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# Investigating the Effects of SGLT2 Inhibitors Combined with Aerobic Exercise on Diabetic Nephropathy via Modulation of the Hippo Pathway

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***Abstract:*** *Hypertension, diabetes, and other factors play a significant role in the progression of kidney disease. These harmful effects can induce renal fibrosis and eventually lead to irreversible end-stage renal disease. Aerobic exercise has been shown to alleviate the progression of kidney disease by reducing oxidative stress and inflammation. The SGLT2 inhibitor dapagliflozin lowers blood glucose levels by inhibiting the activity of the SGLT2 protein, and this glucose-lowering mechanism can act directly on the kidneys to exert therapeutic effects. Given the rising incidence of diabetic nephropathy and other kidney diseases, identifying effective and rational interventions is of great importance. The development of kidney disease is closely linked to molecular mechanisms within biological cells. Currently, interventions primarily involve pharmacological treatments and lifestyle modifications. However, few studies have examined the combined effect of aerobic exercise and SGLT2 inhibitors on kidney disease through modulation of the Hippo pathway. Therefore, this article reviews the impact of aerobic exercise combined with dapagliflozin on diabetic kidney disease via the Hippo pathway, aiming to provide insights for potential treatment strategies.*

***Keywords:*** *SGLT2 Inhibitors, Aerobic Exercise, Hippo Signaling Pathway*

## 1. Introduction

The main manifestations of diabetic kidney disease (DKD) include glomerular basement membrane thickening, mesangial expansion, and podocyte injury. In advanced stages of DKD, significant alterations in the renal tubules and interstitium are observed, accompanied by tubular atrophy, interstitial fibrosis, and renal inflammation[1]. Non-hemodynamic factors induced by hyperglycemia promote the production of reactive oxygen species (ROS), alter energy substrate metabolism, and contribute to chronic renal hypoxia. These changes collectively drive the onset and progression of DKD.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated protective effects on the heart and kidneys in diabetic patients. Studies have shown that SGLT2 inhibitors not only influence blood glucose levels but also affect other molecular pathways, offering protective effects on the kidneys, liver, and pancreas. These inhibitors reduce blood glucose by blocking SGLT2 protein activity in the proximal convoluted tubules of the kidney, thereby enhancing urinary glucose excretion. Since this class of glucose-lowering agents does not target the core pathophysiological defects of type 2 diabetes—namely insulin resistance and impaired insulin secretion—they are associated with a lower risk of hypoglycemia and a favorable safety profile. In addition to effectively controlling blood glucose levels in patients with type 2 diabetes mellitus (T2DM), SGLT2 inhibitors have been shown to reduce complications[2]. They can lower proteinuria levels in patients with DKD and non-DKD, and significantly reduce the risk of T2DM-related complications and the incidence of end-stage renal disease (ESRD).

Meanwhile, according to the American College of Sports Medicine's updated physical activity guidelines for diabetic patients, exercise provides direct benefits by improving insulin sensitivity, lowering blood glucose levels, and mobilizing free fatty acids, thereby contributing to the prevention and management of diabetes and its complications[3]. Numerous human studies have demonstrated that exercise can slow the progression of diabetic nephropathy. A meta-analysis, along with animal studies, indicates that increased oxidative stress in diabetes contributes to renal damage, and that glutathione (GSH) plays an essential protective role[4]. Exercise has been shown to alleviate proteinuria, glomerular hypertrophy, tubular and glomerular damage, and to reduce the expression of related

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pathological markers[5].

## 2. Introduction to Hippo pathway

The Hippo pathway is a highly conserved protein kinase signaling cascade that plays an important role in regulating cell proliferation, apoptosis, and organ size [6]. It consists of three interconnected modules: a core protein kinase module, an upstream regulatory module, and a downstream transcriptional module. The core kinase module includes Ste20-like serine/threonine kinases 1 and 2 (MST1/2), large tumor suppressor kinases 1 and 2 (LATS1/2), and their adaptor proteins Salvador (SAV) and Mps one binder 1 (MOB1).

Activation of the Hippo pathway leads to the phosphorylation of the downstream effectors Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), resulting in their inactivation through cytoplasmic sequestration and/or proteasome-mediated degradation [7]. In contrast, inhibition of the Hippo pathway reduces serine phosphorylation, allowing YAP/TAZ to translocate into the nucleus, where they interact with transcription factors such as the TEA domain (TEAD) family to activate the expression of downstream target genes. These targets include cyclin E and connective tissue growth factor (CTGF), which promote cell proliferation [8].

Studies have shown that dysregulation of the Hippo pathway contributes to the development of kidney disease. YAP, in particular, plays a key role in promoting diabetes-associated renal interstitial fibrosis through the activation of epithelial–mesenchymal transition (EMT). Notably, proximal tubular epithelial cell-specific deletion of YAP or treatment with YAP inhibitors has been shown to significantly reduce renal interstitial fibrosis.

## 3. Mechanism of action of SGLT2 inhibitors

Glucose reabsorption in the kidney requires the active transport of sodium ($Na^+$) and potassium ($K^+$) ions across the basolateral membrane by $Na^+/K^+$-ATPase, generating an electrochemical gradient that drives glucose uptake at the apical membrane [9]. SGLT2 is primarily expressed in the kidneys and is responsible for the reabsorption of glucose filtered through the glomerulus. Compared to SGLT1, SGLT2 has a greater glucose transport capacity, accounting for approximately 90% of renal glucose reabsorption and playing a crucial role in maintaining glucose homeostasis.

Studies in SGLT1 and SGLT2 knockout mice, as well as micropuncture experiments, have demonstrated that SGLT2 is responsible for about 97% of glucose reabsorption in the early segment of the proximal tubule. In contrast, SGLT1 is expressed in the later segments of the proximal tubule and accounts for the remaining ~3% of glucose reabsorption under euglycemic conditions with intact SGLT2 function. Thus, SGLT2 and SGLT1 together are responsible for complete renal glucose reabsorption under normal physiological conditions [10].

Studies have shown that SGLT2 inhibitors are effective in improving renal outcomes [11]. These agents have become an integral part of clinical practice guidelines for slowing disease progression in patients with diabetes and kidney disease. Although originally developed as glucose-lowering drugs, the renoprotective effects of SGLT2 inhibitors are multifactorial, largely due to the resulting glycosuria and natriuresis caused by their action at the proximal tubule.

The associated hemodynamic and metabolic alterations mediate several beneficial effects, including reduced workload on proximal tubular cells, prevention of abnormal glycolysis, and a decreased risk of acute kidney injury (AKI). Previous studies have shown varying effects of SGLT2 inhibitors on glucose excretion in diabetic patients and also suggest that long-acting agents exert direct protective effects on renal function [12]. Therefore, the use of SGLT2 inhibitors represents an effective therapeutic approach for patients with diabetic kidney disease (DKD) as well as for non-diabetic individuals with kidney disease.

## 4. Effects of aerobic exercise combined with SGLT2 inhibitors on renal fibrosis

In patients with diabetes, chronic hyperglycemia increases metabolic burden on multiple organs, including the kidneys. This metabolic overload can lead to kidney damage, and in cases of diabetic kidney disease (DKD), progression to renal fibrosis is a particularly severe complication associated with high mortality. Therefore, effective treatment of renal fibrosis is urgently needed.

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Over the years, various therapeutic strategies have been developed, especially pharmacological interventions tailored to individual patient conditions. Although lifestyle modifications, including moderate aerobic exercise, are recommended for DKD patients, limited research has explored the combined use of pharmacologic treatment and exercise to modulate the Hippo signaling pathway.

Existing studies suggest that targeting the Hippo pathway may have therapeutic value in DKD. However, most of these studies have focused solely on drug-based interventions. To date, no detailed investigations have addressed whether combining aerobic exercise with SGLT2 inhibitors could yield more effective or potentially adverse outcomes in DKD patients by acting through the Hippo pathway. This question forms the central aim of the present study.

### *4.1 Effect of SGLT2 inhibitors on renal fibrosis through Hippo-YAP pathway*

The Hippo pathway regulates organ size and prevents tumor formation by controlling cell proliferation, differentiation, and apoptosis. In kidney disease, it plays a key role by inducing pathological changes under hyperglycemic conditions. High glucose levels lead to the loss of polarity in proximal tubular epithelial cells, promote nuclear translocation of YAP, and increase the secretion of connective tissue growth factor (CTGF), which results in excessive cell proliferation and accumulation of extracellular matrix (ECM) in the renal tubulointerstitium [13].

The Hippo-YAP pathway is also involved in the inflammatory microenvironment of diabetic kidney disease (DKD). Studies have shown that SGLT2 inhibitors can reduce mRNA expression of pro-inflammatory cytokines [14]. Therefore, it is hypothesized that SGLT2 inhibitors may promote YAP phosphorylation by modulating NF-κB activity, thereby reducing inflammation and exerting anti-fibrotic effects.

MST1/2 are core components of the Hippo pathway. MST1 has been found to play a crucial role in the development of fibrotic diseases, not only in kidney tissue but also in other organs [15]. Another key mechanism by which hyperglycemia induces renal fibrosis is through the promotion of epithelial–mesenchymal transition (EMT), characterized by the loss of epithelial markers such as E-cadherin and ZO-1. High glucose environments have been shown to enhance EMT. In streptozotocin (STZ)-induced diabetic nephropathy models, overexpression of MST1 reduces both renal fibrosis-related protein levels and EMT markers [16].

Moreover, glomerular mesangial cell proliferation is a major contributor to renal fibrosis. Under high glucose conditions, the PI3K/AKT and Hippo-YAP pathways exhibit crosstalk, jointly promoting mesangial cell proliferation and CTGF expression. Phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K pathway, is inactivated when YAP is dephosphorylated, leading to loss of PTEN function and uncontrolled signaling [17]. The regulation of PTEN by YAP is therefore a key link in the progression of renal fibrosis under hyperglycemic stress.

Hyperglycemia also reduces the activity of AMP-activated protein kinase (AMPK) and increases phosphorylation of AKT. As a downstream effector of AMPK, PTEN expression is suppressed, further exacerbating PI3K/AKT signaling [18]. SGLT2 inhibitors have been shown to activate AMPK by lowering blood glucose levels, regulate PTEN expression, and thereby influence the PI3K–AKT–Hippo–YAP axis to inhibit fibrosis. While initially developed for diabetes, SGLT2 inhibitors have also demonstrated promising therapeutic potential in other diseases, including pancreatic cancer. In the context of DKD, they have shown clear benefits by promoting YAP phosphorylation and degradation, leading to a more robust anti-fibrotic response. These findings highlight the significant clinical relevance of targeting the Hippo–YAP pathway in treating renal fibrosis in DKD patients.

In conclusion, the Hippo–YAP pathway undergoes pathological alterations in the kidneys of DKD patients. Numerous studies have indicated that SGLT2 inhibitors exert anti-fibrotic effects through modulation of this pathway, underscoring their important clinical value in the treatment of diabetic kidney disease.

### *4.2 Effects of aerobic exercise on renal fibrosis through Hippo-YAP pathway*

Glucose uptake in skeletal muscle is significantly reduced in patients with diabetes. As skeletal muscle is responsible for approximately 30% of whole-body energy metabolism and glucose uptake, its impairment plays a central role in diabetic complications. The association between sarcopenia and albuminuria in diabetic kidney disease (DKD) is partly attributed to insulin resistance. Studies have shown that muscle atrophy in patients with DKD is proportional to disease severity. Overexpression of

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microRNA-23a (miR-23a) in myotubes significantly upregulates myosin heavy chain expression, enhances protein synthesis, increases ATP activity, and promotes glucose uptake [19]. Moreover, elevated miR-23a levels in skeletal muscle lead to increased Akt phosphorylation, suppression of FoxO1 and PTEN protein levels, and reduction in the phosphorylation of SMAD2/3, α-SMA, fibronectin, and collagen in the kidney. These changes collectively prevent muscle atrophy and alleviate renal fibrosis. Therefore, skeletal muscle mass is closely related to renal health in DKD, and exercise-based interventions that increase muscle mass may contribute to improved DKD management.

The Hippo signaling pathway remains active during myoblast proliferation, with YAP and TAZ serving as key downstream effectors [20]. Myogenic factor 5 (Myf5), known for promoting myoblast proliferation, is positively regulated by YAP, while inhibition of YAP, TAZ, or both leads to decreased Myf5 expression [20]. TEAD family transcription factors interact with malonyl-CoA acyl carrier protein transacylase (MCAT) binding elements in the promoter regions of muscle development genes, such as α-SMA and β-myosin heavy chain (β-MHC) [21]. Silencing of TEAD1, TEAD2, and TEAD4 has been shown to strongly inhibit C2C12 myoblast differentiation.

Mechanical loading of myoblasts results in YAP overexpression and induces muscle hypertrophy. An important contributor to muscle atrophy is dysregulation of autophagy, and evidence indicates a reciprocal inhibitory relationship between YAP and autophagy. mTORC1-mediated activation of autophagy leads to sustained suppression of YAP levels, thereby inhibiting pathological growth in cancer cells. In transgenic mouse models, YAP has been shown to undergo degradation via autophagy-related mechanisms [22]. Additionally, several Hippo pathway proteins, such as LATS1, negatively regulate autophagy by targeting Beclin-1 for ubiquitination and degradation. The mTORC2-specific regulatory pathway involving RPTOR-independent companion of mTOR (RICTOR) is also directly linked to YAP/TAZ expression, and inhibition of mTORC2 can attenuate YAP/TAZ activity and mitigate renal fibrosis. Conversely, knockout of TSC1/2—negative regulators of mTOR—leads to increased mTOR activity, suppression of autophagy, and consequent YAP overexpression, contributing to renal interstitial damage.

Interestingly, human exercise-induced serum has been shown to inhibit the proliferation of YAP-overexpressing breast cancer cells via catecholamines, suggesting a potential regulatory role of exercise in YAP-associated cellular processes. Although this evidence is indirect, it provides a compelling hypothesis that exercise interventions may influence kidney disease progression through mTOR-mediated regulation of YAP. Further experimental validation is required to clarify the mechanistic relationship, offering a promising direction for future DKD research.

### *4.3 Effect of SGLT2 inhibitor dapagliflozin combined with aerobic exercise on diabetic kidney disease through Hippo pathway*

In kidney diseases, the Hippo-YAP pathway acts as a key sensor regulated by tubular and glomerular feedback mechanisms triggered by hyperglycemia. Hyperglycemia increases blood pressure and induces shear stress, which inhibits the Hippo pathway. This inhibition leads to YAP overexpression, promoting cell proliferation, excessive extracellular matrix (ECM) accumulation, and ultimately renal tubulointerstitial fibrosis. In hyperglycemia-induced atherosclerosis, YAP expression is elevated, while the activity of silent information regulator 1 (Sirt1) is reduced. However, induction of autophagy by rapamycin upregulates Sirt1 activity, facilitating YAP degradation [23].

In diabetic mice with renal inflammation and metabolic disorders, exercise has been shown to induce Sirt1 activity and enhance PGC-1α function, thereby reversing disease progression. Moreover, exercise can mitigate renal fibrosis [24]. These findings suggest that exercise interventions may exert therapeutic and preventive effects on kidney-related diseases by modulating the Hippo pathway or related crosstalk mechanisms.

SGLT2 inhibitors are well established to exert hypoglycemic, anti-inflammatory, and antioxidant effects in the treatment of kidney diseases. In particular, dapagliflozin has been demonstrated to induce anti-fibrotic effects by activating the Hippo pathway. However, the combined effect of SGLT2 inhibitors and exercise on diabetic nephropathy through the Hippo pathway has not yet been directly investigated. Preliminary studies indicate that combined pharmacological and exercise interventions may provide more effective therapeutic benefits for patients with DKD, but further experimental validation is required.

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## 5. Conclusion

Based on the above discussion on the Hippo pathway mediating renal fibrosis, it is evident that aerobic exercise offers significant benefits in the treatment of DKD patients. Concurrently, numerous studies have reported that SGLT2 inhibitors exhibit a prominent therapeutic effect on kidney diseases, partly through modulation of the Hippo pathway. It is also clear that SGLT2 inhibitors can directly target kidney pathology and exert anti-fibrotic effects.

However, regarding whether the combination of SGLT2 inhibitors with aerobic exercise produces an additive effect on kidney disease intervention via the Hippo pathway, this review finds evidence supporting an additive therapeutic benefit in the treatment of renal fibrosis. Contrarily, some studies have reported that aerobic exercise combined with the SGLT2 inhibitor dapagliflozin did not produce additive effects on skeletal muscle mitochondrial mass in T2DM rats [25].

Therefore, whether this combined intervention results in non-additive or additive effects on Hippo pathway activity remains an important question, highlighting the necessity for further experimental research on the treatment of DKD. This article's exploration provides a foundation for such studies and offers relevant treatment recommendations for the clinical management of DKD patients.

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