JOJ Ophthalmology
ISSN: 2473-5477

Juniper Publishers
key to the Researchers

Review Article
Volume 12 Issue 1 - January 2025
DOI: 10.19080/JOJO.2025.12.555828

JOJ Ophthalmol

Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions

Imran Ali[1†], Shoaib Muhammad[2†], Syed Shah Zaman Haider Naqvi[3], Ahmad Mahmood[4], Lingxi Wei[5], Wenqi Yan[6], Pengyu Yan[2], Huifang Wang[2], Huan Li[7], Muhammad Faiz Khan[8], Arshad Mehmood[9], Wahid Shah[10,11*] and Hong Liu[1*]

[1]*Department of Hepatobiliary Surgery, The First Hospital of Shanxi Medical University, China 030001 Taiyuan*

[2]*Department of Urology, The First Hospital of Shanxi Medical University, 030001, Taiyuan, China*

[3]*Department of Endocrinology, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences; Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan 030032, China*

[4]*Department of Hepatobiliary and Echinococcosis Surgery, Digestive and Vascular Surgery Center, First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, China*

[5]*Laboratory of Physiology, Shanxi Medical University, Jing Zhong China 030607*

[6]*Biomedical Science, Shandong University, Ji Nan, Shandong, China 250000*

[7]*Department of Nursing, Jiangxi Maternal and Child Health Hospital, Jiangxi 330000*

[8]*Department of Zoology, Hazara University, Mansehra, Khyber Pakhtunkhwa, Pakistan*

[9]*Department of Neurology, The Second Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei, China*

[10]*School of Basic Medical Sciences, Shanxi Medical University, Taiyuan 030001, China*

[11]*Shanxi Eye Hospital Affiliated to Shanxi Medical University, Taiyuan 030002, China*

[†]*These authors contributed equally.*

Submission: January 03, 2025; **Published:** January 16, 2025

***Corresponding author**: Wahid Shah, School of Basic Medical Sciences, Shanxi Medical University, Taiyuan 030001, China, Shanxi Eye Hospital Affiliated to Shanxi Medical University, Taiyuan 030002, China. Hong Liu, Department of Hepatobiliary Surgery, The First Hospital of Shanxi Medical University, China

Abstract

Purpose: A sedentary lifestyle is associated with an increased likelihood of developing diabetes mellitus. However, regular physical activity helps regulate metabolism, which may help prevent several long-term health issues.

Methods: Diabetic kidney disease is the most prevalent microvascular complication of diabetes mellitus and increases the risk of death from cardiovascular disease in individuals with diabetes. The primary pathophysiological mechanisms leading to tissue damage, extracellular matrix formation, and reduced renal function are oxidative stress, renal inflammation, and activation of the renin-angiotensin-aldosterone system.

Results: Although exercise has proven beneficial in cardiovascular disease, there is a lack of understanding of how it affects the pathophysiological processes that lead to diabetic kidney disease. Moreover, there is a scarcity of physical rehabilitation programs and standardized experimental models for individuals with diabetic renal disease.

Conclusion: This review article provides a concise overview of the pathophysiological mechanisms of diabetic kidney disease and discusses its etiology. It then highlights recent research on the effects of exercise on the development of this disease.

Keywords: Chronic Kidney Disease; Diabetes Mellitus; Diabetic Nephropathy; Resistance; Training

Abbreviations: DKD: Diabetic Kidney Disease; CKD: Chronic Kidney Disease; ESKD: End-Stage Renal Disease; DM: Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetic Mellitus; RAAS: Renin-Angiotensin-Aldosterone System; GFR: Glomerular Filtration Rates; Egfr: Estimated Glomerular Filtration Rate; AMPK: AMP-Activated Protein Kinase; PIKK: Akt/Phosphatidylinositol-3-Kinase/Protein Kinase B; MAPK: Mitogen-Activated Protein Kinase; ESRD: End-Stage Renal Disease; IRS: Insulin Receptor Substrate; GLUT4: Glucose Transporter 4; LKB1: Liver Kinase B1; mTOR: Mammalian Target of Rapamycin; HIIT: High-Intensity Interval Training; CaMKII: Calmodulin-Dependent Protein Kinase II; ROS: Reactive Oxygen Species; Sirt1: Silencing Information Regulator 1; NOS: Nitric Oxide Synthase; GEC: Glomerular Endothelial Cell; NO: Nitric Oxide; ECM: Extracellular Matrix; NF-κB: Nuclear Factor Kappa-B; PKC: Protein Kinase C; Nrf2: Nuclear Factor Erythroid-Related Factor 2; MDA: Malondialdehyde; GSH-Px: Glutathione Peroxidase; iNOS: Inducible Nitric Oxide Synthase; AngI: Angiotensin I; ACE: Angiotensin-Converting Enzyme; AngII: Angiotensin II; AT1R: Angtype II Receptor 1; TGF-β1: Transforming Growth Factor Beta-1; ND: non-disease; RCTs: Randomised Controlled Trials

Introduction

The worldwide escalation in type 2 diabetes mellitus is linked to a growing cardiovascular risk and significant health consequences [1]. Type 2 diabetes can lead to complications such as diabetic nephropathy, a disorder that affects the tiny blood arteries in the kidneys and causes urine protein loss [2]. This can result in kidney damage and a decline in their function [3]. The continuum of renal dysfunction spans from a slight to a severe reduction in nephron count [4]. Pharmacological interventions are the primary method used, although in severe situations, further interventions such as hemodialysis, peritoneal dialysis, kidney transplantation, or other renal replacement therapy may be required. The prevalence of diabetic kidney disease (DKD) in our country has surpassed 24 million individuals, which is attributable to the confluence of economic development and altered lifestyles. The projected expenses for DKD patients with accompanying conditions over the ensuing five years are estimated to reach 148 million [5]. Diabetes mellitus (DM) affects 463 million people globally, and 20% to 40% of DM patients may develop DKD, according to the American College of Sports Medicine [6]. Globally, DKD is not only the primary cause of chronic kidney disease (CKD) and end-stage renal disease (ESKD) but also functions as a distinct risk factor for cardiovascular disease. Furthermore, the incidence of cardiovascular and cerebrovascular diseases, as well as premature mortality, is 20 to 40 times greater in individuals with DKD than in those without DKD [7,8].

DM, a systemic metabolic disorder, can be classified into two types: type 1 diabetes mellitus (T1DM) and type 2 diabetic mellitus (T2DM). T2DM is more prevalent in the development of DM. In the context of T2DM, the disruption of renal metabolism and hemodynamics, as well as their interplay, contribute to the advancement of DKD [9]. The disruption of blood glucose management primarily characterizes the development of DKD, increased oxidative stress and inflammation in the kidneys, and dysregulation of the renin-angiotensin-aldosterone system (RAAS). Clinically, DKD results in glomerular hypertrophy, basement membrane thickening, mesangial hyperplasia, interstitial fibrosis, and other related changes. Current medication treatment of DKD can result in hypoglycemia, hypokalemia, and severe pancreatitis in certain DKD patients [10]. Exercising is a non-pharmaceutical intervention therapy that can improve DKD in many ways, including restoring glomerulus and basement membrane function, reducing interstitial fibrosis, and alleviating renal oxidative stress and inflammatory response (Figure 1). Even though their albuminuria levels are within the normal range, people with type 2 diabetes that begins in childhood, diabetic nephropathy (DN), DKD, or CKD have a higher risk of cardiovascular disease [11,12]. The heightened risks are contributed by metabolic compensation resulting from insufficient glycemic management, hypertension, and dyslipidemia in individuals with DKD/CKD [13,14].

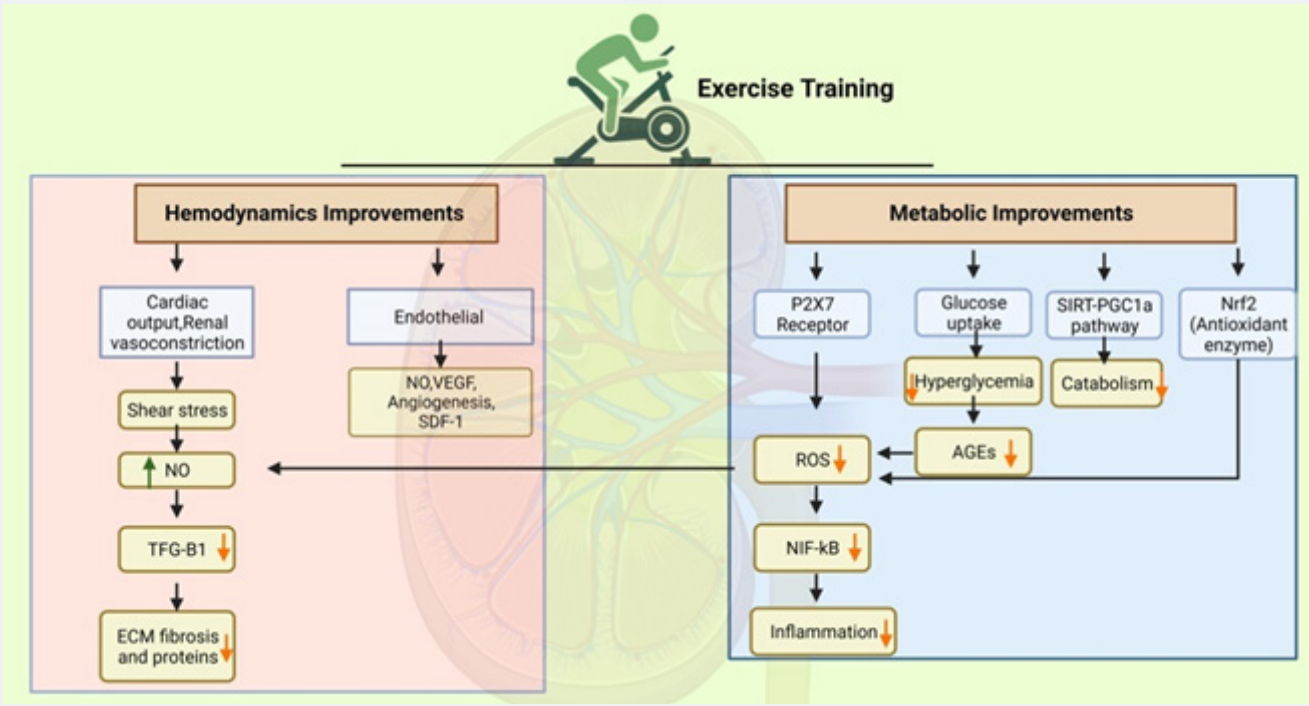

Figure 1: The mechanism by which exercise improves DKD.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

Early screening is crucial, as around 7% of persons diagnosed with type 2 diabetes show signs of microalbuminuria, while 30% with normoalbuminuria experience reduced glomerular filtration rates (GFR) [15,16]. In addition to albuminuria and GFR, current guidelines include evaluating serum creatinine levels [17,18]. The increasing prevalence of diabetes and nephropathy is a significant problem for healthcare providers and carers [19,20]. The identified risk factors for DN and its progression include age, male gender, long duration of diabetes, estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 m2 (indicating early hyperfiltration), systolic blood pressure higher than 130 mm Hg, and chronic proteinuria with concurrent retinopathy [21,22]. These conditions have a negative effect on people's physical abilities, general health, and quality of life. They can cause anemia, exhaustion, pain, dyspnea, sarcopenia, and frailty.

Patients with CKD typically exhibit a substantial decline in physical function, which can range from 50% to 80% compared to healthy individuals. This decrease can be attributed to protein-energy waste, protein breakdown, and mitochondrial dysfunction [23,24]. DN is characterized by the activation of many molecular pathways due to chronic inflammation and hyperglycemia [25,26]. Physical activity and limiting calorie intake have shown promise in delaying the onset of kidney failure and fibrotic alterations [27]. The significance of rehabilitation in renal dysfunction has garnered attention, emphasizing the necessity for more studies to elucidate the renoprotective benefits of exercise. Preventive interventions, early detection, patient education, promotion of lifestyle adjustments, and the incorporation of exercise are critically necessary for patients with type 2 diabetes and nephropathy. This systematic review aims to investigate how exercise affects renal function in individuals with nephropathy and type diabetes mellitus.

Exploring Mechanisms Underlying the Positive Impact of Physical Activity on Chronic Kidney Disease

Organized exercise, even for a brief duration, induces various changes at many tissue levels that may help explain why it is effective in preventing the development or progression of renal disease (Figure 2). The mitigation of the pathophysiological manifestations of DKD is well established. Our objective was to enhance clinical exercise recommendations and heighten the practical relevance of our findings by identifying the types and durations of exercise that yield the most substantial health benefits for individuals with DKD. The beneficial effects of physical activity in the management of DKD are garnering increasing attention. This study concentrated on the potential of individualized exercise programs to operate as crucial supplementary treatments in this context. Our study aimed to evaluate the intricate role of exercise in mitigating the adverse consequences of DKD. Research has demonstrated that patients with DKD can significantly benefit from engaging in aerobic exercises, which enhance cardiovascular fitness and insulin sensitivity [10]. Regular moderate-to-vigorous aerobic activities, such as jogging, swimming, or cycling, can assist individuals with DKD in managing their condition by reducing their blood pressure and improving their glycaemic control. Additionally, resistance training has been found to be as effective as aerobic exercises in enhancing metabolic health and muscle strength.

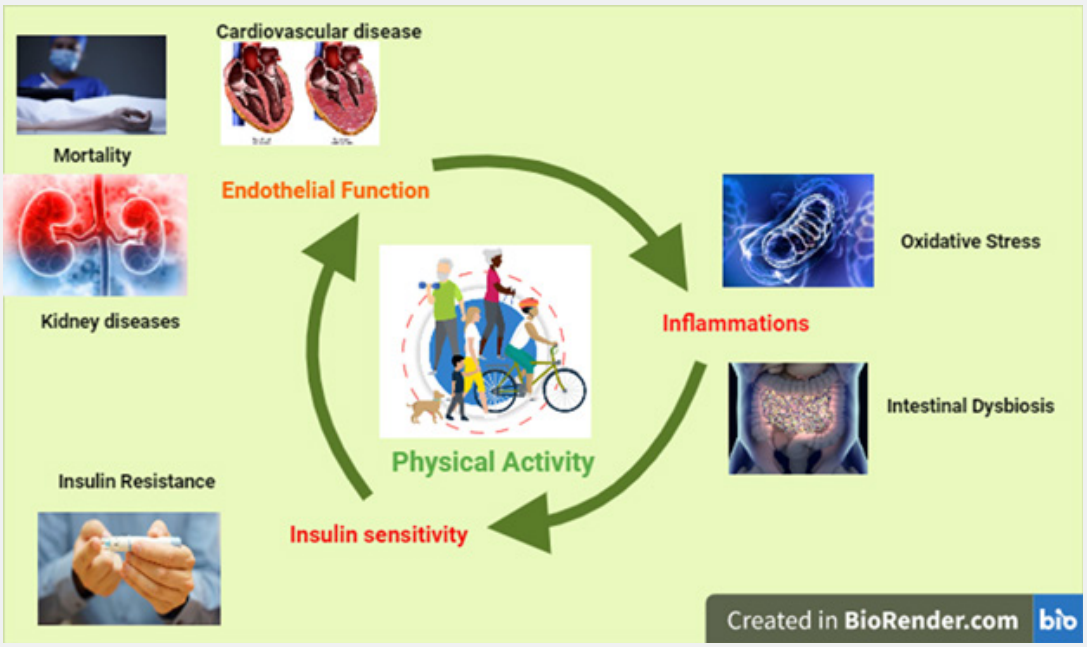

Figure 2: The illustration shows how physical activity positively affects individuals suffering from DKD.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

Weight training and resistance band exercises are examples of this type of physical activity, which helps slow the progression of type 2 diabetes by increasing insulin sensitivity and improving glucose uptake in the muscles [28]. Although aerobic and resistance training are essential components of an exercise regimen for individuals with DKD, it is also recommended that they incorporate balance and flexibility routines for optimal health. Although these exercises may not have an immediate impact on DKD parameters, they play a crucial role in overall disease management, particularly in preventing falls and enhancing the quality of life of those suffering from it. It also emphasizes the significance of customizing exercise schedules and durations, considering each patient's medical history and individual preferences. For patients with DKD, personalized exercise is crucial to maximize therapeutic benefits and ensure adherence. Comprehensive research has demonstrated the central role of exercise in treating DKD, highlighting the forms and quantities of physical activity that yield the most substantial benefits. This review aims to enhance the health outcomes and quality of life of patients with DKD by offering evidence-based, personalized exercise recommendations that cater to their unique requirements. This can be accomplished by refining and informing clinical practices.

Exercise Enhances Endothelial Performance

Physical exercise controls the manufacture of nitric oxide (NO) by increasing the bioavailability of the precursor of NO, L-arginine, and the activity of endothelial NO synthase [29,30]. In addition, engagement in physical activity contributes to the reduction of NO degradation by diminishing the presence of reactive oxygen species (ROS). NO is recognized as an essential paracrine modulator affecting multiple aspects of renal function, such as renal self-regulation, glomerular filtration, renin release [31], and salt excretion as shown that inadequate NO levels have been associated with the decline in renal health, including the exacerbation of ailments like glomerulosclerosis and tubulointerstitial inflammation with fibrosis [32,33].

Physical Exercise Improves Insulin Resistance

Regardless of weight loss, engaging in a single exercise session increases insulin sensitivity. More precisely, it aids in absorbing glucose in skeletal muscle without insulin and triggers the activation of AMP-activated protein kinase (AMPK). As a result, this activation causes the phosphorylation of TBC1D1, a crucial component in controlling intracellular membrane trafficking, which belongs to the Tre-2/BUB2/CDC 1 domain family. TBC1D1 is deactivated through phosphorylation, which facilitates the binding of GTP and Rab proteins on the GLUT4 vesicles. As a result, this process encourages the movement of GLUT4 vesicles from the cytosol to the cell membrane, increasing glucose absorption into the cell [34,35]. Hence, physical activity significantly improves glucose absorption by muscles, regardless of the presence of insulin. Insulin resistance is principally linked with reduced muscle phosphatidylinositol 3-kinase/Akt signaling in advanced renal disease, which may result in heightened catabolism, a restricted anabolic response, and muscle wasting [36,37]. Activating the AMPK Akt/phosphatidylinositol-3-kinase/protein kinase B (PIKK) pathway, insulin resistance leads to hyperinsulinemia even in the initial stages of renal disease. Activation in endothelial cells leads to a decrease in NO generation dependent on Akt and an increase in vasoreactivity dependent on mitogen-activated protein kinase (MAPK). This contributes to the destruction of microvessels [38]. The significance of insulin signaling at the podocyte level is particularly intriguing. Podocytes exhibit a notable ability to respond to insulin to facilitate the uptake and metabolism of glucose. Lab experiments have shown that when podocytes develop insulin resistance, albumin is produced in the urine. This is accompanied by a thickening of the glomerular basement membrane and the development of glomerulosclerosis [39,40]. Nevertheless, it is still unclear whether the enhancement in insulin sensitivity caused by exercise can result in improved podocyte insulin signaling.

Physical Activity Alters Adipose Tissue & Adipocytokines

Research indicates that visceral adipocytes generate several adipocytokines, such as resistin, ghrelin, leptin, TNF-α, plasminogen activator inhibitor-1, and angiotensinogen. These adipocytokines have been found to affect the development of endothelial damage in the kidney, which may contribute to the development of CKD [41]. Weight loss protects against the advancement of CKD [42]. Additionally, decreased levels of inflammation and ROS are linked to modified adipose tissue distribution, especially loss of visceral adiposity. This could lead to better results for the kidneys [43].

Exercises against Diabetic Kidney Disease

Progressive renal failure is a common complication of diabetes in patients who also have proteinuria. Hence, it is of great clinical interest to determine whether physical exercise can slow the progression of renal disease in this population. Although aerobic training has been proven to slow the evolution of nephropathy in rats with type 1 diabetes in animal models [44], there is still a lack of information regarding the effects of exercise on diabetic patients derived from intervention trials. Immediate albuminuria is worsened in individuals with type 2 diabetes who engage in vigorous exercise [45]. Following intense exercise, there is an increase in the levels of Angiotensin-2, which leads to an increase in glomerular membrane permeability. Consequently, the urinary albumin excretion rate also increased. Furthermore, tubular proteinuria may occur when lactic acid generated during exercise enters the tubular lumen and impairs the ability of the proximal tubule to reabsorb proteins [46]. The current state of research on the effects of exercise on nephropathy in individuals with type 1 diabetes lacks extensive randomized controlled studies. In the first study to examine the impact of exercise on microvascular complications in type 1 diabetes, researchers in

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

Pittsburgh discovered that males with higher levels of physical activity both now and when they were adolescents had a lower risk of developing DN and neuropathy. However, this correlation was not observed in women. Additionally, compared with normoalbuminuric patients, microalbuminuric individuals in the FinnDiane cross-sectional survey were less active, which is an intriguing finding [47].

Two large cohorts have provided prospective data on the impact of exercise on nephropathy. Despite the lack of a correlation between exercise and the development of nephropathy, the DCCT cohort, which included patients with newly diagnosed type 1 diabetes, suggested that exercise should be promoted as part of managing type 1 diabetes [48]. Thus, to determine risk factors for DN and other consequences, the FinnDiane study included individuals with type 1 diabetes at different phases of the disease. Over a mean follow-up time of 6.4 ± 3.1 years, 1424 patients with a diabetes duration exceeding 20 years were monitored for changes in albumin excretion rate or the onset of ESKD in a study that examined the impact of exercise on DN [49]. This study represents the first attempt to investigate the relationship between physical activity and DN. Notably, research has revealed that exercise intensity, as opposed to quantity, plays a crucial role in this connection. It was discovered that the higher the intensity, the lower the chances of developing or worsening DN. Surprisingly, this correlation persisted regardless of smoking status, age at diabetes onset, sex, or duration of diabetes. Although the association weakened after adjusting for variables such as triacylglycerol, blood pressure, HbA1c, and body mass index, it remained significant. The study's longitudinal design allows for the possibility of reverse causality. Recent Mendelian randomization data from three large case-control cohorts suggest that obesity is a causative factor in DKD [50]. Consequently, exercise may slow the development of DKD by reducing the prevalence of obesity.

Exercise and Blood Glucose Homeostasis

Hyperglycaemia, a hallmark of type 2 diabetes, arises gradually from factors such as insulin resistance, diminished insulin secretion, and aberrant glucagon metabolism. Moreover, sustained high blood sugar levels within the body ultimately result in DKD [51]. The insulin receptor substrate (IRS) is crucial in transmitting insulin signals and facilitating glucose absorption by skeletal muscle [52]. Previous research has demonstrated that mice lacking IRS1 exhibit peripheral insulin resistance and delayed growth and development; animals lacking IRS2 exhibit metabolic abnormalities in the liver, skeletal muscle, and fat in addition to pancreatic β cell death [53]. Simultaneously, activation of AMPK, a sensor for energy metabolism, also facilitates glucose transporter 4 (GLUT4) in skeletal muscle. GLUT4 protein translocates from intracellular cisterns to cell membranes, facilitating glucose transport from the bloodstream into cells [54]. However, it has been noted that amidst high glucose levels, AMPK and liver kinase B1 (LKB1) undergo dissociation [55]. Furthermore, another study highlighted that the activation of the mammalian target of rapamycin (mTOR) could impede the insulin signal mediated by S6K1 in the skeletal muscle of obese mice who were fed a high-fat diet [56]. IRS1 and IRS2 undergo degradation, leading to diminished glucose absorption and glycogen buildup in skeletal muscle. Additionally, an elevated level of S6K1 phosphorylation in the skeletal muscle of patients with T2DM was observed [57]. Therefore, IRS1 and IRS2 are crucial in maintaining appropriate blood glucose levels, while AMPK protein levels decrease and its signaling pathway is obstructed in conditions of elevated glucose. Conversely, the expression of the mTOR protein is heightened, resulting in the activation of its signaling pathway.

The examination of the relationship between exercise intensity and the advancement of DKD is of paramount importance for the development of more effective therapeutic strategies for this condition. It is crucial to possess a comprehensive understanding of the precise impacts of varying exercise intensities on the progression of DKD in order to develop tailored exercise plans that patients can adhere to at different stages of the disease [58]. The correlation between exercise intensity and its favorable effects on DKD is not strictly linear. A recent study has suggested that moderate-intensity exercise is preferable due to its cardiovascular and metabolic benefits [59]. Such exercises involve a level of exertion that is both achievable and challenging, and they often aid in improving glucose control and regulating blood pressure, which are critical factors in managing DKD. However, it is essential to thoroughly investigate the potential influence and efficacy of high-intensity interval training (HIIT) in this particular group. HIIT, characterized by short bursts of strenuous exercise alternating with rest periods or low-intensity exercise, may offer distinct advantages, including enhanced cardiovascular fitness and insulin sensitivity. This is particularly advantageous for individuals with DKD. It is vital to take into account the impact of exercise intensity while simultaneously prioritizing patient safety and ensuring the exercise routine can be sustained in the long run. While intense exercises may offer specific advantages, they may only be suitable for certain patients, particularly those with advanced stages of DKD or other medical conditions. Therefore, it is essential to conduct a comprehensive evaluation to determine the most appropriate intensity level based on the patient's clinical condition, abilities, and personal preferences. This discussion encompasses the adaptation of workout routines, with a focus on the varying characteristics of DKD and its progression. Patients in the early stages of DKD may derive significant benefits from exercise regimens that differ from those with advanced disease. This underscores the need for a flexible and adaptable approach when prescribing exercises. This adaptive approach should not only consider the disease stage but also incorporate other individual factors, such as age, comorbidities, and overall physical condition.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

The Exercise-Glucose Connection

Research on glucose homeostasis revealed that a 10-week program of aerobic exercise led to an increase in IRS1 protein expression in insulin-resistant rats. Moreover, PI3-K, a protein highly associated with IRS1, is more active in human skeletal muscle during intermittent aerobic activity [60]. Furthermore, it enhances the glucose absorption by GLUT4 in skeletal muscle [61]. Another study showed that moderate-intensity aerobic exercise in rats with DM resulted in higher levels of IRS2 protein content, GLUT4 protein content, and IRS2 phosphorylation [62]. Furthermore, the growing impact of GLUT4 protein content and IRS2 phosphorylation persisted for 48 hours. Meanwhile, through IRS1/PI3-K/AKT/GLUT4, aerobic exercise can alleviate insulin resistance [63]. Hence, physical activity can enhance peripheral insulin resistance by activating the IRS1/PI3-K/AKT/GLUT4 pathway. Aerobic exercise might raise the levels of LKB1 and AMPK proteins in rats but had no discernible effect on the LKB1/AMPK signal in the islet beta cells of insulin-resistant rats [64]. Exercise activates AMPK and its preceding complex, UNC51-like kinase 1, ULK1. Activated ULK1 can enhance islet beta cell activity by phosphorylating autophagy proteins ATG13 and FIP200 [65]. Furthermore, resistance training with a 70% to 80% load was performed on DKD patients, and the patient's blood glucose, glycated hemoglobin, and blood creatinine levels considerably dropped [66]. Hence, physical activity enhances the production of LKB1 and AMPK and maintains blood glucose levels by regulating the autophagy process in islet beta cells.

Exercise Boosts Bone-Related Blood Glucose Control

The role of calcium concentration and the number of calmodulin complexes in muscle contraction is well established. Calmodulin-dependent protein kinase II (CaMKII) is a critical component of the calcium-dependent calmodulin signaling pathway and plays a vital role in enabling skeletal muscles to take up glucose [67]. Meanwhile, It was observed that inhibiting the expression of the CaMKII gene in skeletal muscle resulted in a 35% decrease in CaMK activity and a 30% decrease in glucose intake [68]. However, the amount of GLUT4 protein remained the same, and there was a considerable increase in the degree of AMPK phosphorylationAnother research showed that aerobic exercise could potentially enhance the level of perinuclear phosphorylation of CaMKII in skeletal muscle [69]. Additionally, they observed a 2.2-fold rise in GLUT4 mRNA content and a 1.8-fold increase in protein content of CaMKII. At the same time, it was verified that compared to resting time, AMPK and CaMKII phosphorylation in healthy volunteers' lateral femur muscles rose 2.9 and 2.7 times, respectively, following HIIT [70]. There was no rise in AMPK and CaMKII phosphorylation levels after 3 hours. Hence, achieving a specific intensity level during exercise is imperative to stimulate CaMKII effectively. Additionally, there may be some overlap between CaMKII and AMPK in their regulation of the mechanism responsible for maintaining blood glucose levels in the body.

Exercise Optimizes mTOR for Glucose Homeostasis

Inhibition of the mTOR pathway can result in a reduction in the body's susceptibility to inflammation, proliferation, and autophagy activation. This is because mTOR inhibitors can prevent the activation of mTOR, which is often observed under diseased conditions [71]. It was shown that the high-fat diet group exhibited elevated mRNA expression levels of mTOR and S6K1 [72]. Conversely, aerobic exercise reduced the expression levels of both genes and enhanced the protein levels of PI3K and AMPK. Nevertheless, It was highlighted that aerobic and resistance exercise can enhance the phosphorylation level of mTOR in normal rats, with resistance training resulting in a higher phosphorylation level than aerobic exercise [73]. Simultaneously, previous research has demonstrated that post-exercise, the phosphorylation level of mTOR in healthy individuals' exercised and non-exercised legs increased by 45% to 65%. In contrast, there was a 40% increase in AMPK phosphorylation [71]. Therefore, during disease states, physical activity can enhance AMPK function and inhibit mTOR function, leading to anti-inflammatory, anti-proliferative, and autophagy-promoting responses in the body. In good health, exercise increases the level of mTOR phosphorylation, which may serve as an indicator of metabolic demand. In summary, exercise can improve peripheral insulin resistance and maintain stable blood sugar levels, thus delaying the onset of DKD by regulating the skeletal muscle's glucose uptake through the I RS 1 / GLUT4, AMPK, CaMKII, and mTOR pathways. These pathways are interconnected and exert reciprocal influences on each other.

Exercise Alleviates Renal Stress and Inflammation

Mitochondria regulate the proliferation, differentiation, and inflammation of other cells and produce energy and ROS, as well as mitochondrial self-proliferation and mitochondrial development [74]. As DM mice were given high glucose, their glomerular endothelium cells' respiratory reserve capacity was significantly decreased. Additionally, the kidneys of the mice showed an increase in ROS and poor renal podocyte mitotic activity compared to normal mice [75]. Meanwhile, a decrease in the mRNA level of silencing information regulator 1 (Sirt1) in renal podocytes treated with high glucose was observed [76]. Additionally, they found that progranulin, a precursor of renal granuloprotein in DM mice, was enhanced. Knocking down the PGRN gene resulted in a significant decrease in the expression level of the Sirt1 gene and a considerable increase in the acetylation level of PGC-1α. Extra proteinuria and an amplified renal inflammatory response can result from DKD-related protein misfolding in the endoplasmic reticulum, impacting protein expression and glycosylation. Furthermore, the endoplasmic reticulum can generate a specific quantity of ROS through the process of nitric oxide synthase (NOS) decoupling reaction [77].

The initial sign of DKD is glomerular endothelial cell (GEC) malfunction. Subsequently, the kidneys may become dysfunctional due to prolonged hyperglycemia and elevated ROS. Both NO levels

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

and the expression of the visceral NOS gene were suppressed [78,79]. Furthermore, AGEs persist in the kidney, where they bind to collagen covalently and continue to accumulate. This process not only causes an increase in the thickness of the glomerular basement membrane and stimulates mesangial cells to produce more extracellular matrix (ECM) but also triggers the activation of nuclear factor kappa-B (NF-κB) and PI3K/AKT/mTOR pathways, leading to a decrease in the levels of antioxidant enzymes, glutathione, and NOS [80,81]. Also, the polyol route can increase fructose and decrease coenzyme I (NADH), and an increase in NADH can increase ROS production through the mitochondrial electron respiratory chain, among other things. Additional glycerin can be generated by glycolysis and the tricarboxylic acid cycle [82]. Prolonged elevation of blood sugar levels and diglycerol can also trigger the activation of the protein kinase C (PKC) pathway. This pathway not only suppresses the expression of the NOS gene but also activates the NF-κB pathway [83]. In the meantime, It was shown that the renal tubulointerstitial of DM mice had transformed growth factor-β1 in addition to an increase in PKC mRNA [84]. The mRNA levels of collagen, fibronectin I, fibronectin III, and fibronectin IV were upregulated by TGF-β1. Overall, oxidative stress and inflammation in the kidneys affected by DKD are attributed to various contributing variables. The main contributors to renal oxidative stress and inflammation include renal mitochondrial dysfunction, renal endothelial cell dysfunction, AGE aggregation, the polyol pathway activation, and the PKC pathway. When these factors interact, they can also result in the loss of kidney-related structural function and apoptosis of related cells. In light of this, DKD's trajectory will inevitably deteriorate.

The lack of sufficient data from intervention trials on the effects of exercise in patients with diabetes is a significant challenge in DKD research. This gap underscores the pressing need to thoroughly investigate the intricacies of designing and conducting exercise-based intervention studies in this particular group. It is crucial to address these difficulties and develop strategies to overcome them to advance our understanding and establish evidence-based exercise guidelines for managing DKD. Acquiring a sufficient number of participants who fulfill the specific criteria for DKD can be challenging. Additionally, maintaining their ongoing involvement throughout the study was difficult, mainly because of the extensive time commitment and possible fluctuations in participants' health. The heterogeneity in disease progression, coexisting medical conditions, and individual patient reactions to exercise challenges in establishing standardized intervention protocols. The presence of heterogeneity in a study can diminish the clarity of the outcomes, thereby impeding the ability to derive generalized conclusions. Ensuring compliance with prescribed exercise protocols is a significant obstacle. Physical restrictions, lack of motivation, or absence of immediate benefits may impact participant compliance [85]. Close monitoring is necessary for individuals with different stages of DKD and comorbidities because of the potential risk of adverse events associated with exercise [86]. However, this monitoring method requires a significant amount of resources. Measuring the impact of exercise on DKD progression with precision requires intricate and frequently invasive procedures, which may sometimes only be practical or morally justified.

Recruitment can be improved through the use of social media, patient registries, and community engagement. Offering incentives, ongoing support, and regular feedback can enhance retention. Tailored exercise plans that consider an individual's comorbidity profile, disease stage, and personal preferences can improve adherence and reduce safety risks. The use of telehealth and digital monitoring tools can provide immediate supervision, increase participant involvement, and ensure compliance with exercise protocols [87,88]. By involving a team of healthcare professionals, including nephrologists, endocrinologists, exercise medical specialists, and physical therapists, a comprehensive strategy can be developed to effectively manage participants' health, resulting in improved safety and effectiveness of therapy. A combination of subjective and objective evaluations, such as biomarkers, physical fitness assessments, and patient-reported outcome measures, can be used to assess progress. Extensive calculations are crucial for researchers to devise and execute exercise intervention trials for patients with diabetes, particularly those with DKD. Such endeavors are instrumental in filling the existing gaps in knowledge and devising future clinical protocols, thereby enhancing the quality of care and outcomes for patients with DKD.

Exercise Eases Oxidative Stress in Kidneys

DM-obese rats that participated in 8 weeks of aerobic exercise saw increased NO and eNOS in their kidneys and decreased lipid peroxidation in the renal cortex [89,90]. Levels of endothelial nitric oxide synthase (iNOS) decreased. This intervention effectively reduced the renal sinus fat area of overweight or obese individuals, with the most notable impact observed after six months [91]. Furthermore, It was demonstrated that moderate-intensity aerobic exercise might lower the amount of TGF-β1 mRNA expression in the renal interstitium, the amount of NF-κB gene expression, and the number of macrophages and lymphocytes in the glomerulus of DM mice [92]. Furthermore, researchers noted that aerobic exercise can increase the expression of the SIRT1 gene in the kidneys of mice with DM while inhibiting the acetylation of NF-κB [93]. In the study conducted, it was found that aerobic exercise reduced the level of ROS in the kidneys and enhanced the overall activity of superoxide dismutase in mice with DKD [94]. The protein level of nuclear factor erythroid-related factor 2 (Nrf2) and heme oxygenase-1 in proximal tubules can also be increased through the Nrf2/HO-1 pathway. Higher protein concentration was observed in HO-1. Furthermore, in a clinical setting, it was implemented a regimen of lower limb power cycling three times per week for 4 weeks to engage dialysis

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

patients in physical exercise [95]. The objective was to decrease the concentration of malondialdehyde (MDA) in the bloodstream. Remarkably, the MDA levels significantly reduced after 16 weeks of continuous exercise. On the other hand, while the mRNA expression levels of Nrf2 mRNA and glutathione peroxidase (GSH-Px) increased after the three months of anti-resistance exercise administered to patients with CKD, the expression levels of NF-κB did not shift significantly [96]. Simultaneously, It was noted that the levels of uric acid, ROS, and inducible nitric oxide synthase (iNOS) protein in healthy rats were markedly elevated compared to the control group following intense anti-resistance exercise [97]. These changes were accompanied by increased glomerular volume, the basement membrane's thickening, and the mesangial matrix's proliferation. In summary, the activation of the Nrf2/NF-κB, SIRT1/NF-κB, and Nrf2/HO-1 pathways, as well as the upregulation of antioxidant enzyme activity and an increase in NO production, are the mechanisms by which exercise intervenes on renal oxidative stress and inflammation in DKD. Further research is necessary to determine whether resistance exercise is appropriate for clinical joint intervention and how to arrange the amount of exercise, even though it can raise the expression levels of Nrf2 and GPS-Px. It is also unclear how precisely resistance exercise affects DKD.

Exercise Influence on the Renin-Angiotensin-Aldosterone Pathway

The RAAS is extensively present throughout the human body and is crucial in maintaining the balance of blood flow dynamics. This is achieved by carefully controlling the equilibrium of water, electrolytes, and circulating blood pressure. The RAAS consists of two axes: vasoconstrictor and vasodilator. Within the ascending axis, renin catalyzes the conversion of angiotensinogen into angiotensin I (AngI), which is subsequently transformed into AngII by angiotensin-converting enzyme (ACE). Angiotensin II (AngII) is the primary regulator of the up-pressure axis by interacting with Angtype II receptor 1 (AT1R). This interaction causes constriction of tiny arterioles throughout the body, stimulates the kidneys to reabsorb water and sodium, and releases aldosterone. The depressor axis consists of ACE2, endogenous heptapeptide, AT2R, and Mas receptors [98,99]. In DKD, the ascending axis of the RAAS is constantly stimulated, leading to elevated pressure in the glomerular vein and glomerulus. This, in turn, increases the production of AngII and ROS, resulting in an increase in ECM and the production of transforming growth factor beta-1 (TGF-β1) by mesangial cells. Ultimately, this leads to glomerular sclerosis and fibrosis [100]. The study found that ACE2-transfected DM rats exhibited lower blood pressure, renal sclerosis index, and urine protein excretion [101].

Additionally, endothelial development was linked to TGF-β1 and vascular endothelial growth factor. In superoxide dismutase activity, Ang-(1-7) concentration and the content of Nephrin, a protein associated with podocytes. Thus, in the case of DKD, the ascending axis of the RAAS is excessively stimulated, leading to elevated levels of renal AngII and its associated downstream components. Conversely, the descending axis, renal ACE2, and its associated downstream components are suppressed. The RAAS can increase blood pressure through direct effects on the smooth muscle of tiny arteries and indirectly by promoting the synthesis of aldosterone. Simultaneously, AngII can stimulate aldosterone production by acting on the circular layers of the adrenal cortex [102]. Furthermore, it was observed that the mRNA expression level of renal aldosterone synthetase in DM rats was 12 times higher than in control rats [103]. Furthermore, they found that administering an AT1R antagonist reduced the mRNA expression level of renal aldosterone synthetase. Furthermore, It was highlighted in a separate study that while the blood glucose and kidney aldosterone levels in rats with double adrenal resection and DM were elevated, the plasma aldosterone levels were reduced [104]. Furthermore, following the administration of aldosterone synthetase inhibitors, the blood glucose levels of diabetic rats remained unaltered. The levels of renal aldosterone, NF-κB, and TGF-β1 protein were reduced. Thus, in the context of DKD, the systemic aldosterone system can contribute to the control of the local aldosterone system, and the elevation of local aldosterone levels in the kidney can intensify the kidney's inflammatory response and further accelerate the progression of DKD.

Motion's Impact on Renin-Angiotensin-Aldosterone

Research indicates that physical activity can activate the ACE2/Ang-(1-7)/Mas axis and inhibit the ACE/AngII/AT1R axis [105]. Healthy participants could also raise the amount of Ang-(1–7) in their urine after exercise and maintain their AngII content at a low level [106]. It was found that both aerobic exercise and a combination of aerobic exercise and metformin intervention can decrease the expression level of urine ACE2 in DM mice [107]. This reduction was observed as early as the 2nd week and continued until the 10th week. Furthermore, DM mice's glomeruli showed higher levels of ACE2 expression following exercise compared to the control group. In the meantime, DM patients with low daily living activities saw increases in their glomerular filtration rate, blood creatinine level, and glycosylated haemoglobin level in the 4-year follow-up survey [108]. Conversely, moderately intense daily living activities could lower the above metabolic level, lessening the adverse effects on the kidneys. Furthermore, It was observed that the serum aldosterone level in obese rats was notably elevated compared to the control group [109]. However, following exercise intervention, the serum aldosterone level in obese rats was significantly reduced. In contrast, It was found that performing 95% OIC exercise led to a substantial increase in serum aldosterone and AngII concentrations in healthy individuals [110]. However, no significant difference was observed between the two groups in the subgroup with less than 75% participation. The OIC exercise exhibits a rising tendency compared to the silent group. However, it is not statistically significant. Furthermore, It was shown that ascending stairs in the early stages of DKD patients results in elevated levels of urine microalbumin and urinary transferrin immunoglobulin excretion [111,112].

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

In the context of DKD, physical activity can stimulate the ACE2/Ang-(1-7)/Mas pathway in the RAAS system, leading to a decrease in pressure within the glomerular vein and glomerulus. This, in turn, reduces the production of AngII, ROS, ECM, and TGF-β1, reducing kidney inflammation and the extent of glomerular sclerosis and fibrosis. After exercise, the ascending pressure axis-controlled aldosterone production also decreased simultaneously. In healthy individuals, the rise in serum aldosterone levels following exercise promotes the reabsorption of sodium ions in bodily fluids and helps maintain a balanced circulating blood volume. Furthermore, engaging in high-intensity exercise might lead to an imbalance in the RAAS.

The Impact of Culture on Physical Rehabilitation

Cultural values and traditions surrounding health, illness, and physical activity can have a significant impact on an individual's readiness to participate in rehabilitation programs that involve exercise [113,114]. In some cultures, a more rest-oriented approach may be favored when someone is unwell, while in others, a greater emphasis may be placed on natural or holistic remedies rather than structured exercise routines. The influence of family and community, which varies greatly across cultures, can also affect an individual's participation in rehabilitation programs. Family involvement is crucial in certain cultures for adhering to treatment plans and making healthcare decisions. Disparities in health literacy and communication styles across cultures can also impact how individuals from different backgrounds understand and interact with healthcare providers regarding the use of exercise as a therapeutic intervention. Culturally sensitive communication can help healthcare providers engage with patients and enhance patient education. The effectiveness of physical rehabilitation programs and the use of fitness centers are heavily influenced by an individual's socioeconomic status [115]. Those with lower status may require assistance in the form of facilities, recreational parks, or safe pedestrian zones. The costs associated with these activities, such as transportation, program fees, and lost wages, can be prohibitively high for individuals with restricted financial resources. In areas with limited resources, healthcare priorities often focus on acute care and infectious diseases, whereas chronic disease management, including physical rehabilitation for DKD, may receive less attention [116].

Discrepancies in accessibility, adherence, and efficacy of physical rehabilitation programs for DKD may stem from the interplay of cultural and socioeconomic factors. Individuals from culturally diverse backgrounds or lower socioeconomic statuses may encounter hindrances when attempting to access healthcare services, which can result in diminished participation in rehabilitation programs and, consequently, suboptimal health outcomes. Thus, to enhance patient participation and adherence, it is crucial to develop exercise and rehabilitation plans that are culturally sensitive and respectful of patient customs and values [117]. Furthermore, utilizing community resources to provide accessible and affordable rehabilitation services can help alleviate socioeconomic barriers. Advocating policies that increase the availability of rehabilitation services for marginalized and economically disadvantaged populations is essential. Conducting research aimed at understanding and addressing cultural and socioeconomic obstacles to effectively managing DKD can provide invaluable insights and inform the development of more targeted interventions. A comprehensive examination of these variables would emphasize the importance of holistic and inclusively managing DKD, leading to more equitable healthcare outcomes for diverse populations.

Conclusions and Future Prospective

In summary, the existing evidence suggests that physical activity may have a positive impact on risk factors associated with disease progression; however, the precise impact on renal function is still under debate [118]. The conclusions reported in recent meta-analyses are influenced by variations in the methodologies and studies included. This ambiguity is further compounded by the diverse methodologies employed in different studies, particularly with regard to the duration and intensity of the exercise programs. Additionally, the commitment of participants to the exercise program is another factor that complicates the establishment of a definitive result.DKD is a form of CKD caused by DM [119,120]. The primary mechanism underlying its development involves the disruption of renal metabolism and hemodynamics due to prolonged exposure to high glucose levels. Exercise delays the progression of DKD by improving glucose regulation, reducing oxidative stress and inflammation in the kidneys, and controlling the RAAS. However, further research is needed to fully understand the precise mechanisms and pathways through which exercise exerts these effects. It is important to note that DKD follows a well-defined trajectory and stage during clinical diagnosis. Patients with CKD often face several barriers that hinder their ability to exercise, which can lead to non-adherence to their treatment plans [121,122]. This complexity highlights the real-world impact of exercise training and complicates the evaluation of the effectiveness of recommended programs. It is crucial to concentrate on making exercise training programs more accessible and motivating to increase compliance, ideally without decreasing the physiological load. Using this approach, researchers can be confident that their investigations will continue to address this core scientific subject. Additional research is necessary, as our understanding of the systems that regulate the influence of exercise on renal function still needs to be improved. Future studies examining the impact of exercise on the progression of DKD should focus on selecting patients with the highest likelihood of benefiting from the intervention. Thus, to accomplish this, it is essential to have a better understanding of the processes by which the kidneys adapt to exercise in order to (1) identify individuals who are at risk of developing the disease and (2) target populations where exercise-induced adaptations are likely to have the most significant effect.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

According to current guidelines, patients with non-disease (ND-CKD) ought to engage in moderate aerobic exercise for 150 minutes per week, with strength and flexibility training added at least two days a week [107]. Research in this area should encompass both aerobic and resistance exercises, as they are frequently included in studies that assess their effects on DKD risk variables. Resistance training is particularly important as it encompasses processes that affect inflammatory levels, some of which depend on muscle stretching or have been observed in resistance-only programs. Furthermore, it is unreasonable to exclude either aerobic or resistance exercise, as both have demonstrated advantages for DKD unrelated to kidney function. While the effects of exercise on the course of CKD remain uncertain, there is no evidence of a negative impact from randomized controlled trials (RCTs) thus far. However, it would be premature to include exercise training in licensing or national guidelines based solely on this lack of evidence. Although there is no evidence that exercise interventions harm kidney function, there are several other benefits of increased physical activity. Therefore, doctors should recommend and prescribe exercise more frequently. However, existing studies on the correlation between exercise interventions and DKD require further investigation. Moreover, given the significant risk that DKD poses for cardiovascular disease, it is crucial to conduct exercise load testing before engaging in physical activity to determine the appropriate exercise intensity for a patient's condition. Future studies, such as cost-effectiveness assessments, may provide sufficient data to support the integration of exercise training with standard care.

Acknowledgment

We express our sincere gratitude to all the participants who generously volunteered their time and effort to take part in this study. Their valuable contributions have significantly advanced our understanding of this field. Additionally, we extend our appreciation to the Natural Science Foundation of Shanxi Province.

Author Contributions

Imran Ali and Shoaib Muhammad designed the review. Syed Shah Zaman Haider Naqvi and Ahmad Mahmood created figures. Lingxi Wei and Wenqi Yan collected data from the literature. Pengyu Yan and Huifang Wang provided guidelines. Huan Li, Muhammad Faiz Khan, and Arshad Mehmood drafted, proofread, and revised the manuscript. Wahid Shah and Hong Liu supervised the review. All authors have read and agreed to the published version of the manuscript.

Funding

This project was funded by the General Project of the Natural Science Foundation of Shanxi Province (201901D111350).

Data Availability Statement

Data available on request from the authors.

References

1. Pálsson R, UD Patel (2014) Cardiovascular complications of diabetic kidney disease. Advances in chronic kidney disease 21(3): 273-280.
2. Gross JL, Mirela J de Azevedo, Sandra P Silveiro, Luís Henrique Canani, Maria Luiza Caramori, et al. (2005) Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes care 28(1): 164-176.
3. Belete R, Zerihun Ataro, Ahmedmenewer Abdu, Merga Sheleme (2021) Global prevalence of metabolic syndrome among patients with type I diabetes mellitus: A systematic review and meta-analysis. Diabetology & Metabolic Syndrome 13(1): 1-13.
4. Shaw AD, Ashish K Khanna, Nathan J Smischney, Apeksha V Shenoy, Isabel J Boero, et al. (2022) Intraoperative hypotension is associated with persistent acute kidney disease after noncardiac surgery: a multicentre cohort study. British journal of anaesthesia 129(1): 13-21.
5. George C, Justin B Echouffo-Tcheugui, Bernard G. Jaar, Ikechi G. Okpechi, Andre P. Kengne (2022) The need for screening, early diagnosis, and prediction of chronic kidney disease in people with diabetes in low- and middle-income countries-a review of the current literature. BMC medicine 20(1): 1-12.
6. Kanaley JA, Sheri R Colberg, Matthew H Corcoran, Steven K Malin, Nancy R Rodriguez, et al. (2022) Exercise/physical activity in individuals with type 2 diabetes: a consensus statement from the American College of Sports Medicine. Medicine and science in sports and exercise 54(2): 353-368.
7. Ricciardi CA, L Gnudi (2021) kidney disease in diabetes: From mechanisms to clinical presentation and treatment strategies. Metabolism 124: 154890.
8. Yang W, Ning Ding, Ran Luo, Qian Zhang, Zhenhua Li, et al. (2023) Exosomes from young healthy human plasma promote functional recovery from intracerebral hemorrhage via counteracting ferroptotic injury. Bioactive Materials 27: 1-14.
9. Warren AM, ST Knudsen, ME Cooper (2019) Diabetic nephropathy: an insight into molecular mechanisms and emerging therapies. Expert opinion on therapeutic targets 23(7): 579-591.
10. Liliany Souza de Brito Amaral, Cláudia Silva Souza, Hernando Nascimento Lima, Telma de Jesus Soares (2020) Influence of exercise training on diabetic kidney disease: A brief physiological approach. Experimental Biology and Medicine 245(13): 1142-1154.
11. Amatruda, M., et al. (2021) The aggressive diabetic kidney disease in youth-onset type 2 diabetes: pathogenetic mechanisms and potential therapies. Medicina 57(9): 868.
12. Ene-Iordache B, Perico N, Bikbov B, Carminati S, Remuzzi A, et al. (2016) chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study. The Lancet Global Health 4(5): e307-e319.
13. Adler AI, Richard J Stevens, Sue E Manley, Rudy W Bilous, Carole A Cull, et al. (2003) Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney International 63(1): 225-232.
14. Okojie J, S McCollum, J Barrott (2023) The Future of Antibody Drug Conjugation by Comparing Various Methods of Site-Specific Conjugation. Discov. Med 35: 921-927.
15. Gerstein HC, JF Mann, Q Yi, B Zinman, S F Dinneen, et al. (2001) Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. Jama 286(4): 421-426.
16. MacIsaac RJ, Con Tsalamandris, Sianna Panagiotopoulos, Trudy J Smith, Karen J McNeil, et al. (2004) Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes care 27(1): 195-200.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

17. Kramer HJ, Quan Dong Nguyen, Gary Curhan, Chi-Yuan Hsu (2003) Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. Jama 289(24): 3273-3277.

18. Norris KC, Karen E Smoyer, Catherine Rolland, Jan Van der Vaart, Eliza Beth Grubb (2018) Albuminuria, serum creatinine, and estimated glomerular filtration rate as predictors of cardio-renal outcomes in patients with type 2 diabetes mellitus and kidney disease: a systematic literature review. BMC nephrology 19(1): 1-13.

19. Zhou Z, Paresh Chaudhari, Hongbo Yang, Anna P Fang, Jing Zhao, et al. (2017) Healthcare resource use, costs, and disease progression associated with diabetic nephropathy in adults with type 2 diabetes: a retrospective observational study. Diabetes Therapy 8(3): 555-571.

20. Chen Y, Y He, G Xing (2023) Using Machine Learning to Identify Risk Factors and Establishing a Clinical Prediction Model to Predict Atherosclerosis Complications in Idiopathic Membranous Nephropathy. Discovery Medicine 35(177): 517-524.

21. Elshahat S, Paul Cockwell, Alexander P Maxwell, Matthew Griffin, Timothy O'Brien, et al. (2020) The impact of chronic kidney disease on developed countries from a health economics perspective: a systematic scoping review. PloS one 15(3): e0230512.

22. Alwakeel JS, Arthur C Isnani, Abdulkareem Alsuwaida, Ali Alharbi, Shaikh Ahmed Shaffi, et al. (2011) Factors affecting the progression of diabetic nephropathy and its complications: a single-center experience in Saudi Arabia. Annals of Saudi medicine 31(3): 236-242.

23. Tamaki M, Kazutoshi Miyashita, Shu Wakino, Masanori Mitsuishi, Koichi Hayashi, (2014) Chronic kidney disease reduces muscle mitochondria and exercise endurance and its exacerbation by dietary protein through inactivation of pyruvate dehydrogenase. Kidney international 85(6): 1330-1339.

24. Tamaki M, Aika Hagiwara, Kazutoshi Miyashita, Shu Wakino, Hiroyuki Inoue, et al. (2015) Improvement of physical decline through combined effects of muscle enhancement and mitochondrial activation by a gastric hormone ghrelin in male 5/6Nx CKD model mice. Endocrinology 156(10): 3638-3648.

25. Yaribeygi H, AE Butler, A Sahebkar (2019) Aerobic exercise can modulate the underlying mechanisms involved in the development of diabetic complications. Journal of cellular physiology 234(8): 12508-12515.

26. Yao H, Anqi Zhang, Delong Li, Yuqi Wu, Chong-Zhi Wang, et al. (2024) Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. Bmj 384: e076410.

27. Dong L, Jie Li, Yu Lian, Zu-Xia Tang, Zheng Zen, et al. (2019) Long-term intensive lifestyle intervention promotes improvement of stage III diabetic nephropathy. Medical science monitor: international medical journal of experimental and clinical research 25: 3061-3068.

28. Colberg SR, Ronald J Sigal, Jane E Yardley, Michael C.Riddell, David W Dunstan, et al. (2016) Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes care 39(11): 2065.

29. Nosarev AV, Lyudmila V Smagliy, Yana Anfinogenova, Sergey V Popov, Leonid V Kapilevich (2015) Exercise and NO production: relevance and implications in the cardiopulmonary system. Frontiers in cell and developmental biology 2: 73.

30. Guo W, Zengliang Zhang, Lingru Li, Xue Liang, Yuqi Wu, et al. (2022) Gut microbiota induces DNA methylation via SCFAs predisposing obesity-prone individuals to diabetes. Pharmacological Research 182: 106355.

31. Baylis C (2008) Nitric oxide deficiency in chronic kidney disease. American Journal of Physiology-Renal Physiology 294(1): F1-F9.

32. Wagner L, Janet D Klein, Jeff M Sands, Chris Baylis (2002) Urea transporters are distributed in endothelial cells and mediate inhibition of L-arginine transport. American Journal of Physiology-Renal Physiology 283(3): F578-F582.

33. Hu B, Promi Das, Xianglin Lv, Meng Shi, Jiye Aa, et al. (2022) Effects of 'healthy'fecal microbiota transplantation against the deterioration of depression in fawn-hooded rats. Msystems 7(3): e0021822.

34. Bird SR, John A Hawley (2017) Hawley, Update on the effects of physical activity on insulin sensitivity in humans. BMJ open sport & exercise medicine 2(1): e000143.

35. Zhu Y, Ruiqi Huang, Zhourui Wu, Simin Song, Liming Cheng, et al. (2021) Deep learning-based predictive identification of neural stem cell differentiation. Nature Communications 12(1): 2614.

36. Bailey JL, Bin Zheng, Zhaoyong Hu, S Russ Price, William E Mitch (2006) chronic kidney disease causes defects in signaling through the insulin receptor substrate/phosphatidylinositol 3-kinase/Akt pathway: implications for muscle atrophy. Journal of the American Society of Nephrology 17(5): 1388-1394.

37. Roshanravan B, Leila R Zelnick, Daniel Djucovic, Haiwei Gu, Jessica A Alvarez, et al. (2018) Chronic kidney disease attenuates the plasma metabolome response to insulin. JCI insight 3(16): e122219.

38. De Cosmo S, C Menzaghi, S Prudente, V Trischitta (2013) Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. Nephrology Dialysis Transplantation 28(1): 29-36.

39. Welsh GI, Lorna J Hale, Vera Eremina, Marie Jeansson, Yoshiro Maezawa, et al. (2010) Insulin signaling to the glomerular podocyte is critical for normal kidney function. Cell metabolism 12(4): 329-340.

40. Zhao X, Yumeng Zhang, Yili Yang, Jay Pan (2022) Diabetes-related avoidable hospitalisations and its relationship with primary healthcare resourcing in China: A cross-sectional study from Sichuan Province. Health & Social Care in the Community 30(4): e1143-e1156.

41. Zoccali C, Francesca Mallamaci (2011) Mallamaci, Adiponectin and leptin in chronic kidney disease: causal factors or mere risk markers? Journal of Renal Nutrition 21(1): 87-91.

42. Straznicky NE, Mariee T Grima, Elisabeth A Lambert, Nina Eikelis, Tye Dawood, et al. (2011) Exercise augments weight loss induced improvement in renal function in obese metabolic syndrome individuals. Journal of hypertension 29(3): 553-564.

43. Kang SH, Kyu Hyang Cho, Jong Won Park, Kyung Woo Yoon, Jun Young Do (2015) Association of visceral fat area with chronic kidney disease and metabolic syndrome risk in the general population: analysis using multi-frequency bioimpedance. Kidney and Blood Pressure Research 40(3): 223-230.

44. Keng-Hee Koh, Bolonghoge Dayanath, James Cg Doery, Kevan R Polkinghorne, Helena Teede, et al. (2011) Effect of exercise on albuminuria in people with diabetes. Nephrology 16(8): 704-709.

45. Rodrigues AM, Cássia T Bergamaschi, Ronaldo C Araújo, Margaret G Mouro, Thiago S Rosa, et al. (2011) Effects of training and nitric oxide on diabetic nephropathy progression in type I diabetic rats. Experimental Biology and Medicine 236(10): 1180-1187.

46. Bellinghieri GV (2008) Savica, and D. Santoro, Renal alterations during exercise. Journal of Renal Nutrition 18(1): 158-164.

47. Johan Wadén, Carol Forsblom, Lena M Thorn, Markku Saraheimo, Milla Rosengård-Bärlund, et al. (2008) Physical activity and diabetes complications in patients with type 1 diabetes. Diabetes care 31(2): 230-232.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

48. Makura CB, Krishnarajah Nirantharakumar, Alan J Girling, Ponnusamy Saravanan, Parth Narendran (2013) Effects of physical activity on the development and progression of microvascular complications in type 1 diabetes: retrospective analysis of the DCCT study. BMC Endocrine Disorders 13(1): 1-6.

49. Wadén J, Heidi K Tikkanen, Carol Forsblom, Valma Harjutsalo, Lena M Thorn, et al. (2015) Leisure-time physical activity and development and progression of diabetic nephropathy in type 1 diabetes: the FinnDiane Study. Diabetologia 58(5): 929-936.

50. Todd JN, Emma H Dahlström, Rany M Salem, Niina Sandholm, Carol Forsblom, et al. (2015) Genetic evidence for a causal role of obesity in diabetic kidney disease. Diabetes 64(12): 4238-4246.

51. Nuha A ElSayed, Grazia Aleppo, Vanita R Aroda, Raveendhara R Bannuru, Florence M Brown, et al. (2022) 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of medical care in diabetes-2022. Diabetes Care 45(Supplement_1): S113-S124.

52. Machado-Neto JA, Bruna Alves Fenerich, Ana Paula Nunes Rodrigues Alves, Jaqueline Cristina Fernandes, Renata Scopim-Ribeiro, et al. (2018) Insulin Substrate Receptor (IRS) proteins in normal and malignant hematopoiesis. Clinics 73(suppl 1): e566s..

53. Long YC, Zhiyong Cheng, Kyle D Copps, Morris F White (2011) Insulin receptor substrates Irs1 and Irs2 coordinate skeletal muscle growth and metabolism via the Akt and AMPK pathways. Molecular and cellular biology 31(3): 430-441.

54. Han JH, MT Kim, CS Myung (2022) Garcinia Cambogia Improves High-Fat Diet-Induced Glucose Imbalance by Enhancing Calcium/CaMKII/AMPK/GLUT4-Mediated Glucose Uptake in Skeletal Muscle. Molecular nutrition & food research 66(10): 2100669.

55. Jiang P, Lejiao Ren, Li Zhi, Zhong Yu, Fengxiang Lv, et al. (2021) Negative regulation of AMPK signaling by high glucose via E3 ubiquitin ligase MG53. Molecular cell 81(3): 629-637.e5.

56. Sung Hee Um, Francesca Frigerio, Mitsuhiro Watanabe, Frédéric Picard, Manel Joaquin, et al. (2004) Absence of S6K1 protects against age-and diet-induced obesity while enhancing insulin sensitivity. Nature 431(7005): 200-205.

57. Williamson DL, Cory M Dungan, Abeer M Mahmoud, Jacob T Mey, Brian K Blackburn, et al. (2015) Aberrant REDD1-mTORC1 responses to insulin in skeletal muscle from Type 2 diabetics. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 309(8): R855-R863.

58. Hajime Tamiya, Yuma Tamura, Yasuko Nagashima, Tomoki Tsurumi, Masato Terashima, et al. (2023) Long-Term Tailor-Made Exercise Intervention Reduces the Risk of Developing Cardiovascular Diseases and All-Cause Mortality in Patients with Diabetic Kidney Disease. Journal of Clinical Medicine 12(2): 691.

59. MacIntosh BR, Juan M Murias, Daniel A Keir, Jamie M Weir (2021) What is moderate to vigorous exercise intensity? Frontiers in physiology 12: 682233.

60. J P Kirwan, L F del Aguila, J M Hernandez, D L Williamson, D J O'Gorman, et al. (1985) Regular exercise enhances insulin activation of IRS-1-associated PI3-kinase in human skeletal muscle. Journal of Applied Physiology 88(2): 797-803.

61. Mariana Aguiar de Matos, Vinícius de Oliveira Ottone, Tamiris Campos Duarte, Pâmela Fiche da Matta Sampaio, Karine Beatriz Costa, et al. (2014) Exercise reduces cellular stress related to skeletal muscle insulin resistance. Cell Stress and Chaperones 19(2): 263-270.

62. Ferrari F, Patrícia Martins Bock, Marcelo Trotte Motta, Lucas Helal (2019) Biochemical and molecular mechanisms of glucose uptake stimulated by physical exercise in insulin resistance state: role of inflammation. Arquivos brasileiros de cardiologia 113(6): 1139-1148.

63. Copps K, M White (2012) Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia 55(10): 2565-2582.

64. So WY, PS Leung (2016) Irisin ameliorates hepatic glucose/lipid metabolism and enhances cell survival in insulin-resistant human HepG2 cells through adenosine monophosphate-activated protein kinase signaling. The international journal of biochemistry & cell biology 78: 237-247.

65. Barlow AD, DC Thomas (2015) Autophagy in diabetes: β-cell dysfunction, insulin resistance, and complications. DNA and cell biology 34(4): 252-260.

66. Madsen SM, Anne Cathrine Thorup, Kristian Overgaard, Per Bendix Jeppesen (2015) High intensity interval training improves glycaemic control and pancreatic β cell function of type 2 diabetes patients. PloS one 10(8): e0133286.

67. Huang WC, Jin-Wei Xu, Shiming Li, Xin Er Ng, Yu-Tang Tung (2022) Effects of exercise on high-fat diet–induced non-alcoholic fatty liver disease and lipid metabolism in ApoE knockout mice. Nutrition & metabolism 19(1): 1-13.

68. Witczak CA, Niels Jessen, Daniel M Warro, Taro Toyoda, Nobuharu Fujii, et al. (2010) CaMKII regulates contraction-but not insulin-induced glucose uptake in mouse skeletal muscle. American Journal of Physiology-Endocrinology and Metabolism 298(6): E1150-E1160.

69. Smith JA, Tertius A Kohn, Ashley K Chetty, Edward O Ojuka (2008) CaMK activation during exercise is required for histone hyperacetylation and MEF2A binding at the MEF2 site on the Glut4 gene. American Journal of Physiology-Endocrinology and Metabolism 295(3): E698-E704.

70. Combes A, Jeanne Dekerle, Nick Webborn, Peter Watt, Valérie Bougault, et al. (2015) Exercise-induced metabolic fluctuations influence AMPK, p38-MAPK and Ca MKII phosphorylation in human skeletal muscle. Physiological reports 3(9): e12462.

71. Chen Y, X Zhou (2020) Research progress of mTOR inhibitors. European journal of medicinal chemistry 208: 112820.

72. Bae JY, Ki Ok Shin, Jinhee Woo, Sang Heon Woo, Ki Soeng Jang, et al. (2016) Exercise and dietary change ameliorate high fat diet induced obesity and insulin resistance via mTOR signaling pathway. Journal of exercise nutrition & biochemistry 20(2): 28-33.

73. Ogasawara R, Koji Kobayashi, Arata Tsutaki, Kihyuk Lee, Takashi Abe, et al. (2013) mTOR signaling response to resistance exercise is altered by chronic resistance training and detraining in skeletal muscle. Journal of applied physiology 114(7): 934-940.

74. Tang C, Juan Cai, Xiao-Ming Yin, Joel M Weinberg, Manjeri A Venkatachalam, et al. (2021) Mitochondrial quality control in kidney injury and repair. Nature Reviews Nephrology 17(5): 299-318.

75. Sun J, Haiping Zhu, Xiaorong Wang, Qiuqi Gao, Zhuoying Li, et al. (2019) CoQ10 ameliorates mitochondrial dysfunction in diabetic nephropathy through mitophagy. Journal of Endocrinology 240(3): 445-465.

76. Zhou D, Meng Zhou, Ziying Wang, Yi Fu, Meng Jia, et al. (2019) PGRN acts as a novel regulator of mitochondrial homeostasis by facilitating mitophagy and mitochondrial biogenesis to prevent podocyte injury in diabetic nephropathy. Cell death & disease 10(7): 524.

77. Inagi R, Y Ishimoto, M Nangaku (2014) Proteostasis in endoplasmic reticulum—new mechanisms in kidney disease. Nature Reviews Nephrology 10(7): 369-378.

78. An S, G Zong, Z Wang, J Shi, H Du, et al. (2016) Expression of inducible nitric oxide synthase in mast cells contributes to the regulation of inflammatory cytokines in irritable bowel syndrome with diarrhea. Neurogastroenterology & Motility 28(7): 1083-1093.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828.
DOI: 10.19080/JOJO.2025.12.555828

79. Fu J, Chengguo Wei, Weijia Zhang, Detlef Schlondorff, Jinshan Wu, et al. (2018) Gene expression profiles of glomerular endothelial cells support their role in the glomerulopathy of diabetic mice. Kidney International 94(2): 326-345.

80. Rungratanawanich W, Ying Qu, Xin Wang, Musthafa Mohamed Essa, Byoung-Joon Song (2021) Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. Experimental & molecular medicine 53(2): 168-188.

81. Sanajou D, Amir Ghorbani Haghjo, Hassan Argani, Somayeh Aslani (2018) AGE-RAGE axis blockade in diabetic nephropathy: current status and future directions. European journal of pharmacology 833: 158-164.

82. Yan LJ (2018) Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. Animal models and experimental medicine 1(1): 7-13.

83. Yan LJ (2014) Pathogenesis of chronic hyperglycemia: from reductive stress to oxidative stress. Journal of diabetes research 2014: 137919.

84. Yung S, Mel K M Chau, Qing Zhang, Chen Zhu Zhang, Tak Mao Chan (2013) Sulodexide decreases albuminuria and regulates matrix protein accumulation in C57BL/6 mice with streptozotocin-induced type I diabetic nephropathy. PLoS One 8(1): e54501.

85. Gay C, A Chabaud, E Guilley, E Coudeyre (2016) Educating patients about the benefits of physical activity and exercise for their hip and knee osteoarthritis. Systematic literature review. Annals of physical and rehabilitation medicine 59(3): 174-183.

86. Xiao D, Yu Guo, Xi Li, Ji-Ye Yin, Wei Zheng, et al. (2016) The impacts of SLC22A1 rs594709 and SLC47A1 rs2289669 polymorphisms on metformin therapeutic efficacy in Chinese type 2 diabetes patients. International journal of endocrinology 2016: 4350712.

87. Ramage ER, Natalie A Fini, Elizabeth A Lynch, Amanda Patterson, Catherine M Said, et al. (2019) Supervised exercise delivered via telehealth in real time to manage chronic conditions in adults: a protocol for a scoping review to inform future research in stroke survivors. BMJ open 9(3): e027416.

88. Su M, R Hu (2023) Review of the correlation between Chinese medicine and intestinal microbiota on the efficacy of diabetes mellitus. Frontiers in Endocrinology 13: 1085092.

89. Rodrigues AM, Cassia T Bergamaschi, Maria Jose S Fernandes, Edgar J Paredes-Gamero, Marcus V Buri, et al. (2014) P2× 7 receptor in the kidneys of diabetic rats submitted to aerobic training or to N-acetylcysteine supplementation. PLoS One 9(6): e97452.

90. Liang X, Jiaqi Zhang, Yu Wang, You Wu, Hui Liu, et al. (2023) Comparative study of microvascular structural changes in the gestational diabetic placenta. Diabetes & Vascular Disease Research 20(3): 14791641231173627.

91. Spit KA, Marcel H A Muskiet 1, Lennart Tonneijck 1, Mark M Smits 1, Mark H H Kramer, et al. (2020) Renal sinus fat and renal hemodynamics: a cross-sectional analysis. Magnetic Resonance Materials in Physics, Biology and Medicine 33: 73-80.

92. Souza CS, Bianca Silva de Sousa Oliveira, Geovanildo Nascimento Viana, Thiago Macêdo Lopes Correia, Ana Carolina de Bragança, et al. (2109) Preventive effect of exercise training on diabetic kidney disease in ovariectomized rats with type 1 diabetes. Experimental Biology and Medicine 244(9): 758-769.

93. Hung-Wen Liu, Hao-Han Kao, Chi-Hang Wu (2019) Exercise training upregulates SIRT1 to attenuate inflammation and metabolic dysfunction in kidney and liver of diabetic db/db mice. Nutrition & metabolism 16(1): 1-10.

94. Sagoo MK, L Gnudi (2018) Diabetic nephropathy: is there a role for oxidative stress? Free Radical Biology and Medicine 116: 50-63.

95. Clarkson MJ, et al. (2017) Efficacy of blood flow restriction exercise during dialysis for end stage kidney disease patients: protocol of a randomised controlled trial. BMC nephrology 18(1): 1-9.

96. Abreu C, LFMF Cardozo, MB Stockler-Pinto, M Esgalhado , JE Barboza, et al. (2017) Does resistance exercise performed during dialysis modulate Nrf2 and NF-κB in patients with chronic kidney disease? Life Sciences 188: 192-197.

97. Xue T, Xin Zhang, Yiwen Xing, Shuhan Liu, Lijun Zhang, et al. (2021) Advances about immunoinflammatory pathogenesis and treatment in diabetic peripheral neuropathy. Frontiers in Pharmacology 12: 748193.

98. Colafella KMM, DM Bovée, AJ Danser (2019) The renin-angiotensin-aldosterone system and its therapeutic targets. Experimental eye research 186: 107680.

99. Laghlam D, M Jozwiak, LS Nguyen (2021) Renin–angiotensin–aldosterone system and immunomodulation: A state-of-the-art review. Cells 10(7): 1767.

100. Malek V, Sachin V Suryavanshi, Nisha Sharma, Yogesh A Kulkarni, Shrikant R Mulay, et al. (2021) Potential of renin-angiotensin-aldosterone system modulations in diabetic kidney disease: Old players to new hope! Reviews of physiology, biochemistry and pharmacology 179: 31-71.

101. Liu CX, Qin Hu, Yan Wang, Wei Zhang, Zhi Yong Ma, et al. (2011) Angiotensin-converting enzyme (ACE) 2 overexpression ameliorates glomerular injury in a rat model of diabetic nephropathy: a comparison with ACE inhibition. Molecular Medicine 17(1-2): 59-69.

102. Buffolo F, Martina Tetti, Paolo Mulatero, Silvia Monticone, et al. (2022) Aldosterone as a mediator of cardiovascular damage. Hypertension 79(9): 1899-1911.

103. Xue C, HM Siragy (2005) Local renal aldosterone system and its regulation by salt, diabetes, and angiotensin II type 1 receptor. Hypertension 46(3): 584-590.

104. Siragy HM, C Xue (2008) Local renal aldosterone production induces inflammation and matrix formation in kidneys of diabetic rats. Experimental Physiology 93(7): 817-824.

105. Nunes-Silva A, Guilherme Carvalho Rocha, Daniel Massote Magalhaes, Lucas Neves Vaz, Marcelo Henrique Salviano de Faria, et al. (2017) Physical exercise and ACE2-angiotensin-(1-7)-mas receptor axis of the renin angiotensin system. Protein and peptide letters 24(9): 809-816.

106. Magalhães DM, Albená Nunes-Silva, Guilherme Carvalho Rocha, Lucas Nunes Vaz, Marcelo Henrique Salviano de Faria, et al. (2020) Two protocols of aerobic exercise modulate the counter-regulatory axis of the renin-angiotensin system. Heliyon 6(1): e03208.

107. Hari K Somineni, Gregory P Boivin, Khalid M Elased (2014) Elased, Daily exercise training protects against albuminuria and angiotensin converting enzyme 2 (ACE2) shedding in db/db diabetic mice. The Journal of Endocrinology 221(2): 235.

108. Guo VY, S Brage, U Ekelund, S J Griffin, RK Simmons, , et al. (2016) Objectively measured sedentary time, physical activity and kidney function in people with recently diagnosed Type 2 diabetes: a prospective cohort analysis. Diabetic Medicine 33(9): 1222-1229.

109. Alexandre-Santos B, Renata Alves, Cristiane Matsuura, Vinicius Sepúlveda-Fragoso, Larissa Lírio Velasco, et al. (2020) Modulation of cardiac renin-angiotensin system, redox status and inflammatory profile by different volumes of aerobic exercise training in obese rats. Free Radical Biology and Medicine 156: 125-136.

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828

110. Li Yang, Zhong-Wei He, Jun-Wei He (2021) The chemical profiling of aqueous soluble fraction from Lagopsis supina and its diuretic effects via suppression of AQP and RAAS pathways in saline-loaded rats. Journal of Ethnopharmacology 272: 113951.

111. Papadopoulou-Marketou N, Christina Kanaka-Gantenbein, Nikolaos Marketos, George P Chrousos, Ioannis Papassotiriou (2017) Biomarkers of diabetic nephropathy: a 2017 update. Critical reviews in clinical laboratory sciences 54(5): 326-342.

112. Alnoud MA, Wen Chen, Nana Liu, Wei Zhu, Jing Qiao, Shujuan Chang, et al. (2021) Sirt7-p21 Signaling Pathway Mediates Glucocorticoid-Induced Inhibition of Mouse Neural Stem Cell Proliferation. Neurotoxicity Research 39(2): 444-455.

113. Sherwood NE, RW Jeffery (2000) The behavioral determinants of exercise: implications for physical activity interventions. Annual review of nutrition 20(1): 21-44.

114. Li JM, Xianyu Li, Lawrence W C Chan, Ruinian Hu, et al. (2023) Lipotoxicity-polarised macrophage-derived exosomes regulate mitochondrial fitness through Miro1-mediated mitophagy inhibition and contribute to type 2 diabetes development in mice. Diabetologia 66(12): 2368-2386.

115. Yang F, J Zhang (2022) Traditional Chinese sports under China's health strategy. Journal of Environmental and Public Health 2022: 1381464.

116. Shubrook JH, JJ Neumiller, E Wright (2022) Management of chronic kidney disease in type 2 diabetes: screening, diagnosis and treatment goals, and recommendations. Postgraduate Medicine 134(4): 376-387.

117. Yang YY, Zhuo Chen, Xi-Ding Yang, Rong-Rong Deng, Ling-Xing Shi, et al. (2021) Piperazine ferulate prevents high-glucose-induced filtration barrier injury of glomerular endothelial cells. Experimental and Therapeutic Medicine 22(4): 1-10.

118. Yang YY, Xi Li, Hua Liu, Da Zhong, Ke Yin, et al. (2019) Piperazine ferulate ameliorates the development of diabetic nephropathy by regulating endothelial nitric oxide synthase. Molecular medicine reports 19(3): 2245-2253.

119. Chen J, et al. (2023) Bone marrow stromal cell-derived exosomal circular RNA improves diabetic foot ulcer wound healing by activating the nuclear factor erythroid 2-related factor 2 pathway and inhibiting ferroptosis. Diabetic Medicine 40(7): e15031.

120. Chen Y, Shan Tan, Mei Liu, Jianming Li (2018) LncRNA TINCR is downregulated in diabetic cardiomyopathy and relates to cardiomyocyte apoptosis. Scandinavian Cardiovascular Journal 52(6): 335-339.

121. Kirkman DL, Natalie Bohmke, Salvatore Carbone, Ryan S Garten, Paula Rodriguez-Miguelez, et al. (2021) Exercise intolerance in kidney diseases: physiological contributors and therapeutic strategies. American Journal of Physiology-Renal Physiology 320(2): F161-F173.

122. Clarke AL, Hannah ML Young, Katherine L Hull, Nicky Hudson, James O Burton, et al. (2015) Motivations and barriers to exercise in chronic kidney disease: a qualitative study. Nephrology Dialysis Transplantation 30(11): 1885-1892.

DOI: 10.19080/JOJO.2025.12.555828

How to cite this article: Imran A, Shoaib M, Syed Shah Zaman Haider N, Ahmad M, Lingxi W, et al. Decoding the Puzzle: Research Progress on the Mechanisms of Exercise in Attenuating Diabetic Nephropathy - Insights, Challenges, and Future Directions. JOJ Ophthalmol. 2025; 12(1): 555828. DOI: 10.19080/JOJO.2025.12.555828