with low cardiovascular risk and LDL levels <116 mg/dL, with moderate risk and LDL <100 mg/dL, with high risk and LDL <70 mg/dL or those with very high risk and LDL <55 mg/dL, the only strategy intervention is lifestyle changes.[18] These changes include 3.5 to 7 hours of moderate to vigorous exercise per week or 30 to 60 minutes on most days, maintenance of a body mass index (BMI) between 20-25 kg/m^2 and abdominal circumference <94 cm in men and <80 cm in women.[18]

The main impact of adequate physical activity is on HDL cholesterol levels, with an increase in its concentration between 3.1 to 6 mg/dL.[18] Triglycerides levels also change, with a reduction of 5% to 10%.[18] The impact is less impressive at the level of LDL, with a reduction of

<or = 5%.[18] Concerning weight loss and its impact on lipidic profile in obese patients, the decrement of 10 kg is necessary for a reduction of about 8 mg/dL in LDL concentration.[18] Despite this, all the patients, including those who are not overweight, should exercise at moderate intensity for more than 30 minutes daily.[18] In patients with CKD and dyslipidemia, specifically in non-dialysis patients, exercise was not associated with statistic significant differences in lipid levels.[19] Despite of that, it was demonstrated that exercise during hemodialysis sessions, like pedal, could improve lipid profile in these high cardiovascular risk population.[14]

EXERCISE IN CHRONIC KIDNEY DISEASE

There are some concerns about the fragility in CKD patients. The question that remains is whether this fragility should limit the recommendation of exercise.

Across all the globe we have witnessed a significant aging of the population, with an expected increase of the people aged 60 and over, from 900 million in 2015 to 2 billions in 2050.[20]

As we know, ageing is associated with physical frailty and cognitive decline. So, the health of older people should be of great concern.[21]

Skeletal muscles are responsible for secrete signalling molecules that interact with healthy kidneys. In CKD, this relation is compromised, as well as the protein metabolism in skeletal muscle, muscle repair and protein synthesis.[22]

Aging in CKD patients have not only a direct impact in kidneys, with renal senescence and higher prevalence of cardiovascular diseases, but also a negative impact in the muscle mass and functional capacity. All those factors, inherited to aging process, empower each other and contributes to CKD progression and decreases quality of life.[14]

Another problem is muscle fat infiltration which is associated with aging and CKD by itself. This condition compromises muscle strength and quality and is associated with metabolic abnormalities, cardiovascular disease, and increased mortality.[23] In addition, protein-energy wasting (PEW) and cachexia, associated with decreased nutritional intake or loss of nutrients, inflammation, acidemia, mineral and bone disorder and the dialysis procedure by itself (especially among peritoneal dialysis), also compromise the adequacy of body composition and consequently the functional capacity.[24,25]

There is evidence that exercise improves the functional capacity of dialysis patients demonstrated by an increase in maximum VO2 and/or by the performance of capacity tests such as the 6 minute-walk-test and the sit-to-stand test.[26]

Currently, there is still a lack on data regarding the best time to perform exercise in these population, if during dialysis or between sessions.[27] However, intradialytic exercise is recommended, as a complement, to upgrade physical function and cardiovascular health, taking into account its impact on blood pressure control, lipid profile, muscular strength, dialysis efficiency and also in the rate of hospitalizations.[14]

Regarding patients in the first 4 stages of CKD, there are less evidence about the impact of exercise. Most of the studies have included a small amount of patients, with different inclusion/exclusion criteria and training protocols.[26] Even so, there has been some data about the effect of exercise in physical capacity and muscle mass[14] in non-dialysis patients. It was also demonstrated an increase in muscle endurance training and in the size of type I and II muscle fibers, in mitochondrial DNA, pre-albumin, and leucine oxidation (signs of anabolism).[26] Regarding the progression of kidney disease and exercise, the number of studies available about this subject is small and the ones that exist are not very robust, which makes it difficult to take conclusions. Despite of that, no study has shown a worsening on renal function.[14,26]

Chronic training increases sensitivity to anabolic hormones (e.g., testosterone, insulin growth factor 1, insulin, and growth hormone) which leads to an improvement on musculoskeletal health.[23] Concerning to PEW, low levels of physical activity exacerbate its pathophysiology. However, there is also a lack of data about which structured interventions reduce muscle fat infiltration or PEW in CKD patients, and witch type, frequency, and intensity of exercise is associated with better results. Nevertheless, the current evidence points to an improvement in muscle quality with programmed and supervised exercise on haemodialysis patients.[23-25]

In general population, exercise is important for bone health and osteoporosis.[28,29] In CKD patients weight bearing activities were excluded from clinical practice guideline exercise because of lack of scientific evidence of its safety. However, maintaining lean mass is crucial for functional capacity and prevention of falls, so multi-component strength and balance activities are recommended.[14]

The WHO defines healthy aging as the process of developing and maintaining the functional ability that enables well-being. Taking this into account, exercise training is a tool that can and should be used to improve physical function in frail older adults.[20]

Despite the various benefits that result from exercise, some aspects deserve particular attention. Within recommendations from the American College of Sports Medicine (ACSM), a pre-exercise evaluation should be done by professionals before the patient engages in physical activity or a structured exercise program. This evaluation includes: informed consent process, exercise pre-participation health screening, health history, and cardiovascular risk analysis.[30] Some important notes, specific for CKD patients: pre-training evaluation on end-stage CKD patients under dialysis should be performed on non-dialysis days; in the particular cases of peritoneal dialysis patients, the evaluation should be done with a smaller amount of dialysate in the peritoneal cavity.[31]

Traditional tests to assess physical fitness, cardiovascular capacity, and muscle strength on these patients must be adapted and consider their functional capacity. For example, the quantification of 1RM (1 maximum repetition) in the evaluation of strength is usually contraindicated.[30]

The recommendations in the exercise prescription follow the FITT principle (frequency, intensity, time, type, volume, pattern, progression).[30]

According to the ACSM guidelines the plans must include:

1. Aerobic exercise, lasting 20 to 60 minutes, 3 to 5 times a week, at moderate-intensity (40% - 59% of the reserve VO2 or 12 - 13 on a scale of 6 to 20 of rate of perceived exertion).[30] However, if the patient does not tolerate the previous plan, interval exercises with intensity peaks of 3 to 5 minutes can be used until he reaches the optimal duration.[30] Exercises should privilege large muscle groups (e.g., quadriceps, back, glutes).[30]

2. Resistance training performed 2 to 3 times a week, with moderate intensity, formed by sets of 10 to 15 repetitions, and progress to higher number as the patient adapts.[30]

3. Flexibility should be exercised 2 to 3 times a week.[30]

Taking into the account the particularities of CKD patients, not only associated with CKD and dialysis, but also with the numerous pathologies associated with this disease, the prescription must always be done by trained professionals, with the knowledge and competence needed.[14,30]

Another important life change in all CKD patients is the smoke cessation.[14]

DISCUSSION

Regular physical exercise should be recommended in CKD. The main limitation in the interpretation of the present studies carried out is the difference in the exercise prescription protocols used, namely in the definition of frequency, duration, type, volume, pattern, progression, and intensity and its impact on CKD with its particularities. On the other hand, there are still few studies on CKD and exercise. It is important to note that the current evidence points to better results at higher intensities but most of the CKD patients are not able to perform this kind of exercise due to his age and comorbidities. In these cases, we can always suggest some lighter physical activity.

As we know, there is a lack of data about this subject in this population, despite of the inclusion of physical activity in most of the guidelines. To properly promote exercise activity, it is then crucial to increase knowledge in this area, with proper studies that include CKD patients in different stages of the disease and in different types of dialysis.

Understanding the complexity of CKD and its complications, like bone anomalies, and its impact on physical performance, as well as the comorbidities often associated with this disease, is necessary to properly conduct these patients.

In addition, the exercise prescription implies a detailed pre-training evaluation excluding possible contraindications, an implementation of an individualized and achievable plan for the patient. It is known that motivation can be an additional limiting factor in adherence to training plans, which justifies additional monitoring concerning behavioral change strategies.

Faced with all the possible obstacles to verifying the improvement of health with exercise, some strategies can be facilitative. The implementation of multidisciplinary teams has been pointed out as fundamental. We consider that the integration of exercise professionals, namely physiologists trained in prescribing in patients, psychologists with competence in the approach to behavioural change and acquisition of tools that increase adherence to training, and nutritionists, in addition to doctors with training in the area of exercise, is crucial. Another limitation may be the cost associated with the integration of gyms as well as the identification of spaces that have trained professionals. Thus, we consider that a future approach involves the execution of training plans at the hospital level in addition to those already implemented in dialysis clinics. The safety in the execution of the training protocols in a supervised manner by competent professionals, as well as the monitoring by the multidisciplinary teams and the possibility of quick action in the face of complications would be difficult to match in another context.

Finally, the absence of this investment and the inclusion of exercise in the approach of the patient with chronic kidney disease lead to sub-optimal treatment and all the consequences that result from it. The implementation of new strategies of approach with the creation of protocols with multidisciplinary teams would be an added value in the treatment of CKD. As long as this is not possible it is recommended that all doctors, even if not trained in exercise prescription, encourage the practice of it, question patients about their habits, encourage physical exercise, provide material on the subject, and refer patients to professionals trained in prescribing exercise to special populations. This approach should be adopted in the early stages of the disease in order to prevent or delay the onset of several of its complications.

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