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# Exercise in Diabetic Kidney Disease: Protective Effects and Molecular Mechanisms

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## Abstract

Diabetic kidney disease represents a significant complication of diabetes mellitus, contributing to the escalating global burden of end-stage renal disease. Exercise has emerged as a crucial non-pharmacological intervention for managing DKD, offering protective effects against its development and progression. This article reviews the epidemiological evidence supporting the benefits of exercise in DKD and elucidates the underlying molecular mechanisms involved. Epidemiological studies consistently demonstrate an inverse relationship between physical activity levels and DKD risk, with regular exercise associated with improvements in renal function, reduction in albuminuria, and attenuation of renal fibrosis. At the molecular level, exercise exerts multifaceted effects on key pathophysiological pathways implicated in DKD. These include enhancing insulin sensitivity, promoting glucose uptake, reducing systemic inflammation and oxidative stress, modulating the renin-angiotensin-aldosterone system and endothelin pathways, and inducing adaptations in skeletal muscle metabolism. Furthermore, exercise activates anti-inflammatory and antioxidant responses within the kidney, mitigating renal inflammation, oxidative stress, and fibrosis. Understanding the molecular mechanisms by which exercise confers renal protection in DKD is essential for optimizing therapeutic strategies and promoting early intervention to delay disease progression. Therefore, integrating exercise into comprehensive management plans for individuals with diabetes may offer significant benefits in preserving renal structure and function, ultimately improving clinical outcomes and reducing the burden of DKD.

**Keywords:** Kidney disease • DKD • Renal inflammation

## Introduction

Regular physical activity has emerged as a cornerstone in the management of various chronic diseases, including diabetes mellitus and its complications such as diabetic nephropathy. This article explores the protective effects of exercise on diabetic kidney disease and delves into the underlying molecular mechanisms that contribute to its beneficial effects. Physical activity has been shown to exert protective effects against the development and progression of DKD. Epidemiological studies consistently demonstrate an inverse association between physical activity levels and the risk of DKD development and progression. Regular exercise has been associated with improvements in renal function, reduction in albuminuria, and attenuation of renal fibrosis in individuals with diabetes [1].

## Literature Review

At the molecular level, exercise exerts multifaceted effects on various pathophysiological pathways implicated in DKD. Physical activity enhances insulin sensitivity, promotes glucose uptake by skeletal muscles, and improves glycemic control, thereby reducing systemic inflammation and oxidative stress, key drivers of DKD progression. Moreover, exercise induces adaptations in renal hemodynamics, leading to improved renal blood flow and glomerular filtration rate. Physical activity also modulates the renin-angiotensin-aldosterone system and endothelin pathways, resulting in vasodilation, reduced glomerular hypertension, and preservation of renal function. Exercise-induced changes in skeletal muscle metabolism, particularly the activation of AMP-activated protein kinase and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1$\alpha$), contribute to the systemic metabolic benefits observed with exercise, including improved glucose homeostasis and lipid metabolism, which indirectly impact renal health. Additionally, exercise promotes anti-inflammatory and antioxidant responses within the kidney through the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and inhibition of nuclear factor-kappa B (NF-$\kappa$B) signaling pathways. These molecular adaptations mitigate renal inflammation, oxidative stress, and fibrosis, thereby preserving renal structure and function in the setting of diabetes [2,3].

## Discussion

Diabetes is a leading contributor to end-stage renal disease globally, with approximately one in three adults with diabetes developing chronic kidney disease a statistic that continues to rise. Diabetic nephropathy is a chronic condition characterized by elevated blood pressure, urinary albumin excretion, and cardiovascular risk, often accompanied by a decrease in glomerular filtration rate ultimately progressing to ESRD. The mortality rate for individuals with DN is significantly higher compared to those without kidney damage, highlighting the critical need for early intervention to delay disease progression. Management of DN encompasses four primary aspects: mitigating cardiovascular risk, regulating glycemic levels, controlling blood pressure, and inhibiting the renin-angiotensin system. These interventions aim to improve outcomes in DN. In addition to pharmaceutical interventions, exercise, particularly aerobic exercises like brisk walking or jogging, has been established as an effective approach for preventing and managing cardiovascular disease, thus presenting benefits for slowing DN progression. Engaging in moderate physical activity at least twice a week has been associated with a reduced risk of adverse renal outcomes and a decreased incidence of albuminuria. Studies investigating different exercise intensities on DN have indicated that patients with DN derive the greatest benefit from moderate-intensity exercise. Furthermore, research using diabetic animal models has demonstrated that exercise can lower the levels of advanced glycation end products and ameliorate glomerular sclerosis in various areas of the renal cortex, reducing damage [4-6].

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## Conclusion

In conclusion, exercise exerts protective effects against DKD through a myriad of molecular mechanisms involving improvements in glycemic control, insulin sensitivity, renal hemodynamics, and modulation of inflammatory and oxidative stress pathways. Incorporating regular physical activity into the management of diabetes holds great promise for mitigating the burden of DKD and improving long-term renal outcomes in affected individuals.

## Acknowledgement

None.

## Conflict of Interest

There are no conflicts of interest by author.

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