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*Review*

# Preventive Effect of Exercise on Kidney Fibrotic Pathway in Hypertension

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**Abstract.** Uncontrolled hypertension can progress to kidney damage characterized by structural and functional changes, ultimately contributing to kidney fibrosis. Although, hypertension can be treated. However, the prevalence of hypertension in Indonesia is increasing. Therefore, proper treatment is necessary. Elevated levels of Transforming Growth Factor-β1 and Connective Tissue Growth Factor are critical factors that are key drivers of fibrogenic pathway. Appropriate exercise can control blood pressure, renal function, and prevent kidney fibrosis due to hypertension by activating the nitric oxide signaling pathway and reducing the regulation of the TGF-β, p-Smad2/3 and CTGF. This study aims to determine the optimal type of exercise to prevent kidney fibrosis caused by hypertension. Articles used are limited to the publication year between 2018 and 2024. We analyzed the role of exercise on kidney fibrotic pathway in hypertension using PRISMA methods from PubMed, ScienceDirect, Scopus, and Google Scholar. We found 7 articles and proved several significant effects of exercise on hypertension subjects. This study summarized that moderate-intensity exercise is more influential in controlling blood pressure and renal function, as well as inhibits kidney fibrosis due to hypertension.



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## 1. Introduction

As reported by the World Health Organization (WHO), hypertension is estimated to impact 33% of individuals aged 30 to 79 years old globally. The prevalence of hypertension in the WHO Southeast Asia Region increased from 29% to 32%, including in Indonesia. Just over half of those with the condition have been identified, less than half are undergoing treatment for their high blood pressure, and 21% have their hypertension successfully managed [1]. Meanwhile, based on RISKESDAS 2018, the prevalence of hypertension in Indonesia is 34,1% [2]. Despite the fact that hypertension is a preventable and treatable condition, only a few countries manage it effectively [1].

Hypertension can cause harm to various organs, particularly heart, brain, and kidney [1]. Hypertension is associated with endothelial dysfunction, which is marked by diminished relaxation of the endothelium and decreased availability of nitric oxide (NO). It is known that NO produced in vascular endothelial cells has a strong vasodilator effect [3]. High blood pressure poses a substantial risk for the development of chronic kidney disease, as it can lead to the formation of kidney damage and fibrosis that can ultimately cause kidney failure [4-6]. Hypertension produces kidney damage characterized by structural (glomerular, tubule-interstitial, and vascular) and functional changes [7-8]. Early identification and appropriate treatment of hypertension can slow the progression and prevent complication to kidney [9-10].

Kidney fibrosis is marked by an excessive buildup of extracellular matrix (ECM), caused by a disproportion between collagen production and breakdown, resulting in fibrotic tissue that will replace normal kidney tissue [4][11]. Prior studies indicate that transforming growth factor-β1 (TGF)-β1 and connective tissue growth factor (CTGF) is a powerful profibrotic agent that drives excessive buildup of ECM and are regarded as a key promoters of fibrogenic pathways [4]. Previous research indicates that exercise serves as an effective non-drug-based intervention for managing hypertension and kidney fibrosis [11][12]. Aerobic exercise increases heart rate, blood flow, and shear stress, which helps maintain endothelial barrier function. This is because exercise triggers the release of vasoprotective molecules, such as nitric oxide [13]. Aerobic physical activity may help alleviate kidney complications in hypertensive rats by reducing the levels of TGF-β, p-Smad2/3, and CTGF, thereby preventing further progression of kidney fibrosis [4][14].

This review provides updated information on the effect of physical exercise on the fibrotic pathway in kidney fibrosis due to hypertension, so that it can optimize early prevention. Exercise can be classified into distinct categories that vary in terms of their frequency, intensity, time, and type (FITT). However, there is still a lack of studies regarding appropriate exercise modalities based on FITT for hypertension to prevent kidney fibrosis. For this reason, it is important to identify the exercise modalities for therapeutic strategies to control hypertension and prevent its complication to kidney fibrosis.

## 2. Experimental Section

This study was a systematic review focused on animal hypertension models to assess the effect of exercise on kidney fibrosis in hypertension. This study is based on the Population, Intervention, Comparison, and Outcome (PICO) procedure, with hypertensive rat models as the population and exercise as the intervention. The comparator was a control condition where participants performed no exercise, and the outcomes were reduced blood pressure, controlled renal function, and suppressed kidney fibrosis. Article search was done through electronic databases (i.e., PubMed, ScienceDirect, Scopus, and Google Scholar) using the following search strategy: (“exercise” OR “physical activity”) AND (“hypertension") AND (“renal fibrosis” OR “kidney fibrosis”). The articles used in this study are limited to the publication years between 2018 and 2024. The included studies must follow these inclusion criteria: (a) the research subjects must be hypertensive (BP ≥ 140/90mmHg); (b) the interventions were exercise; and (c) the presence of kidney fibrosis because of hypertension.

Exclusion criteria were as follows: (a) the research is a narrative review and abstract without a full script; (b) there are other complications besides kidney fibrosis and; (c) subjects were consuming drugs that might affect the results. First, the researchers reviewed the articles by titles and abstracts, and then retrieved the full texts of relevant articles. Subsequently, the full-text articles were re-evaluated against the inclusion and exclusion criteria. The study initially identified 176 potentially eligible articles, but after manually removing duplicates, 32 of these were excluded from the analysis. After reviewing abstracts and applying inclusion and exclusion criteria, 137 articles were removed from the analysis. Finally, seven articles met the inclusion criteria and were available for review. The parameters looked at include blood pressure, exercise method (type of exercise, intensity, frequency, and how long it is done), kidney fibrosis markers such as TGF-β, CTGF, signaling pathway, and structural changes such as the percentage of fibrosis area seen from the histopathological picture. Figure 1 illustrates the workflow for the article selection process.

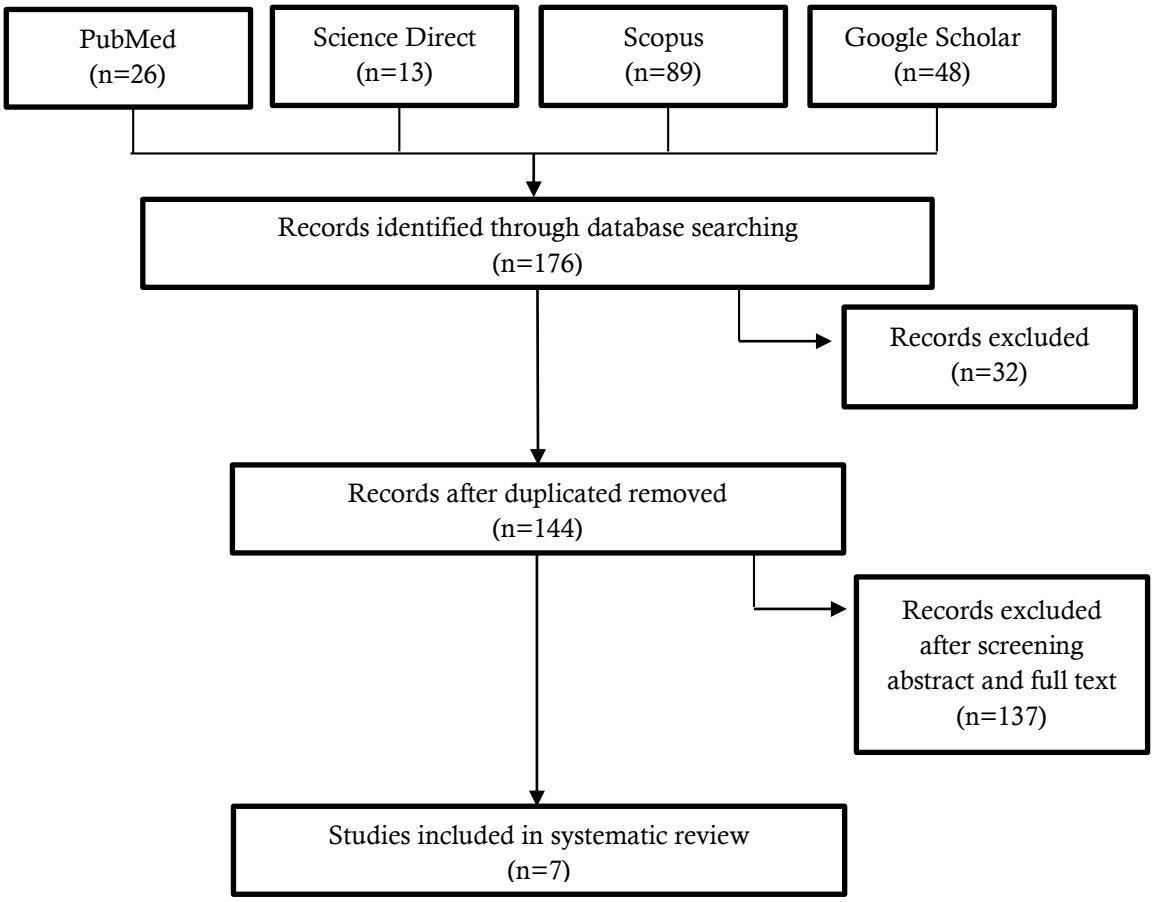


**Figure 1.** PRISMA workflow

## 3. Results and Discussion

### 3.1 Effect of Exercise on Blood Pressure in Hypertensive Rat Models

Hypertension was defined by SBP above 140 mmHg and DBP above 90 mmHg. These guidelines correspond to rats' hypertension range [15-16]. Animal models of hypertension have been useful for investigating the pathophysiology of the condition, enabling the identification of the specific genetic, cellular, and molecular mechanisms involved, as well as the testing of new potential treatments to reduce blood pressure [17-18]. Vascular endothelial cells are crucial in controlling vascular tone by generating various potent local vasoactive, such as NO, a powerful vasodilator, and endothelin peptide, a vasoconstrictor [19]. NO production is catalyzed by the enzyme nitric oxide synthase (NOS). Deficiency in NOS leads to a decrease in NO synthesis, which ultimately leads to reduced vasodilation. Reduction in NO production causes increased vascular resistance which ultimately causes hypertension [13][20].

Since the 1980s, physical activity has been recognized as a non-drug approach for managing hypertension [15]. Numerous studies have demonstrated that regular exercise provides cardiovascular benefits, such as reducing inflammation, oxidative stress, blood pressure, kidney inflammation, and inhibiting fibrogenesis. Exercise has also been found to have protective and therapeutic effects for kidney disease associated with hypertension or kidney failure [4]. Exercise triggers the endothelial NOS signaling pathway. Exercise generates shear stress, which boosts calcium levels inside endothelial cells, which then interacts with calmodulin. This causes endothelial NOS to break away from caveolin, activating it to produce nitric oxide from L-arginine. The nitric oxide produced in endothelial cells during exercise can diffuse into smooth muscle cells, then it activates an enzyme called soluble guanylyl cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate. In turn, it activates protein kinase G, ultimately leading to the relaxation of the smooth muscle cells [21].

According to these 7 journals, it was found that exercise reduced blood pressure in hypertensive rats compared to those who were not given any exercise. The exercise was carried out on an average of 60 minutes per day, 5-6 days per week for 8-14 weeks by using types of exercise such as treadmills and swimming, blood pressure was reduced. Based on researches conducted by Zhao B et al., (2022) [12] and Cao SY et al., (2022) [22], moderate intensity exercise (20m/min, 50% of the maximum oxygen consumption or the maximum aerobic speed) decreased systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) more when compared to low and high intensity. Similar with previous study that the group given moderate intensity after 6 weeks was decreased in blood pressure [23]. Based on other research, moderate intensity exercise was found to improve structural and functional changes in the endothelium of hypertensive by reducing oxidative stress and enhancing NO production. On the other hand, high intensity exercise was observed to worsen these changes by increasing reactive oxygen species and decreasing NO levels [24]. We summarized that moderate intensity, such as treadmill or swimming, for 60 minutes per day, 5-6 days per week for 8-14 weeks, significantly reduced blood pressure.

**Table 1.** Effects of exercise on blood pressure, renal function, fibrosis markers, and structural changes such as the percentage of fibrosis area seen from the histopathological study in hypertension.

| Study (year) | Animal studies | Exercise Methods | | | | Blood Pressure | Renal Function | Fibrosis Markers |
|---|---|---|---|---|---|---|---|---|
| | | Frequency | Intensity | Time | Type | | | |
| Xu L et al., 2023 | Dahl salt sensitive rats, male, 5 weeks | 5 days/week | 20m/min (moderate intensity) | 60 min/ day until 11 weeks | Treadmill | SBP was lower in the group given exercise compared to those not given exercise | - | Glomerular sclerosis and interstitial fibrosis decreased in the group who exercised compared to those who did not exercise. |
| Zhao B et al., 2022 | Spontaneous hypertensive (SHR) rats, male, 8 weeks | 5 days/week | SHR - Moderate intensity 20 m/min (50% of maximum oxygen consumption), SHR-High intensity 26 m/min (65% of maximum oxygen consumption) | 60 min/ day until 14 weeks | Treadmill | SBP, DBP, and MAP were reduced in the SHR-M group compared to the SHR and SHR-H groups. | SCr and plasma BUN were markedly reduced in the SHR-M group compared to the SHR group. | The renal cortices of the SHR group and the SHR-H group exhibited a much greater extent of fibrosis compared to the SHR-M. Additionally, the levels of key fibrotic proteins, including TRPV4, TGFβ-1, p-Smad2/3, and CTGF, were significantly reduced in the SHR-M group. |
| Cao SY et al., 2022 | SHR rats, male, 8 weeks | 5 days/week | SHR - Low intensity 14 m/min (35% of the maximum aerobic speed), SHR-Moderate intensity group 20 m/min (50% of the maximum aerobic speed) | 60 min/ day until 14 weeks | Treadmill | Blood pressure in SHR-M groups decreased significantly compared to SHR and SHR-L groups. | Serum SCr and BUN in SHR – M decreased significantly compared to SHR and SHR-L groups. | AngII, AT1R, TGF-β, CTGF expression, and percentage fibrotic area in SHR-M groups decreased significantly compared to SHR and SHR-L groups. |
| Souza et al., 2020 | Wistar high sodium (HS) rats, male, 4 weeks | 5 days/week | Low intensity | 2 hours/day for 9 weeks | Swimming | Exercise normalizes BP levels in HS rats | Maintain renal function | Exercise prevents an increase in the intraglomerular matrix of the kidney |

| Study (year) | Animal studies | Exercise Methods | | | | Blood Pressure | Renal Function | Fibrosis Markers |
|---|---|---|---|---|---|---|---|---|
| | | Frequency | Intensity | Time | Type | | | |
| Duan YC et al., 2021 | SHR rats, male, 4 weeks | 6 days/week | - | 60 min/day for 8 weeks | Swimming | SBP, DBP, and MAP were reduced in the SHR-Exercise groups | Creatinine and BUN in SHR-Exercise groups decreased significantly compared to the SHR group | In the exercise group, exercise significantly suppressed renal cortex fibrosis and reduced expression of pro-fibrosis factors such as TGF-β1 and Smad2/3. |
| Huang et al., 2018 | SHR rats, male, 6 weeks | 5 days/week | 18m/min gradually increased by 3 m/min every 2 weeks until 27 m/min | 60 min/day for 12 weeks | Motor-driven leveled treadmill | SBP was reduced in the SHR-Exercise group compared to SHR group | - | Exercise significantly suppressed renal cortex fibrosis and reduced expression of pro-fibrosis factors such as TGF-β, p-Smad2/3, and CTGF in SHR-EX |
| Luo M et al., 2023 | SHR rats, male, 8 weeks | 5 days/week | SHR-Low intensity 30–40% (14 m/min), SHR – Moderate intensity 45–55% (20 m/min), and SHR – High intensity 60 –70% (26 m/min) of the maximum exercise capacity | 60 min/day for 14 weeks | Treadmill | - | BUN and SCr were lower in the SHR-L and SHR-M groups However, SHR-H did not improve renal function in SHR | Renal *p*-AKT, *p*-ERK, and p-p38 expression was significantly lower in the SHR-L and SHR-M groups compared to the SHR-S group. |

### 3.2 Effect of Exercise on Renal Function in Hypertensive Rat Models

Hypertension and kidney disease have a bidirectional relationship, where high blood pressure can lead to kidney damage, which in turn can exacerbate the hypertension condition [25]. Hypertension often leads to chronic inflammation that contributes to hypertensive complications. Research indicates that immune cell receptors play a key role in this process, driving inflammation, oxidative stress, and vascular changes in hypertension [26]. Uncontrolled hypertension can cause the renal afferent arterioles to vasoconstrict. Over time, these afferent arterioles will become hypertrophic due to prolonged vasoconstriction, causing an increase in intraglomerular pressure. Damage to the renal arterioles causes a decrease in blood flow to the kidney tissue so that the kidneys do not receive sufficient oxygen and nutrients. This prompts renal epithelial cells to elevate the generation of pro-inflammatory factors, leading to a decreased in glomerular permeability and filtration. This in return will cause creatinine and blood urea nitrogen (BUN) levels to increase in the blood [27][28].

Creatinine and BUN are parameters measured to determine renal function. Creatinine and urea are filtered by the kidneys and excreted in the urine. High levels of plasma creatinine and BUN, indicate damage to the kidneys in filtering and eliminating materials that should be excreted by the body [29-31]. Based on the results obtained from 5 out of 7 articles, it was found that plasma creatinine and BUN levels are greater in the hypertensive group. Regular physical exercise exposes the body to shear stress, which increases the availability of nitric oxide-induced vasodilation, thereby enhancing renal blood flow. As a result, increase in glomerulus filtration rate and renal clearance occurred [21][32]. In this study found that plasma creatinine and BUN levels is lowered in the exercising hypertensive group compared to the non-exercising group. Serum creatinine (SCr) and BUN levels in the exercising hypertensive group at moderate intensity, 60 minutes per day, 5 days per week for 14 weeks, carried out with a type of exercise such as a treadmill were lower compared to low and high intensity.

This is similar to previous studies showing that moderate intensity exercise helped maintain renal blood flow and estimated glomerular filtration rate [33]. Based on other study, moderate intensity improved renal function (creatinine and BUN) after 14 weeks training [34]. On the other hand, based on Luo M et al., (2023) [11], high-intensity (60–70% of maximum exercise capacity) exercise did not improve renal function in spontaneous hypertensive rats (SHR). They assumed that high intensity exercise leads to the conversion of nitric oxide into peroxynitrite, a free radical that contributes to oxidative stress. Additionally, moderate intensity and high intensity training have a differential impact on oxidative stress [11]. In addition, there is a lack of study on the effects of high intensity hypertension on renal function [12]. We concluded that engaging in moderate-intensity exercises, such as treadmill or swimming, 60 minutes per day, 5-6 days per week for 8-14 weeks can significantly improve renal function.

### 3.3 Effect of Exercise on Kidney Fibrosis in Hypertensive Rat Models

Inflammation is a crucial factor that accelerates the development of kidney scarring and substantially impacts the transformation of cellular phenotypes [35]. Kidney tissue damage triggers inflammatory and fibrotic responses that aim to facilitate regeneration and restoration [36]. The body's normal tissue repair mechanisms, including the activation of myofibroblasts, deposition of collagen, and overall wound healing response, work in a coordinated manner to facilitate the regeneration of damaged tissue [36]. Prolonged exposure to hypertension can lead to sustained inflammatory signaling. This abnormal and chronic inflammation is associated with the release of prolonged factors, including chemokines, growth factors, and mast cell-derived inflammatory and profibrotic mediators. Additionally, activating the angiotensin II signaling pathway contributes to a profibrotic state [35]. Angiotensin II (AngII) and its activated Angiotensin receptor 1 (AT1R) can induce the production and elevate the levels of TGF-β in the kidney [37-38]. Similar to this, based on Cao SY et al., (2022) [22], showed that the levels of Angiotensin II and AT1R were increased in SHR groups [22].

TGF-β can induce kidney fibrosis by triggering the Smad signaling cascade. It is considered a crucial promoter of the fibrogenic pathway, which activates Smad2 and Smad3, then transports these proteins into the nucleus, driving kidney cells to transform into myofibroblasts and producing excessive ECM component accumulation [4][35]. TGF-β can stimulate the production of CTGF through ERK, p38, Smad, and MAPK signaling pathways, contributing to kidney fibrosis [4][39]. In this study, levels of fibrotic protein (TGFβ1-SMAD2/3-CTGF) were increased in hypertensive group [4][14]. In kidneys, have proteolytic enzymes such as matrix metalloproteinases. The equilibrium between extracellular matrix production and breakdown can be preserved through effective ECM degradation by regulation of matrix metalloproteinases. The imbalance between its production and breakdown can cause kidney fibrosis [40].

Exercise promotes the release of beneficial vascular molecules, such as nitric oxide. This directly causes a reduction in the expression of endothelial angiotensin II type 1 receptors, leading to decreased activity of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and lower production of superoxide anions. As a result, reactive oxygen species (ROS) generation is diminished [13], and the signaling pathways involving TGF-β, phospho-Smad2/3, CTGF are suppressed, ultimately reducing kidney fibrosis [4]. The study by Cao SY et al., (2022) [22] showed that the levels of Angiotensin II and AT1R were decreased in the SHR low intensity and SHR moderate intensity groups, with an even more pronounced decrease in the SHR moderate intensity group. Based on the results obtained from 4 out of 7 articles found that the key fibrotic protein levels of TGFβ-1, p-Smad2/3, and CTGF were lower in the exercising hypertensive rats compared to the non-exercising hypertensive rats [4][12][14][22]. Based on research by Zhao B et al., (2022) [12] and Cao SY et al., (2022) [22] levels of the fibrotic protein were lower in hypertensive rats given moderate intensity exercise.

On the other side, high intensity exercise found have different effects. Based on Zhao B's research [12], high intensity can produce more lactic acid. Then, transient receptor potential vanilloid 4 (TRPV4) have a transducer to identify low pH. High levels of lactic acid can exacerbate kidney fibrosis by activating the TRPV4-TGFβ1-SMAD2/3-CTGF pathway, which promotes kidney fibrotic processes. Yet, it was found that TRPV4 levels were reduced in the SHR moderate intensity group [12]. Apart from molecular fibrosis, the percentage of fibrotic area was evaluated from histopathological images using special Masson trichrome staining to assess collagen. It was found that the percentage of renal cortex fibrosis area was higher in the non-exercising hypertensive rats compared to the exercising hypertensive rats. According to studies by Zhao B et al., (2022) [12] and Cao SY et al., (2022) [22], hypertensive rats given moderate-intensity exercise had a lower percentage of fibrosis area. However, in Zhao B's research [12], The SHR high intensity group showed a substantially greater degree of fibrosis compared to the control group.

In addition, based on research by Duan YC et al., (2021) [14], it was found that increased Smad 7 expression levels in a group of hypertensive rats with exercise. Smad 7 functions to inhibit the phosphorylation of Smad2/3 so that it can prevent kidney fibrosis due to hypertension [14]. Furthermore, based on Luo M et al., (2023) findings [11], the kidney signaling pathway, including p-AKT, p-ERK, and p-p38 expression, in the SHR low intensity and SHR moderate intensity groups were significantly lower compared to the SHR group. As a result, participating in moderate-intensity physical activities, such as treadmill or swimming, 60 minutes daily, 5-6 times per week for 8-14 weeks can significantly lower profibrotic proteins like TGF-β, phospho-Smad2/3, CTGF, and diminish extensive fibrosis.

## 4. Conclusion

Hypertension can be a driver of the development of kidney fibrosis. Uncontrolled hypertension can lead to chronic inflammation, causing the release of inflammatory and fibrosis-promoting factors. This can activate the Angiotensin II and AT1R pathway, stimulating the production of TGF-β in the kidney. TGF-β then induces the synthesis of CTGF, which further promotes fibrosis. Thus,

encouraging phenotypic changes into myofibroblasts contributes to ECM deposition and ultimately, kidney fibrosis. Exercise has been shown to provide benefits for individuals with hypertension, such as lowering blood pressure, reducing kidney inflammation, decreasing oxidative stress, and inhibiting fibrosis. The shear stress generated during exercise activates the nitric oxide signaling pathway and suppresses the fibrotic pathway involving Angiotensin II, Angiotensin II receptor type 1, TGF-β, phosphorylated Smad2/3, CTGF, which can help prevent kidney fibrosis-associated with hypertension. Moderate-intensity exercise can significantly control blood pressure and renal function and inhibit kidney fibrosis due to hypertension. Our results indicate that exercise has significant potential as an antihypertensive and kidney-protective intervention before severe hypertension leads to kidney failure.

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