

Aerobic and Resistant Physical Exercise on Chronic Kidney Disease (CKD) Patients: are there any Benefits?

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Abstract

Chronic kidney disease (CKD) has become an epidemic condition, with increasing incidence worldwide, generating high mortality rates and high health care costs. Several studies have demonstrated that inflammation is common in patients with CKD and it is associated with a high mortality rate in this population. Regular exercise has been described as a therapeutic strategy for reducing the risk of chronic and metabolic diseases, in part because of exercise training seems to exert anti-inflammatory effects. Therefore, the aim of the present review was to analyze the effects of aerobic and resistance exercise on inflammatory biomarkers in patients with CKD. CKD results in serum accumulation of toxic substances, the uremic toxins. These activate immune and inflammatory response in experimental models and in patients with CKD. Several studies involving non-pharmacological interventions have focused on CKD patients, aiming at reducing the inflammatory state, improving quality of life and extending the survival of these patients. It has been found that using treadmill for walking in patients undergoing pre-dialysis treatment was effective in reducing CRP and IL-6, showing that this type of aerobic exercise may also promote an anti-inflammatory effect. In contrast, some studies have not been able to show any beneficial effect on inflammation; e.g., a study using an intradialytic cycling protocol for HD patients 3x / week for 6 months found no decrease in IL-6, CRP and TNF- α . There are a number of studies reporting favorable effects of exercise training on the inflammatory response triggered by hypertension, diabetes, obesity, dyslipidemia and cardiovascular events in the general population; however, this review showed that the role of the anti-inflammatory effect of aerobic and resistance exercise remains controversial in CKD patients, particularly in those undergoing dialysis. Conversely, data from the literature found that high intensity aerobic exercise training for a sustained period of time seems to have anti-inflammatory effects when compared to resistance exercise, in particular when PCR is used as a marker of inflammation.

Keywords: Kidney Disease; Inflammation; Exercise Effect

Introduction

Chronic kidney disease (CKD) is now a leading cause of mortality and morbidity around the world with increasing worldwide incidence and high health care costs [1]. It is estimated that the prevalence of chronic kidney disease (CKD) affects between 11% and 13% of population [2], affecting around 750 million people worldwide [3]. Besides, it is estimated that five million are currently on dialysis (dialysis) [2] and the increased incidence and prevalence of CKD will have a 33% increase in the impact on health costs by 2020 [4]. CKD is defined by the presence of renal injury or glomerular filtration rate (GFR <60 ml/min per 1.73 m²) for ≥ 3 months, regardless of the underlying disease, and is classified into five stages, according to GFR [5]. CKD is a progressive condition, and it is characterized by a decrease in GFR <15 ml/min per 1.73m² (uremia) due to the accumulation of toxic substances (uremic toxins) that should be excreted by the kidney,

GFR <15 ml / min per 1.73 m² is incompatible with survival [6], requiring dialysis treatment or kidney transplantation [7]. The major risk factors involved in the decline of renal function include hypertension, diabetes, obesity and primary renal disorders [8]. These diseases share the pathophysiological mechanism of inflammation. Several studies have reported that CKD patients have higher concentrations of oxidative stress markers, C-reactive protein and inflammatory cytokines when compared to healthy individuals [9,10]. Moreover, inflammation is associated with high cardiovascular mortality rates [11-13] and muscle catabolism, due to protein restriction [14] and malnutrition [15], which also contribute to skeletal muscle mass loss, decreased muscle performance and worse quality of life in patients with CKD [16]. Uremia "per se" and inflammation appear to be associated with protein degradation and consequently marked catabolic state

in this population [17]. Thus, patients with CKD often complain of weakness, fractures, functional disability [18], which are associated with the lack of regular physical activity [19]. Both low level of physical activity [18] and loss of physical function capacity [20] are independently associated with adverse outcomes that impair the quality of life of these individuals [20]. In recent years, several studies have proposed that exercise training in the general population reduces the risk of chronic and metabolic diseases, and has anti-inflammatory effects [21,22]. However, there are few studies addressing the effect of aerobic exercise and exercise resistance to inflammation modulation in CKD patients on dialysis and pre-dialysis [23].

Materials and Methods

Searches were performed in five databases; PubMed, ProQuest, Bireme, Scielo and ScienceDirect. Relevant publications from the last ten years (2009 to 2019) were selected. The keywords selected were: “Kidney disease and inflammation”, “physical exercise in kidney disease”, “physical exercise in inflammation”, “effects of physical exercise on chronic kidney disease”, “anti-

inflammatory effects of physical exercise on kidney disease” and “anti-inflammatory effects of exercise”.

Hypertension

The progression of renal failure is associated with risk factors such as hypertension, diabetes and obesity [8,24]. Hypertension is characterized by increased blood pressure (BP) and the overall prevalence of this condition affects around 40% of the adult population worldwide [25]. Hypertension is the/a major risk factor associated with CKD, and as such strongly contributes to cardiovascular diseases (CDVs) and mortality [26,27]. In hypertension, renal function self-regulation is impaired, resulting in glomerular hypertension [28]. Elevated intraglomerular pressure signals local inflammatory responses with the production of proinflammatory cytokines and oxygen radicals, inducing glomerular injury and progressive loss of renal function [29]. The loss of renal function and the progression of CKD-related hypertension induce structural changes in the kidney, vascular sclerosis, glomerular hypertrophy, tubular injury and fibrosis, leading to kidney failure (Figure 1).

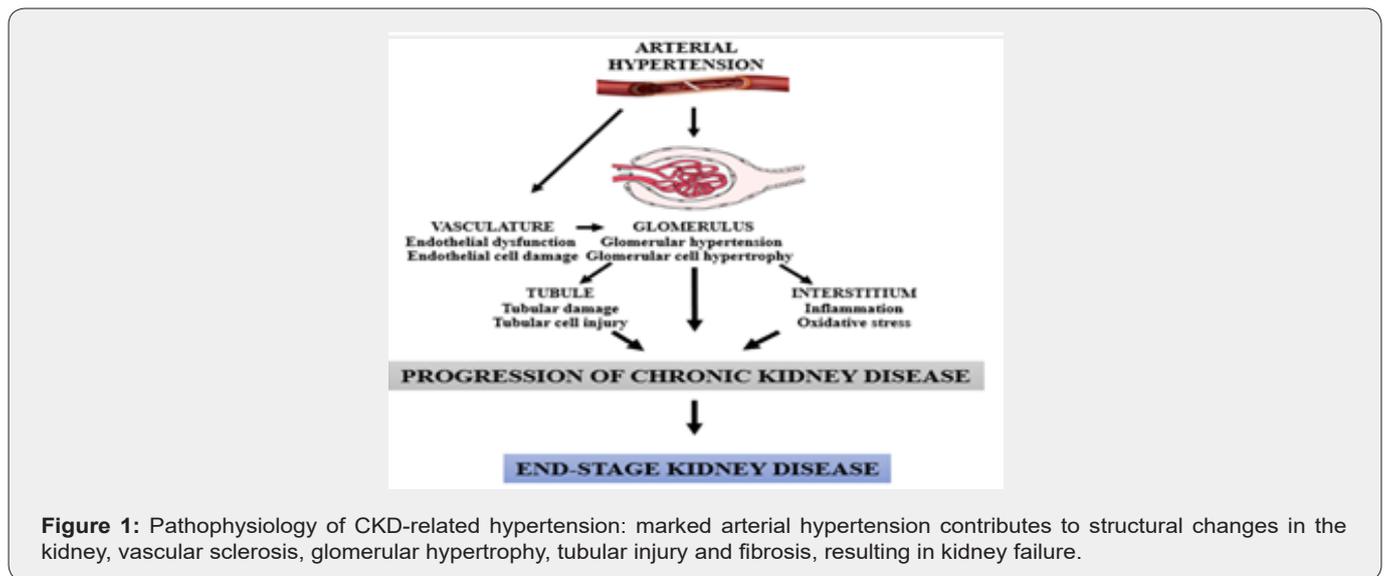


Figure 1: Pathophysiology of CKD-related hypertension: marked arterial hypertension contributes to structural changes in the kidney, vascular sclerosis, glomerular hypertrophy, tubular injury and fibrosis, resulting in kidney failure.

Diabetes

The number of individuals with diabetes is estimated to reach 642 million by 2040 [30]. Diabetes is also associated with an increased incidence of chronic kidney disease (CKD) [31,32]. Studies have found that hyperglycemia induces glomerular injury and dysfunction through increased oxygen radical generation and formation of AGEs.

These mechanisms contribute to endothelial dysfunction, glomerular hyperfiltration and increased vascular permeability, resulting in glomerular injury and consequent albuminuria [33] and CKD progression [34,35]. (Figure 2).

Obesity

Obesity has also been found to be a risk factor for CKD. Adipose tissue consists of adipocytes, which in excess are capable of producing TNF- α , IL-6, oxygen radicals (ROS) having autocrine and paracrine action. These inflammatory mediators increase the activity of the renin angiotensin aldosterone system (RAAS) contributing to hypertension and promote insulin resistance, which results in hyperglycemia. In addition, obesity is associated with low levels of adiponectin, a hormone with a protective effect on the regulation of inflammatory response, including in endothelial cell. Thus, the adverse effects of obesity on blood pressure, insulin resistance, inflammation, dyslipidemia and

systemic hemodynamic changes contribute to glomerular lesions and may eventually lead to CKD [36-39] (Figure 3).

Inflammation and CKD

Chronic Kidney disease (CKD) results in serum accumulation of toxic substances, uremic toxins [40]. These toxins in turn activate immune and inflammatory response in experimental models and in patients with CKD [41-45]. Dialytic procedures are the treatment necessary to maintain CKD patients alive. However, despite the technological advances in the dialysis procedures, peritoneal dialysis and hemodialysis are not able to remove all toxins, particularly those too large to be filtered and/or protein bounded 46 [46]. Therefore, patients on dialysis still have serum circulating uremic toxins. In addition, some studies have demonstrated a direct relationship between uremic toxins and

inflammation, and impact on cardiovascular disease (CVD), the main cause of mortality of CKD patients [47, 48]. Uremic toxins, such as indoxyl sulfate and p-cresyl, which originate from the bowel metabolism, have been found to cause immune activation with production of proinflammatory cytokines, including TNF- α , IL-6 and MCP-1 [49, 50] mainly by monocytes [51,52]. Although these proinflammatory cytokines enhance host defense, excessive production leads to unresolved inflammation [53]. The causes of inflammation in CKD patients are multifactorial (Figure 4) and are associated with presence of uremic toxins, acidosis, dialytic procedures “per se”, bioincompatibility of the membrane, quality of water used in hemodialysis, besides traditional risk factors as hypertension, diabetes, obesity, smoking and dyslipidemia [54] (Figure 4).

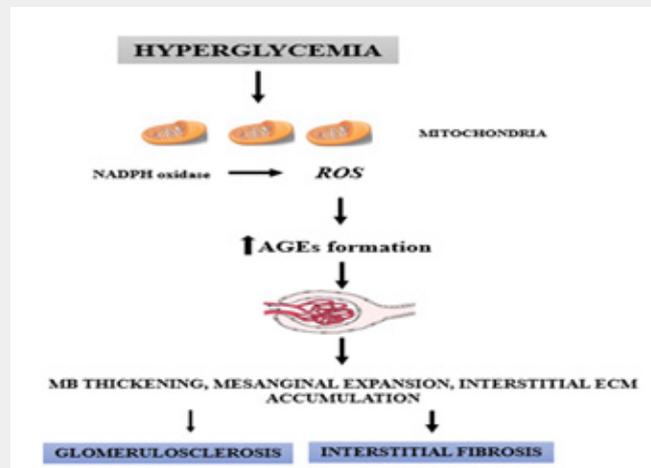


Figure 2: Hyperglycemia induces glomerular injury and dysfunction through increased oxygen radical generation, formation of AGES, increased endothelial dysfunction, glomerular hyperfiltration and vascular permeability, resulting in glomerular injury, interstitial fibrosis, and albuminuria and CKD progression.

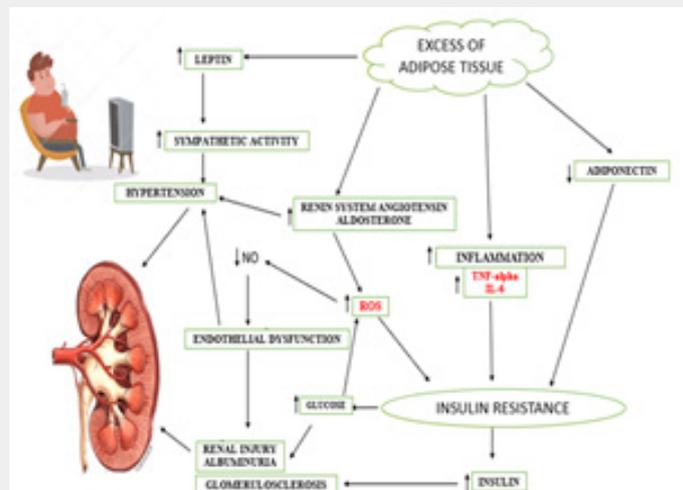


Figure 3: Impact of obesity on blood pressure, insulin resistance and endothelial function, contributing to increased inflammation, glomerular injury and CKD progression.

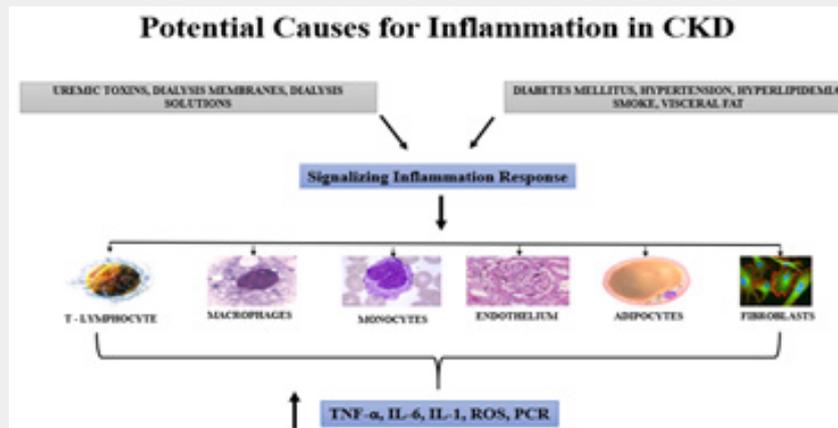


Figure 4: Potential causes for inflammation in CKD.

Loss of Skeletal Muscle Mass in CKD

Loss of muscle mass in patients with CKD is common and is associated with low calorie intake, protein restriction, metabolic acidosis, hyperkalemia and uremia control) [55-57] and protein energy loss (PEW) [58]. These changes are common and increase the risk of mortality in this population, especially in the later stages of CKD with glomerular filtration rate (GFR) <60 ml / min / 1.73 and in dialysis patients [59-61]. PEW in CKD patients is a result of uremia [59], inadequate nutrition and inflammation, which contribute to a marked catabolic state [62], excessive energy loss and decreased muscle mass [63]. In addition, changes in insulin and/or insulin grow factor-1 (IGF-1) signaling are also risk factors for muscle loss [64-66] and mortality in this population [67]. In summary, CKD patients are more susceptible to skeletal muscle loss, with a consequent increased risk for mortality [67].

Physical Exercise and Inflammation in the Drc-Free Population

Cross-sectional and population cohort studies have consistently shown an inverse association between systemic inflammation and physical exercise; the lowest the concentration of inflammatory biomarkers is observed in individuals who exercise frequently [68,69]. Studies have demonstrated that both aerobic and acute exercise may play a proinflammatory role due to increased oxidative stress [70]. Immediately after exercise, the increased inflammatory response due to muscle stimulation stimulates repair and remodeling [71]. Thus, after adaptation, these responses may have a beneficial effect, resulting in reduced inflammatory response [70,72]. The repair mechanism of muscle tissue damage in response to exercise is divided into degeneration, regeneration and tissue remodeling in response to exercise [73]. After acute exercise and / or trauma, muscle fiber destruction, inflammation, injury and necrosis occur. Macrophages are then recruited into the lesion area and produce MCP-1 (Monocyte Chemotactic Protein-1) and IL-10

[74,75] to promote muscle tissue regeneration [76-78]. Besides macrophage recruitment, muscle regeneration also occurs in response to damage to myofibers and activation of myogenic cells which, after proliferation, differentiation and fusion, stimulate the formation of new fibers and the reconstitution of the injured tissue [79]. Therefore, physical exercise seems to play anti-inflammatory role, stimulating the increase of myocin production from muscle contraction, with a subsequent increase in plasma level of anti-inflammatory cytokines (IL-10 and IL-1ra) [80-83]. In addition, regular exercise can also reduce visceral fat and increase adiponectin release, thus promoting an anti-inflammatory environment. In a study involving pre hypertensive young individuals, Beck et al. [84] have observed that endothelial function was improved after aerobic exercise. In another study, Beck et al. [85] have demonstrated that aerobic exercise increases the bioavailability of NO and prostaglandins, in addition to reducing circulating levels of endothelin 1 (ET-1; vasoconstrictor). Several studies have also reported the beneficial effects of aerobic exercise on decreasing CRP and IL-6 [86-89] and increasing of IL-10 [90].

Effect of Physical Exercise On CKD

Several studies have demonstrated the positive impact of non-pharmacological interventions on the inflammatory state, quality of life and survival of CKD patients. Protocol have used both acute and resistance aerobic exercise or a combination of the two. In fact, Liao et al [91] have found that cycling (exercise on an exercise bike) during intradialytic periods for 3 months, 3x week reduced CRP and IL-6 levels. Moreover, in the same study patients who underwent cycling training presented increased endothelial progenitor cells and improved bone mineral density. In a study using treadmill for walking in patients undergoing pre-dialysis treatment, Zang et al [92] have demonstrated that exercise was effective in reducing CRP and IL-6, showing that this type of aerobic exercise may also have an anti-inflammatory effect.

However, some studies have not been able to show any beneficial effect on inflammation. Dungey et al. [93] have also evaluated the impact of an intradialytic cycling program on HD patients 3x week for 6 months and found no decrease in IL-6, CRP and TNF- α . Similarly, Wilund et al. [94], after 4 months of intradialytic cycling for 45 minutes 3x week, did not observe any effect on CRP and IL-6 decrease. Leehey et al. [95], in a randomized pilot study, have not observed any significant effects of treadmill for walking 3x week for 24 weeks on decreased CRP levels in CKD patients in pre-dialysis stages. There are few studies evaluating the acute effect of exercise in patients with CKD. Peres et al. [96] have observed increased IL-10 expression after 20 minutes of an acute intradialytic cycling session. In contrast, Dungey et al. [97] did not observe any significant impact of an acute 30 minute intradialytic cycling session on IL-6 and TNF- α . Moraes et al. [98] have reported a reduction in serum CRP levels after performing exercises with elastic (Theraband) on the lower limbs during the first 2 h of HD, 3x / week, for 6 months. In a study conducted by Barcellos et al. [99], CKD patients in pre-dialytic stages performed resistance-associated aerobic training sessions for 60 min / 3x week for 16 weeks, and CRP was not reduced when compared to the control group. Likewise, Esgalhado et al [100], have found no changes in CRP levels after 30 min of acute session in a 3-set protocol with 10 repetitions of lower-limb resistance exercise.

Conversely, different results were observed in a study conducted by Afshar et al. [101], who compared the effects of cycling for 10 to 30 minutes vs. resistance exercise through the use of knee-extension ankle weights, hip abduction, and flexions in the patients hemodialysis for 8 weeks (3x wk). which CRP levels decreased in both groups ($P = 0.005$ and $P = 0.036$), but the reduction was greater for aerobic exercise training. Similarly, Moraes et al. [98] have found that a 6-month resistance exercise program reduced CRP levels, but had no impact on both IL-6 and TNF- α . However, Kopple et al. [102], did not observe changes in CRP, TNF- α and IL-6 concentrations in HD patients undergoing training for 20 - 40 min / 3x / 20 without / 20 weeks of aerobic, resistance and aerobic training + resistance. Similarly, other studies using aerobic + resistance exercise had no effect on decreasing inflammation biomarkers in HD patients [103-105]. Watson et al. [106] evaluated the effects of resistance exercise with 3 sets of 10 to 12 leg extension repetitions, 3x 8 week[s] in CKD patients undergoing pre-dialytic treatment and found no decrease in IL-6, MCP-1, and TNF- α or IL-15 expression.

Conclusion

There are several studies reporting the favorable effects of exercise counteracting the inflammatory response triggered by hypertension, diabetes, obesity, dyslipidemia and cardiovascular events in the general population. However, the present review in patients with CKD showed that the anti-inflammatory properties of aerobic and resistance exercise remains controversial in this population, particularly in dialysis patients. However, the practice of aerobic exercise with greater intensity and duration which

does seem to have an anti-inflammatory effects when compared to resistance exercise, especially when PCR is used as a marker of inflammation. Further research is needed to fully elucidate the impact of exercise on the complex state of immune dysfunction of CKD patients.

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