Minireview

Influence of exercise training on diabetic kidney disease: A brief physiological approach

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Impact statement

Diabetic kidney disease (DKD) is associated with increased mortality in diabetic patients and has a negative impact on public health. The identification of potential therapies that help the management of DKD can contribute to the improvement of health and quality of life of patients. Thus, this paper is timely and relevant because, in addition to presenting a concise review of the pathogenesis and major pathophysiological mechanisms of DKD, it addresses the most recent findings on the impact of exercise training on this disease. Thus, since non-pharmacological interventions have gained increasing attention in the fight against chronic diseases, this paper appears as an important tool to increase knowledge and stimulate innovative research on the impact of exercise on kidney disease.

Abstract

Sedentary lifestyle is associated with increased incidence of diabetes mellitus, whereas exercise training improves metabolic control and therefore may contribute to prevention of various chronic complications. Diabetic kidney disease is the most common microvascular complication of diabetes mellitus, and is associated with increased mortality from cardiovascular disease in diabetic patients. The literature highlights oxidative stress, renal inflammation, and activation of the renin-angiotensin-aldosterone system as the main pathophysiological mechanisms underlying tissue damage, extracellular matrix accumulation, and renal function deficit. Unfortunately, although the benefits of exercise training on cardiovascular diseases are well established, their impact on the pathophysiological mechanisms involved in the development and progression of diabetic kidney disease is not well understood. In addition, standardization of experimental models and physical rehabilitation programs in diabetic kidney disease are scarce. In this article, we present a brief review of the pathogenesis and pathophysiological mechanisms of diabetic kidney disease,and bring to light the latest findings in the literature on the impact of exercise training on diabetic kidney disease progression.

Keywords: Diabetes mellitus, exercise training, diabetic kidney disease

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Introduction

Sedentary behavior is associated with metabolic disruption, contributing to the increased incidence of diabetes mellitus (DM). According to the International Diabetes Federation, about 463 million people worldwide have DM, and this number may rise to 700,2 million in 2045.[1] On the other hand, regular physical activity is an important element of the therapeutic plan of diabetic patients, effectively contributing to metabolic control and the prevention of chronic complications.[2] However, the role of exercise in diabetic kidney management is not well established.

Diabetic kidney disease (DKD) is the most common microvascular complication of DM, associated with increased mortality due to cardiovascular disease in diabetic patients,[3] and considered as one of the main causes of end-stage renal disease (ESRD).[4] The main modifiable risk factors associated with the development of DKD include hyperglycemia, hypertension, dyslipidemia, and smoking.[5] Because of its high morbimortality and large socioeconomic costs, it is urgent to identify effective therapeutic strategies against the DKD progression in order to improve the prognosis of these patients.

Experimental studies have shown that early stages of DKD are characterized by glomerular hyperfiltration, adaptive renal hypertrophy, and microalbuminuria, which may be attributed to DM-induced hemodynamic

and metabolic disorders.[6–8] The perpetuation of these conditions leads to dense proteinuria, loss of nephron, and progressive fall in glomerular filtration rate (GFR).[9,10] Hyperfiltration is an initial common stage observed in patients with type 1 diabetes mellitus (T1DM), which predisposes to the development of micro or macroalbuminuria.[11] However, renal hyperfiltration in some diabetic patients was not a risk factor for the development of microalbuminuria.[12] In addition to mesangial expansion and diffuse thickening of the glomerular basement membrane, histological changes in the tubulointerstitial compartment are also consistent feature of DKD. Tubulointerstitial lesions in DKD are characterized by interstitial inflammation, thickening of the tubular basement membrane, tubular atrophy, and interstitial fibrosis.[13]

The pathophysiological mechanisms by which DM causes kidney injury are complex and not fully understood. However, it is well established that the involvement of metabolic and hemodynamic disorders typical of DM converges to extracellular matrix (ECM) accumulation, oxidative stress, renal inflammation, and activation of renin-angiotensin-aldosterone system (RAAS), which are determinant for the onset and progression of tissue lesions.[14–16]

Currently, despite the renoprotective actions of pharmacological therapies available targeting glycemic and blood pressure controls, the incidence of DKD continues to increase.[1] Therefore, new strategies are necessary to prevent or mitigate the progression of DKD and its effects on target organs. Thus, in the last decade, some studies have shown that regular physical activity can improve tissue function and slow the progression of DKD in both experimental animals and humans. In this sense, moderate exercise training, besides benefiting metabolic control, improves the kidney function, reduces microalbuminuria, restores oxidative balance, and increases nitric oxide (NO) bioavailability in streptozotocin (STZ)-induced diabetic rats[6,17] and diabetic patients.[18] Studies with experimental animals from our laboratory reported that moderate-intensity exercise training, especially when initiated before DM induction, improved metabolic control and attenuated the renal function and structure changes in STZ-induced diabetic female rats.[7] Also, our most recent studies suggest that a reduction of oxidative stress and inflammation induced by exercise can contribute to this process.[8,19]

In the present paper, we have briefly reviewed the main pathophysiological mechanisms of DKD and presented the latest findings on the impacts of aerobic exercise on the progression of DKD.

Methods

We searched the PubMed database for English-language articles, and non-English articles were excluded. The initial screening of literature was based on title and abstract, using keywords such as diabetes mellitus; diabetic kidney/renal disease; diabetic nephropathy; physical exercise and exercise training. Targeted searches were conducted using terms such as pathophysiology of diabetic kidney disease, pathogenesis of diabetic kidney disease, and physical exercise in diabetic kidney disease. We made no restrictions on the publication dates of articles.

Pathophysiology and pathogenesis of diabetic kidney disease

DKD is characterized by several morphological changes that involve all sections of the kidney, culminating in renal dysfunctions. Glomerulosclerosis is one of the major histological changes in DKD. However, histological changes in the tubulointerstitial compartment play a key role in the pathogenesis and progression of this disease.[20]

Early renal changes of DKD include glomerular hyperfiltration, thickening of the basement membrane, ECM expansion, and adaptive renal hypertrophy.[7,9,21] However, often the disease can progress with loss of filtration barrier selectivity and reduction of the filtering surface, resulting in high proteinuria and progressive fall in GFR.[9,10] Although hyperfiltration in diabetic patients is also associated with the development of microalbuminuria, some studies have shown that renal hyperfiltration is not a risk factor for the development of microalbuminuria in T1DM.[10,12] Histological changes in the tubulointerstitial compartment, mainly involving the proximal tubule, are also related to disease progression, activating several signaling pathways that culminate in tubulointerstitial inflammation and fibrosis, which result in impaired renal function.[20]

The mechanisms involved in renal injury induced by DM are complex and not fully understood. However, it is evident that hemodynamic and metabolic disorders interact to promote the accumulation of ECM, oxidative stress, and inflammation, which ultimately are responsible for the classic changes that characterize the DKD, as summarized in Figure 1.

Hemodynamic disorders

The renal hemodynamics disorders leading to glomerular hyperfiltration in early stages of DKD can be explained mainly by adaptation of tubular function to hyperglycemic state and imbalance between vasodilator and vasoconstrictor factors. In the distal tubule, reduced sodium concentration in response to increased filtered glucose load and sodium and fluid tubular reabsorption[22] activates tubuloglomerular feedback, resulting in afferent arteriolar vasodilation, increased intraglomerular pressure and hyperfiltration.[22–24] In fact, it has been shown that the expression of sodium-glucose cotransport (SGLT) 2 in the proximal tubules is upregulated in DM, leading to increased proximal reabsorption of sodium.[25] Furthermore, recently it was demonstrated that in response to acute hyperglycemia, the SGLT1-nitric oxide synthase (NOS)1-tubuloglomerular feedback pathway mediates the glomerular hyperfiltration.[26] Although the tubular reabsorption hypothesis is the major mechanism to explain the glomerular hyperfiltration in early DM, other factors associated with hyperglycemia, such as inflammation and oxidative stress, are associated with increase in nitric oxide[27] and angiotensin II (AII) renal production,[28] which

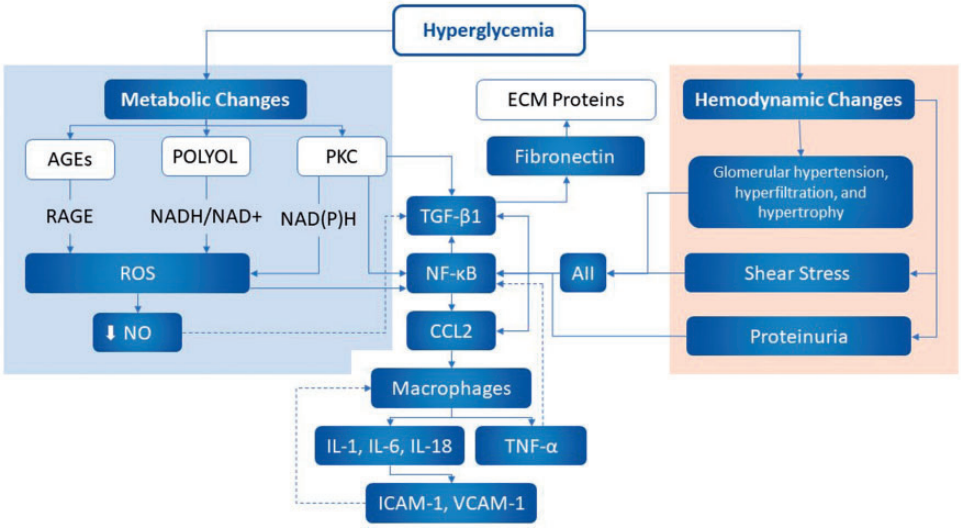

Figure 1. Overview of the pathophysiological mechanisms of diabetic kidney disease. Metabolic changes are related to AGEs formation and activation of the polyol and PKC pathways. These pathways result in the generation of ROS and consequent reduction of NO levels. The NO when reduced exacerbates TGF-β1 bioactivity. ROS and PKC activate NF-κB, which, in turn, increases the expression of TGF-β1 and CCL2. The CCL2 mediates macrophage infiltration, while TGF-β1 increases fibronectin and other ECM proteins (type I, III, IV collagens) deposition. Infiltrated macrophages express pro-inflammatory cytokines such as IL-1, IL-6, IL-18, TNF-α and increase the expression of adhesion molecules that are responsible for facilitating the macrophages infiltration in the diabetic kidney. The TNF-α is also responsible for activating NF-κB. On the other hand, hemodynamic changes are related to AII expression from mesangial cells and shear stress, leading to proteinuria, which directly causes NF-κB activation. Glomerular hypertension and consequent shear stress stimulate local production of AII, which increase NF-κB activation and consequently inflammation. Abbreviations: AGE: advanced glycation end-product; PKC: protein kinase C; NO: nitric oxide; TGF-β1: transforming growth factor-beta 1; ROS: reactive oxygen species; CCL2: C-C motif chemokine ligand 2; ECM: extracellular matrix; IL: interleukin; TNF-α: tumor necrosis factor alpha; NF-κB: nuclear factor-kappa B; AII: angiotensin II. (A color version of this figure is available in the online journal.)

can alter renal vascular tone, leading to increased hydraulic pressure in the glomerular capillaries and consequent hyperfiltration. Together, these phenomena result in increased GFR, compensatory glomerular hypertrophy, and protein passage through the filtration barrier.

On the other hand, the mechanical stress resulting from these hemodynamic changes chronically, besides promoting endothelial shear stress, also stimulates the production of AII and transforming growth factor beta 1 (TGF-β1), which are key molecules for the induction of ECM accumulation and podocyte injury.[9,29] Increased urinary TGF-β1 excretion was associated which proteinuria in patients with diabetic nephropathy.[30] Evidence suggests that increased expression of ECM proteins in the diabetic kidney is mainly mediated by profibrogenic cytokine TGF-β1. The progressive accumulation of ECM is a critical factor in the progression of DKD, present in both humans[31,32] and experimental animals,[7,8] and contributes to the development of glomerulosclerosis and tubulointerstitial fibrosis.[33,34] Under normal conditions, the main mesangial ECM proteins are fibronectin, laminin, type IV collagen (α1 and α2 chains), and proteoglycans.[35,36] However, T1DM metabolic and hemodynamic perturbations activate pathways that lead to imbalance between ECM glycoproteins' synthesis and their degradation, resulting in abnormal protein accumulation, mainly fibronectin, which constitutes a scaffold for the deposition of other proteins, including collagen IV (α3 and α4 chains) and proteins not normally present in healthy glomeruli, such as type I, III, V, and VI collagens.[35,36] High urinary excretion of type IV collagen was related with an annual decline of renal function without overt proteinuria[37] and this relationship may be associated with the degree of glomerular and tubulointerstitial impairment in diabetic patients.[38] Studies from our laboratory have shown that the accumulation of fibronectin and IV collagen was positively correlated with increased TGF-β1 in the kidneys of STZ-induced diabetic female rats.[7] In addition, TGF-β1 stimulated the renal production of type I and III collagens, fibronectin and elastin, and reciprocal inhibition of matrix metalloproteinases and activation of protease inhibitors in STZ-induced diabetic rats.[39]

Metabolic disorders

Accumulation of advanced glycated end-products

Advanced glycated end-products (AGEs) are formed from non-enzymatic glycosylation of proteins, nucleic acids, and lipids after prolonged exposure to the hyperglycemic environment.[40] In the diabetic kidney, AGEs can make stable bonds with long-lived proteins, such as collagen, leading to glomerular basement membrane thickening and inducing greater synthesis of ECM by mesangial cells.[41] Besides, AGEs have been associated with reduced NO vasodilatory and antiproliferative responses.[42] AGEs can also bind to their receptors (RAGE) present in macrophages, podocytes, and mesangial cells, increasing the production of reactive oxygen species (ROS), which activates nuclear factor kappa B (NF-κB). NF-κB, in turn, induces synthesis of inflammatory and profibrotic cytokines and growth factors, such as tumor necrosis factor alpha (TNF-α), TGFβ-1, and vascular endothelial growth factor (VEGF).[43] Thus, the accumulation of AGEs may culminate in increased ECM,

mesangial expansion, tissue injury, and progressive renal function deficit.

Activation of polyol pathway

Chronic hyperglycemia may activate the polyol pathway at supraphysiological levels. The hyperglycemic state and the ROS accumulation activate aldose reductase and sorbitol dehydrogenase, which reduce glucose to sorbitol and sorbital to fructose, respectively.[44] In this pathway, the greater conversion of glucose to sorbitol using nicotinamide adenine dinucleotide phosphate (NADPH) as a co-factor generates oxidation of NADPH to NADP+, and reduction of oxidized glutathione to reduced glutathione.[45] NADPH is required for regenerating reduced glutathione. Therefore, the consumption of NADPH by aldose reductase may lead to decreased antioxidant capacity and oxidative stress. On the other hand, the oxidation of sorbitol to fructose using nicotinamide adenine dinucleotide (NAD+) as a co-factor generates accumulation of NADH.[45] The accumulation of polyol pathway products, with consequent increase in NADH/NAD+ ratio, stimulates the synthesis of diacylglycerol, which is the main physiological activator of protein kinase C (PKC).[46]

Activation of protein kinase C pathways

Chronic hyperglycemia may activate the PKC pathways, which contributes to the pathophysiological process of DKD by increasing oxidative stress and activating pro-sclerotic and pro-inflammatory factors, further increasing tissue damage.[47] Activation of PKC pathways contributes to increased ECM accumulation by inducing expression of TGF-β1, fibronectin and type I, III, and IV collagens in streptozotocin-induced diabetic mice.[48] On the other hand, increased expression of endothelin-1 (ET-1), VEGF, TGF-β, connective tissue growth factor (CTGF), and type IV and VI collagens induced by diabetes in mice were attenuated by the inhibition of PKC.[49] Finally, activation of PKC is capable of activating NF-κB and NAD(P)H oxidase, increasing the expression of multiple pro-inflammatory genes and ROS production, respectively.[45]

Renal inflammation

The inflammatory process participates in the pathophysiology of DKD, and may, at least in part, explain how metabolic and hemodynamic changes of DM converge to development of tissue lesions. Such inflammatory state is mainly characterized by increased pro-inflammatory cytokines, chemokines, adhesion molecules, transcription factors, and immune cells infiltration.[50] However, these features in DKD are considered mild when compared to classic inflammatory diseases, and are therefore termed "microinflammation".[51,52]

The increase in ROS induced by hyperglycemia activates the NF-κB, which stimulates adhesion molecules and expression of proinflammatory genes, including monocyte chemoattractant protein-1 (MCP-1), TNF-α, and interleukin (IL)-6.[53–56] Studies have shown that renal injury was associated with increased expression of NF-κB in STZ-induced diabetic rats.[8,19,57] Activation of NF-κB in renal cells results in increased chemokine CCL2, also known as MCP-1, which is related to macrophage migration to the site of inflammation into kidney tissue.[50,51] This chemokine has also its production increased from renal tubulointerstitial lesions and hyperglycemic environments in response to oxidative stress and the presence of AII.[51]

In addition to attracting macrophages, Tarabra *et al.*[58] demonstrated that increased CCL2 was able to induce downregulation of nephrin, altering podocyte selectivity and contributing to increased proteinuria in streptozotocin-treated mice and human cultured podocytes. On the other hand, macrophages infiltration is correlated with decreased GFR and histological changes in diabetic kidney.[51,59] These macrophages are classified into M1 and M2. M1 macrophages are responsible for pro-inflammatory pathways, while M2 macrophages induce remodeling and resolution of inflammation.[59,60]

Adhesion molecules are critical for the migration of immune cells to injured tissue. The main intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are expressed on the cell surface and their expression is increased by IL-1 and IL-18, respectively.[52] The production of ICAM-1 can be increased by proinflammatory cytokines, shear stress, oxidative stress, activation of PKC and AGEs.[51] Also, adhesion molecules are related to selectin expression and consequently induces leukocyte migration into the field of inflammation.[50,51,59] According to Okada *et al.*[61] and Lim *et al.*,[62] ICAM-1 is elevated in endothelial cells at hyperglycemic milieu and the exclusion of the ICAM-1 gene improved renal inflammation in mice.

Inflammatory cytokines are involved in pathogenesis of DKD.[50,63] IL-1 correlates with prostaglandin E2 production, which has a direct influence on hemodynamics and production of adhesion molecules ICAM-1, VCAM-1, and Selectins E.[51] IL-18 is responsible for the increase of interferon-gamma (IFN-γ), which is related to the induction of TNF-α, TGF-β, and VCAM-1.[52] IL-6 promotes mesangial cells proliferation and increases fibronectin expression and endothelial cell permeability.[54] This cytokine may affect the dynamics of extracellular matrix at mesangial cell and podocytes, promoting to mesangial expansion and glomerular basement membrane thickening.[56] TNF-α is expressed by glomerular and proximal tubule cells. It is related to increased inflammation, endothelial permeability, and cytotoxic pathways.[51] TNF-α induces a variety of biological effects on renal cells including activation of second messengers, transcription factors, synthesis of cytokines, growth factors, and cell adhesion molecules.[64] Macrophages are also responsible for the expression of these cytokines and other pro-inflammatory factors, which contribute to the progression of renal injury.[65,66]

Renin-angiotensin-aldosterone system

The RAAS plays a key role in regulating water, sodium, and blood pressure. However, RAAS is activated by the hyperglycemic state and mechanical stress that raises AII levels in DKD.[66] The glomerulus is affected by AII through

vasoconstrictor action on efferent arteriole, leading to increased intraglomerular pressure.[52,66] Besides, it also alters the permeability of the glomerular basement membrane and results in the worsening of proteinuria.[63] Proteinuria, in turn, is related to increased glomerular expression of NF-κB, which induces TGF-β, MCP-1, ICAM-1, and AGEs accumulation.[52] Thus, proteinuria stimulates the activation of inflammatory pathways and oxidative stress, and contributes to the progression of renal lesions.[50,66]

Importantly, AII is considered a promoter of inflammation and fibrosis by activating NF-κB, MCP-1, TGF-β1, and other proinflammatory cytokines.[66] In addition, AII also culminates in elevated aldosterone levels, that besides to playing a key role in water and sodium retention, may cause toxicity and fibrosis in blood vessels, contributing to the deposition of fibronectin, type I, III, and IV collagens, leading to severe interstitial tubular fibrosis.[63,66]

Type of exercises training recommended for patients with diabetes mellitus

Regular exercise training provides well-being and quality of life, being widely recommended to reduce the risk of cardiovascular problems and cancer in the general population.[67,68] Specifically, regular exercise is an important non-pharmacological method to prevent and treat various metabolic disorders and its complications, including both type 1 (T1DM) and type 2 (T2DM) DM. Although the benefits of exercise in individuals with T2DM are better documented,[69,70] physical activity also promotes beneficial effects in individuals with T1DM in the absence of contraindications and accompanied with all the necessary support for the optimal management of DM.[68,71]

In the over past few decades, a crescent number of studies have been trying to understand the benefits of exercise in various pathological conditions,[72–75] including the renal disease.[76] Usually, physical rehabilitation programs for different human diseases are developed based on the patient's condition, and mainly include the type, frequency, intensity, and duration of exercise.[77,78] Thus, the main types of exercise frequently recommended for patients with DM include aerobic, resistance, combined, and flexibility exercises.[68]

The aerobic exercise involves repeated and continuous movements of large groups of muscles and induces important health benefits including increased insulin sensitivity, mitochondrial density, oxidative enzymes, lung function, immune function, and cardiac output.[67,68] The resistance exercise is characterized by moderate or high intensity physical activity that involves all major muscle groups and activities that use free weights exercise, machines, elastic resistance bands, and even body weight.[78] The benefits of resistance exercise are associated with improved cardiovascular, body mass, physical function, insulin sensitivity, blood pressure, and lipid profile.[78] The association of aerobic and resistance exercises, named combined exercise, is also recommended to optimize health and general cardiovascular benefits, reducing risk factors related to physical inactivity.[79] Other types of physical exercise, such as flexibility, also benefit individuals by stretching the muscles and increasing postural stability and balance, improving movement for other exercises and everyday activities.[67] Table 1 provides additional information regarding the intensity, duration, and frequency of each of these types of exercise recommended in DM.

There are several possible ways to assess exercise intensity in order to better prescribe an exercise protocol.[80] With regard to aerobic exercise, the most used methods to estimate the relative intensity of exercise is the heart rate reserve (%HRR) or oxygen uptake reserve (%VO_2R), maximum heart rate (%HR_{max}), maximum oxygen uptake (%VO_{2max}), and rating of perceived exertion (RPE). Regarding the resistance exercise, the main parameter used to determine the intensity is one-repetition maximum (%1-RM). Table 2 shows the classification of exercise intensity commonly used in practice using these parameters.

Effects of low to moderate aerobic exercise training

Regarding the type of exercise, the table 3 shows the benefits of aerobic exercise training as well as resistance and combined exercise on health parameters in diabetic patient. Aerobic training is considered one of the most effective forms of physical activity in promoting benefits against hyperglycemia-induced complications.[81] Studies have shown that low to moderate intensity aerobic exercise seems to exert renoprotective effects in patients with T1DM and T2DM[18,82–84] and in experimental models of DM.[7,8,85,86] Moderate aerobic exercise improved the insulin sensitivity, glucose uptake[83,87–89] lipid levels, endothelial function, pancreatic beta cell function, and decreased insulin resistance[70,90], tubular injury, and microalbuminuria in

Table 1. Exercise training recommendations for patients with diabetes mellitus.

Type of exercise	Intensity	Duration	Frequency
Aerobic	Moderate to vigorous	At least 150 min/week at moderate to vigorous. For adults able to run steadily at 9.7 km/h for 25 min, 75 min/week	3–7 days/week, with no more than 2 consecutive days without exercise
Resistance	Moderate (15 repetitions) to vigorous (6–8 repetitions)	At least 8–10 exercises with completion of 1–3 sets of 10–15 repetitions to near fatigue per set	A minimum of 2, but preferably 3 nonconsecutive days/week
Flexibility	Stretch to the point of slight discomfort	Hold static or do dynamic stretch for 10–30 s; 2–4 repetitions of each exercise	A minimum 3 days/week

Note: Table adapted.[68]

Table 2. Classification of the relative intensity of aerobic and resistance exercises.

	Aerobic				Resistance exercise
Intensity	**%HRR or VO_2R**	**%HR_{max}**	**%VO_{2max}**	**RPE**	**%1-RM**
Low	30–39	57–63	37–45	9–11	30–49
Moderate	40–59	64–76	46–63	12–13	50–69
High	60–89	64–90	77–95	14–17	70–84

Note: Table adapted.[67]
HRR: heart rate reserve; VO_2R: oxygen uptake reserve; HRmax: maximum heart rate; RPE: rating of perceived exertion; VO_{2max}: maximum oxygen uptake; 1-RM: one-repetition maximum.

Table 3. Benefits of physical training on health parameters in diabetic patients.

Type of exercise	Type 1 diabetes	Type 2 diabetes
Aerobic	• Improves lipid profile • Reduces insulin resistance • Preserves endothelial function • Reduces cardiovascular mortality	• Improves insulin sensitivity and glucose uptake • Improves lipid profile • Improves pancreatic beta cell function • Reduces renal injury and microalbuminuria • Preserves renal function • Reduces inflammation and oxidative stress • Improves blood pressure control • Preserves endothelial function and reduces cardiovascular mortality
Resistance	• Lower risk of hypoglycemia and changes in blood glucose levels compared to aerobic exercise	• Improves glycemic control • Reduces glycated hemoglobin • Improves lean body mass • Improves lipid profile
Combined	• No available evidence	• Improves insulin sensitivity • Reduces fasting insulin and glucose • Reduces glycated hemoglobin • Reduces abdominal subcutaneous and visceral adipose tissue • Increases muscle density • Reduces microalbuminuria • Improves blood pressure control

patients with T2DM.[18] Additionally, a recent study has shown that a calorie-restricted diet associated with this type of exercise reduced inflammation and oxidative stress delayed the development of renal failure by postponing renal fibrosis in patients with T2DM in stage 3 DKD.[90] In patients with T1DM, although some studies have shown that exercise has not improved glycemic control,[91,92] physical activity improves lipid levels, endothelial function, insulin resistance, and reduces cardiovascular mortality, suggesting that moderate aerobic exercise can be also recommended for these patients, including those with chronic kidney disease (CKD).[70,84]

Experimental studies have also shown beneficial effects of exercise on metabolic control as well as on DKD progression. In this sense, aerobic exercise of moderate intensity performed for 12 weeks reduced hyperglycemia, glycated hemoglobin, and systolic and mean blood pressure in obese diabetic rats.[93] In addition, recent studies from our laboratory showed that moderate aerobic exercise, especially when started before induction of DM, improved the metabolic control, preserved the renal structure and function, and reduced proteinuria and local expression of collagen IV and TGF-β1 in type 1 diabetic female rats.[7] We have also demonstrated that this exercise reduced serum creatinine levels, glycosuria, glomerular and tubulointerstitial changes, proteinuria, and lipid peroxidation in ovariectomized diabetic rats.[8,94]

Effects of high aerobic exercise training

The literature presents controversial results about the impact of high-intensity exercise on glucose homeostasis and progression of kidney disease in diabetic individuals. Such controversy may be due to the different methodologies used in the training protocols, types of DM and stage of DKD.[95,96] High-intensity exercise training seems to be a more critical situation for T1DM because these individuals are often more intolerant to exercise and may occur undesirable effects on blood glucose concentrations.[97] In this sense, this type of training increases hepatic glucose production and consequently its levels in the bloodstream,[98,99] which contributes to worsening of DM and its complications, increasing the risk of premature death in these patients. Additionally, clinical[100,101] and experimental studies[102] have shown that high-intensity exercise led to the occurrence of post-exercise hypoperfusion and proteinuria in different types of renal disease due to arteriolar vasoconstrictor action induced by elevated catecholamine plasma

levels, increased renal sympathetic nerve activity, and subsequent formation of AII.[103,104]

On the other hand, patients with T1DM who practiced high-intensity exercise showed lower risk of progression to microalbuminuria than patients who perform low and moderate intensity exercise.[84] This type of exercise was also associated with a lower incidence and progression of kidney disease, as well as a lower risk of cardiovascular events and mortality in patients with DKD.[71,84] Nylen et al.[88] demonstrated that a combined training program of moderate to high intensity (50–80% of HRR) for 12 weeks, in addition to improving the cardiometabolic profile of diabetic patients (T2DM) with mild renal dysfunction (stage 2 and 3), was able to improve the post-exercise estimated GFR by up to 12%.[88] In that study, the authors also demonstrated that 42% of patients with stage 3 DKD improved to stage 2 after the intervention. Besides, high-intensity exercise prevented the albuminuria and glomerulosclerosis in an experimental model of T2DM.[105]

Effects of resistance exercise training

Beneficial effects of resistance exercise have been shown in patients on dialysis, improving the creatinine plasma levels[106] and inflammation markers.[107] Besides, the resistance exercise can also promote benefits to diabetic individuals. In this sense, this type of exercise reduced glycated hemoglobin[108] and improved lean body mass, total cholesterol, low density lipoprotein (LDL)-cholesterol, and triglycerides in T2DM individuals.[108,109] In women with T2DM, the resistance exercise also reduced the concentration of glucose, suggesting that this type of exercise may be an alternative to improve glycemic control in diabetic patients.[110] With regard to the T1DM, the resistance exercise has been less documented. However, this type of exercise was able to induce more stable glucose levels during and after exercise compared to aerobic exercise, inducing less hypoglycemia in these individuals.[111] In agreement with these findings, the resistance exercise also attenuated the risk of exercise-induced hypoglycemia in rats with T1DM.[112]

Effects of combined exercise training

Studies have demonstrated the beneficial effects of combined resistance and aerobic training for glycemic control in diabetic individuals, especially T2DM.[79,113] The combined exercise improved insulin sensitivity and this effect was associated with the loss of abdominal, subcutaneous and visceral adipose tissue and increased muscle density in postmenopausal women with T2DM.[114] Sigal *et al.*[115] demonstrated that aerobic or resistance exercises alone improved the glycated hemoglobin in patients with T2DM. However, glycemic control was greater in patients with T2DM that performed the combined exercise. Thus, Japanese adults submitted to a combined exercise training program improved the fasting insulin and glucose, glycated hemoglobin, and systolic blood pressure and present decreased urinary albumin:creatinine ratio levels.[116]

Pathophysiological mechanisms underlying renoprotective action of exercise training on diabetic kidney disease

The mechanisms by which exercise improves kidney structure and function in individuals with DKD are not fully understood, partly due to the scarcity of clinical studies exploring the effects of different exercise training protocols on pathophysiological pathways involved in disease progression. However, experimental studies have been very useful in this regard, supporting the hypothesis that exercise training provides attenuation of metabolic and hemodynamic changes induced by DM, which converge to reductions of oxidative stress, inflammation, and ECM accumulation in the diabetic kidney, as summarized in Figure 2.

Exercise training improves glucose homeostasis

Skeletal muscle is known to play an important role in glucose homeostasis by increasing insulin-mediated glucose uptake[117] and activation of AMP-activated protein kinase (AMPK) during exercise.[118] Theses mechanisms have been demonstrated in both healthy individuals and patients with T2DM.[119]

With regard to the insulin-dependent pathway, exercise training actives insulin signaling cascade elements, such as insulin receptor substrate 1 (IRS-1), phosphatidylinositol 3-kinase (PI3-K), phosphoinositide-dependent kinase (PDK), atypical protein kinase C (aPKC) and serine/threonine-protein kinases (Akt), inducing GLUT4 expression and translocation to the cell membrane.[89] Holten *et al.*[120] demonstrated that subjects with T2DM had a 40% increase of type 4 glucose transporter (GLUT4) density in the trained muscle when compared to untrained muscle. According to Park *et al.*,[121] the exercise increases GLUT4 expression and translocation in T2DM by increasing the calcium flow during muscle contraction and levels of ADP-ribose/NAADP (cADPR) and d-myo-inositol 1,4,5-triphosphate/nicotinic acid adenine dinucleotide phosphate (NAADP), which results in increased contraction-induced glucose uptake.[121]

On the other hand, AMPK is a kinase that coordinates anabolic and catabolic pathways to balance the supply of nutrients with the demand for energy, both at the cellular level and in the body as a whole.[122,123] When the muscle is stimulated by exercise, the ATP turnover is increased by more than 100 times, which leads to an increase in ATP consumption and a consequent increase in intracellular AMP levels due to the reaction of adenylate kinase.[124] This increase leads to skeletal muscle hyperemia, capillary recruitment, as well as translocation of GLUT4 to the plasma membrane, thereby increasing the uptake of glucose by the muscle,[122,125] as demonstrated in healthy rats[126] and humans.[127] In this sense, it was also demonstrated that exercise increased AMPK $\alpha 2$ activity in both the patients with T2DM and healthy individuals, and this activity was significantly increased by 2.7-fold over basal in T2DM patients.[128] In another study, subjects with T2DM submitted a six-week

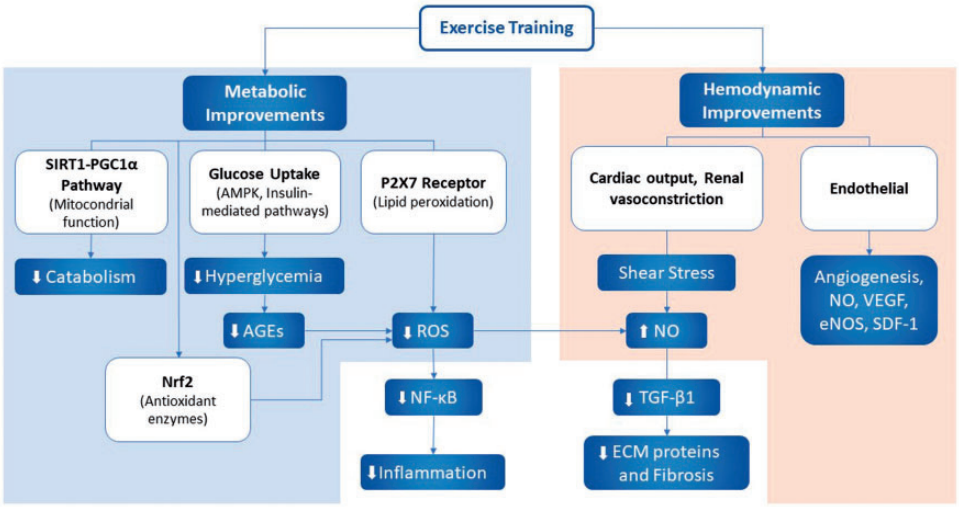

Figure 2. Overview of the exercise training mechanisms attenuating the metabolic and hemodynamic changes of diabetic kidney disease. Exercise promotes metabolic and hemodynamic improvements. Activation of the SIRT1-PGC pathway results in improved mitochondrial function and consequent reduction in muscle catabolism. Glucose uptake is increased by exercise by activating AMPK and insulin-mediated pathways to reduce hyperglycemia, formation of AGEs, and consequently reduction of ROS. Activation of the P2X7 receptor reduces lipid peroxidation and thus attenuates the formation of ROS. Activation of Nfr2 increases the expression of antioxidant enzymes and thus reduces the formation of ROS. Increased cardiac output and renal vasoconstriction provide shear stress, which induces NO production. Elevated NO levels are related to TGF-β1, ECM protein deposition, and fibrosis reductions. Exercise provides angiogenesis and endothelial function by NO, VEGF, eNOS, and SDF-1 production. Abbreviations: SIRT1-PGC: sirtuin 1-gamma coactivator 1-α; AMPK: AMP-activated protein kinase; AGEs: advanced glycation end-products; ROS: reactive oxygen species; Nfr2: nuclear factor erythroid 2-related factor 2; NO: oxide nitric; TGF-β1: transforming growth factor-beta 1; ECM: extracellular matrix; VEGF: vascular endothelial growth factor; eNOS: endothelial nitric oxide synthase; SDF-1: stromal cell-derived factor-1α. (A color version of this figure is available in the online journal.)

strength-training program only in one leg (the other leg remained untrained) present increased protein expression for the α1, β2, and γ1 AMPK subunit isoform in the trained leg when compared to the leg untrained.[119] Taken together, this evidence shows that the AMPK pathway is an important regulator of exercise-mediated glucose homeostasis in both healthy and diabetic individuals.

Exercise training attenuates oxidative stress and inflammation

Literature data have shown that improvement of the catabolic process and up-regulation of antioxidant enzyme activity may be possible mechanisms by which exercise reduces oxidative stress and inflammation, providing attenuation of renal damage in the DKD.[8,19,90] Although few studies have shown the involvement of these mechanisms in humans, recently Dong et al.[90] demonstrated that moderate chronic aerobic exercise plus caloric restriction induced cardiometabolic improvement, reduced the levels of malondialdehyde (lipid peroxidation marker), 8-OHdG (oxidative damage to DNA marker) and IL-6, and increased concomitantly the serum activity of the antioxidant enzyme superoxide dismutase (SOD) in patients with T2DM in stage 3 DKD.[90] However, the set of data available in the literature that support this hypothesis is even greater in experimental studies. Thus, moderate-intensity exercise training reduced the renal lipid peroxidation[8,17,19,86] and increased the glutathione peroxidase (GPx) activity in STZ-induced diabetic rats.[8,86] This type of exercise was also able to reduce advanced glycation in obese diabetic rats[95] and increase the SOD activity in type 2 diabetic model KK-Ay mice.[129] Although the molecular pathway by which exercise attenuates oxidative stress are not fully understood, evidence suggests that exercise training down-regulates the purinoceptor 7 (P2X7), which is related to increased lipid peroxidation in STZ-induced diabetic rat.[86] Other studies demonstrated that exercise up-regulated Sirtuin 1 (Sirt1), the main regulator of mitochondrial function, and increased the mitochondrial complex expression via induction of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) to improve renal enzymatic activity in diabetic mice.[57,85]

Exercise training also increases the nuclear factor erythroid 2-related factor 2 (Nrf2) expression, a transcription factor that up-regulates the antioxidant enzymes and anti-inflammatory cytokines expressions in renal diseases in both patients on dialysis[106,107] and experimental animals.[130,131] The modulation of Nrf2 mediated by exercise can be explained by increased energy demand during physical activity, leading to increase in oxygen consumption and consequent ROS production. The excess of ROS in turn induces a state of temporary oxidative stress that contributes to increased Nrf2 activation.[132]

Studies from our laboratory reported that moderate-intensity aerobic exercise, especially when started before induction of DM, reduced the NF-κB, ED-1 and CD43-positive cells (macrophage and lymphocyte markers, respectively) and attenuated the expression of TGF-β1, fibronectin, and collagen IV in STZ-induced diabetic female rats.[7,8,19] Other studies have also shown that moderate-intensity aerobic exercise suppressed NF-κB activity via restoration of SIRT1 expression in kidney of diabetic db/db mice[57] and reduced the renal expression

of MCP-1.[129] This is important because pro-inflammatory cytokine and chemotactic proteins genes transcription are induced by activation of NF-κB, which leads to further increases in ROS production, creating a cyclic positive feedback mechanism that accelerates the progression of DKD.[133,134]

Exercise training modulates the renin-angiotensin-aldosterone system

Some studies with experimental animals showed the effects of exercise training on classical RAAS components. In the sense, Somineni *et al.*[135] demonstrated that 10 weeks of exercise training program decreased urinary angiotensin-converting enzyme 2 (ACE_2) activity, which was positively correlated to albuminuria, blood glucose, plasma glucagon, and triglycerides and negatively correlated with plasma insulin levels in a model of diabetic rats, suggesting that ACE_2 can be used as a biomarker for DKD.

Studies with other CKD experimental models, besides demonstrating downregulation of RAAS classical components, also showed upregulation of counter-regulatory components of this system. This is important because the effects opposing to the classical arm, such as the ACE_2/Angiotensin (1–7)/Mas receptor axis, are present in anti-inflammatory, vasodilator, antiproliferative, cardioprotective, and renoprotective actions.[136] In this sense, Agarwal *et al.*[133] demonstrated that 16 weeks of aerobic exercise preserved renal structure and hemodynamics by reducing the ACE, angiotensin II receptor type 1 (AT_1R) expressions and plasma AII, besides increasing the ECA_2 and MasR expressions in rats with hypertension-induced CKD. Aerobic exercise also increased the fractional urinary sodium excretion (FE_{Na}), which was associated to reduce the AT_1R, Janus Kinase 2 (JAK-2), and signal transducer and activator of transcription 3 (STAT-3) expressions, and increase the suppressor of cytokine signaling 3 (SOCS-3) and extracellular signal-regulated kinase (ERK1/2) expressions in the kidneys of hypertensive old rats. These effects contributed to the reduction of blood pressure levels found in these animals, thus contributing to the preservation of renal function.[137]

Recently, Magalhães *et al.*[138] investigated the acute effects of two physical exercise protocols, high-intensity-intermittent training (HIIT) and moderate-intensity-continuous training (MICT), on plasma and urinary concentrations of the RAAS components. Thus, these authors demonstrated that the MICT protocol resulted in a decrease in the ACE plasma levels and increased the ACE_2 urine levels, the HIIT protocol induced a significant increase in ACE_2 plasma levels, while both protocols increased Angiotensin (1–7) urine levels in young healthy individuals. These results suggest an enzymatic modulation in both protocols favoring the balance towards the activation of the counter-regulatory axis of RAAS.

Exercise training improves endothelial function

Exercise training can slow the progression of DKD through improvements in endothelial function. Sallam *et al.*[139] reported that moderate-intensity aerobic exercise significantly improved endothelium-dependent relaxation in diabetic mice (db/db). In addition, this type of exercise increased the angiogenesis, NO, and VEGF renal levels, and endothelial nitric oxide synthase (eNOS) and stromal cell-derived factor-1α (SDF-1) expressions. SDF-1 is a chemokine involved in kidney repair in experimental nephrotoxicity models.[140,141]

Furthermore, De Moraes *et al.* proposed that increased endothelial NO production induced by exercise is due to repetitive episodes of increased shear stress resulting from increased cardiac output and renal vasoconstriction. These authors demonstrated in exercised rabbits that increased renal blood flow immediately after a session of physical activity is associated with the increase of antioxidant enzymes, which inactivate ROS, thereby increasing NO bioavailability.[142]

Importantly, NO has been shown to inhibit TGF-β bioactivity and fibronectin synthesis in mesangial cell culture.[143] Increased mesangial expansion, thickening of the glomerular basement membrane, collagen IV expression, and tubulointerstitial fibrosis have been demonstrated in inducible nitric oxide synthase (iNOS) knockout (KO) mice.[144] Other researchers have also pointed to NO as a repressor of ECM expansion and attenuator of tissue fibrosis.[144,145] Thus, it is reasonable to assume that increased NO bioavailability induced by exercise training[19] may contribute, at least in part, to the reduction of TGF-β expression and ECM accumulation in DKD.[7]

Final considerations

In summary, exercise training is considered as an important strategy for achieving metabolic control, glycemic homeostasis, and prevention of DM complications. Therefore, it is particularly important to know the overall effects of different types of exercise in the context that DKD is present. Based on the most recent studies, the evidence suggests that the beneficial effects of exercise on the DKD are directly related to the type and intensity of exercise, as well as the types of DM. Thus, we suggest that the exercise training can contribute positively to improve the health and quality of life of patients with DM, preventing and attenuating the progression of DKD.

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