International Journal of General Medicine Dovepress

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Advances in Understanding Diabetic Kidney Disease Progression and the Mechanisms of Acupuncture Intervention

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Abstract: Diabetic kidney disease (DKD) is a form of kidney damage resulting from diabetes and represents a common, severe complication of the disease. Globally, DKD is a leading cause of chronic kidney disease (CKD). DKD occurs in both type 1 and type 2 diabetes patients, with early clinical manifestations including microalbuminuria and hypertension. As the condition progresses, symptoms such as massive proteinuria, hypoalbuminemia, and severe edema may appear. The key to treating DKD lies in controlling blood glucose and blood pressure, reducing proteinuria, and slowing the deterioration of kidney function. Acupuncture, a traditional Chinese medicine treatment, has shown some therapeutic effects on DKD through mechanisms such as regulating blood glucose, improving renal blood flow and microcirculation, antioxidation and anti-inflammation, and modulating gut microbiota.

Keywords: diabetic kidney disease, acupuncture, mechanism, progress

Introduction

Diabetic kidney disease (DKD) is kidney damage resulting from microvascular complications of diabetes, characterized by excessive urinary albumin excretion, diabetic glomerulopathy, and a decrease in estimated glomerular filtration rate (eGFR).[1] DKD, a prevalent and severe complication of diabetes, is considered to be related to metabolic changes in the body and is a major cause of chronic kidney disease (CKD) worldwide.[2] Despite current treatments, progressive kidney damage may be inevitable or irreversible, and many patients with diabetic nephropathy may still progress to end-stage renal disease (ESRD).[3] DKD is seen in both type 1 diabetes (T1D) and type 2 diabetes (T2D).

Acupuncture demonstrates significant advantages in the treatment of DKD. First, it exerts therapeutic effects through multiple mechanisms, not only enhancing insulin sensitivity but also improving renal hemodynamics, increasing kidney blood flow and microcirculation, and reducing intraglomerular hypertension. Additionally, acupuncture's antioxidant and anti-inflammatory properties help mitigate oxidative stress and inflammation induced by hyperglycemia, thereby protecting renal cells and slowing disease progression.

Moreover, compared to pharmacological treatments, acupuncture as a non-drug intervention presents fewer side effects and is better tolerated by patients, especially those with multiple comorbidities or limitations in medication use. Acupuncture also regulates the nervous and endocrine systems, providing a multi-targeted approach that improves the overall health of patients. This holistic nature makes acupuncture uniquely advantageous for personalized treatment and enhancing patients' quality of life.

In summary, acupuncture not only addresses the pathological mechanisms of DKD from various angles but also stands out in clinical practice due to its high safety profile and broad applicability, making it a promising complementary therapy for comprehensive DKD management.

Received: 4 August 2024
Accepted: 3 November 2024
Published: 27 November 2024

Epidemiology

DKD affects 20–50% of diabetic patients,[4] occurring in approximately 40% of diabetes patients.[5] In 2019, 2.6 million new cases of DKD were reported worldwide, and this incidence is expected to rise in the future.[6] By 2030, the global number of diabetes patients may reach around 439 million.[7] According to the latest reports from 2024 literature, Among T1D and T2D patients, 23% to 36% of T1D patients and about 38% of T2D patients will develop DKD.[8] Both forms of diabetes cause quantitative and qualitative differences in kidney damage; for example, typical nodular fibrosis (Kimmelstiel-Wilson nodules) is mainly seen in T1D, whereas glomerular hypertrophy is predominantly observed in T2D.[9] Although the prevalence of T1D and T2D is similar in men and women globally,[10] there are gender differences in the impact of diabetes on end-organ complications, such as DKD.[11] Specifically, female diabetes patients have higher mortality rates and higher prevalence of DKD risk factors such as hypertension, hyperglycemia, obesity, and dyslipidemia. However, the evidence on gender differences in DKD prevalence and disease progression is limited and inconsistent. While many studies suggest that women have a reduced protective effect against renal disease progression in the context of diabetes, the reasons remain unclear. It is still unclear whether there is a gender difference in DKD risk, with some studies reporting higher risks for men, others for women, and some finding no significant gender differences. Although the debate continues, factors such as age of onset, type, and duration of diabetes may influence gender differences in DKD risk. It is speculated that sex hormones may play a protective role in regulating kidney function.

A study found that lower hemoglobin (Hb) levels significantly increase the risk of DKD in patients with type 2 diabetes.[12] Specifically, compared to those in the highest Hb quartile (Hb $\geq$ 154 g/l), patients in the lowest Hb quartile (Hb $\leq$ 130 g/l) had a 1.6-fold higher risk of developing DKD (HR 1.58, 95% CI 1.19–2.21, $P < 0.001$). Even among patients with normal Hb levels, those with lower Hb (Hb $\leq$ 132 g/l) still faced a 1.3-fold higher risk of DKD (HR 1.29, 95% CI 1.08–1.72, $P = 0.042$). Since women are more prone to lower Hb levels (eg, higher prevalence of anemia), they may be at a greater risk for developing DKD. This Hb difference provides theoretical support for why women with diabetes might be more susceptible to DKD.

Clinical Manifestations

Early Clinical Manifestations

In the early stages of diabetic nephropathy, microalbuminuria is the most common marker.[13] This refers to the increased excretion of small amounts of albumin in the urine, which typically requires urine testing to detect. Hypertension is also an early sign, often occurring in diabetic patients due to the imbalance in blood pressure regulation caused by kidney damage. Mild edema, particularly in the lower extremities, may also appear at this stage, usually due to hypoalbuminemia caused by proteinuria.

Advanced Clinical Manifestations

As diabetic nephropathy progresses, symptoms become more apparent and severe. Patients may exhibit massive proteinuria, indicating significant loss of protein in the urine and leading to hypoalbuminemia.[14] This hypoalbuminemia can cause severe edema, not only in the lower extremities but also extending to the entire body, including the face and abdomen.[15] Declining renal function is another significant feature, manifested by reduced GFR and elevated serum creatinine (Scr) and blood urea nitrogen levels.[16]

Further Advanced Symptoms

In the further advanced stages of the disease, patients may experience various systemic symptoms. Anemia occurs due to decreased renal function affecting erythropoietin secretion, resulting in reduced red blood cell production.[17] Electrolyte imbalances arise because the kidneys cannot effectively regulate sodium, potassium, calcium, and phosphorus, leading to conditions such as hyperkalemia and hyponatremia.[18] Metabolic acidosis is due to the kidneys' diminished ability to excrete acidic metabolic products, causing symptoms like rapid breathing and fatigue. Decreased urine output, or even anuria, indicates severe renal impairment, exacerbating the accumulation of waste and toxins in the body.[19]

Systemic Impact

Diabetic nephropathy affects not only the kidneys but also the entire body. Patients often feel fatigued and weak, which may result from a combination of anemia, electrolyte imbalance, and metabolic acidosis. Nausea and vomiting are also common symptoms, typically due to the accumulation of toxins in the body caused by uremia.[20]

Diagnosis and Biomarkers

The diagnosis and prognosis of DKD primarily rely on key indicators: proteinuria, eGFR, and creatinine levels.[8]

Proteinuria

Proteinuria refers to an abnormal increase in the protein content of urine and is a traditional biomarker for DKD. Normally, albumin is almost completely reabsorbed in the renal tubules. The urine albumin-to-creatinine ratio is the preferred method for detecting albuminuria, requiring only a simple urine sample. Albuminuria is defined as a urinary albumin excretion rate of 30 mg/day or more, indicating glomerular and tubular damage and is closely associated with structural changes in the kidneys.[21] Albuminuria is a strong predictor of renal disease and cardiovascular mortality.[22] However, albuminuria is not a specific prognostic marker for DKD, as approximately 30% of DKD patients do not present with albuminuria in clinical reports. eGFR is considered a better biomarker for predicting DKD development and progression.[23] Studies have shown that T2D patients without albuminuria are at high risk for progression to renal insufficiency due to inflammatory mechanisms and proximal tubular damage, which is related to altered proximal tubular feedback.[24] The presence of non-albuminuric DKD underscores the importance of combining eGFR with albuminuria measurements when assessing DKD. Both GFR and albuminuria are independent predictors of the course of kidney disease and mortality risk, and therefore, both indicators should be evaluated when screening for DKD.[25]

eGFR

The eGFR is calculated using specific formulas that consider Scr, age, sex, and race to assess kidney function. eGFR plays a crucial role in the diagnosis and serves as a biomarker for DKD. Firstly, eGFR helps in the early detection of changes in kidney function.[26] As DKD progresses, the eGFR gradually decreases. A persistent decline in eGFR is a significant indicator of kidney damage, aiding in the early identification of DKD. Moreover, CKD is classified into five stages based on eGFR values, each reflecting different levels of kidney impairment.[27] The staging of DKD also relies on eGFR levels, assisting clinicians in evaluating the severity and progression of the disease.[28]

Regular measurement of eGFR facilitates dynamic monitoring of kidney function in DKD patients. By tracking changes in eGFR, clinicians can promptly adjust treatment plans to slow disease progression.[29] Additionally, changes in eGFR can serve as important indicators for evaluating the effectiveness of treatments. For instance, the efficacy of blood glucose and blood pressure control measures can be reflected in the changes in eGFR.[30] eGFR values are also closely associated with patients' long-term prognosis. Lower eGFR values usually indicate a poorer prognosis, including higher risks of cardiovascular diseases and mortality. Clinicians can assess patients' prognosis through eGFR and implement appropriate interventions.[31]

Scr

Proteinuria reflects early kidney damage, while a decrease in eGFR indicates continued deterioration of kidney function. The combination of the two can provide a more comprehensive assessment of the severity and progression of DKD, as they represent different aspects of kidney damage. Scr is the most commonly used biomarker for assessing kidney function, corresponding to the final product of creatine and phosphocreatine metabolism. However, creatinine measurement can be inaccurate due to physiological and technical interferences.[32] Creatinine levels are influenced by muscle mass, tubular secretion, diet, and comorbid conditions such as advanced liver disease, limiting its clinical application.[33] Additionally, the extrarenal clearance of creatinine may be affected by gut bacteria, which is associated with the progression of advanced CKD. Scr concentration only begins to rise significantly when approximately 40–50% of renal parenchyma is damaged,[34] limiting its effectiveness as an early diagnostic marker for CKD.[35] Although various formulas based on Scr levels are used to estimate the GFR, these formulas lack accuracy as they do not directly measure

renal tissue damage and are not sensitive to subtle changes in kidney function.[36] Furthermore, discrepancies in GFR estimation formulas based on Scr (eGFRcr) further limit their practical application.[37]

Pathological Mechanisms

The pathological mechanisms of DKD are complex and involve various physiological and molecular changes induced by hyperglycemia.[14] These changes include glomerular basement membrane thickening, mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis. Prolonged hyperglycemia results in hyperperfusion, high pressure, and hyperfiltration within the renal microvasculature,[38] ultimately leading to structural and functional damage to the kidneys. Specifically, the major modifiable and non-modifiable risk factors for DKD include the following:

Hyperglycemia

Chronic hyperglycemia is a primary cause of DKD. Hyperglycemia damages the renal microvasculature, leading to glomerulosclerosis and a decline in renal function.[39] Diabetic patients with significant blood glucose fluctuations and high levels of glycated hemoglobin are more prone to developing DKD. Hyperglycemia promotes DKD progression through various mechanisms. Firstly, hyperglycemia-induced oxidative stress damages glomerular and tubular epithelial cells. Enhanced intracellular glucose metabolism increases mitochondrial production of reactive oxygen species (ROS), which oxidize cell membrane lipids, proteins, and DNA.[40] Secondly, hyperglycemia promotes the formation of advanced glycation end-products, which accumulate in tissues and activate inflammatory and fibrotic signaling pathways by binding to receptors.[14]

AGEs are products formed through non-enzymatic reactions between proteins, lipids, and sugar molecules. They not only alter the structure of the extracellular matrix, affecting the filtration function of the glomerulus, but also activate oxidative stress and inflammatory responses by binding to their receptors. This activation promotes the secretion of inflammatory cytokines, which exacerbates the thickening of the glomerular basement membrane and interstitial fibrosis, ultimately leading to further deterioration of kidney structure and function.[41]

Activation of the polyol pathway is an important aspect of the metabolic changes in DKD. Under hyperglycemic conditions, glucose is converted to sorbitol by aldose reductase, a process that consumes NADPH and reduces the production of antioxidants like glutathione, thereby increasing oxidative stress. The accumulation of sorbitol also alters cellular osmolarity, leading to functional impairments and cellular damage.[42,43]

Additionally, hyperglycemia causes hyperperfusion and hyperfiltration of the glomeruli, leading to increased intraglomerular pressure and long-term mechanical injury, eventually resulting in glomerulosclerosis.[44] Hyperglycemia also activates the renin-angiotensin-aldosterone system (RAAS), causing vasoconstriction and increased intraglomerular pressure, and induces excessive deposition of glomerular matrix by promoting TGF-β release, leading to renal fibrosis.[45] Thus, controlling blood glucose levels is crucial for preventing and delaying the onset and progression of DKD, as hyperglycemia drives its development through oxidative stress, AGE formation, hemodynamic changes, and RAAS activation.

Hypertension

Similar to hyperglycemia, hypertension increases intraglomerular pressure, leading to hyperperfusion and hyperfiltration. Hypertension raises pressure in the afferent and efferent arterioles, thereby increasing intraglomerular pressure. Prolonged hypertension causes mechanical damage to the glomerular basement membrane and endothelial cells, ultimately resulting in glomerulosclerosis.[46] Hypertension and hyperglycemia share similarities in their profibrotic responses. Hypertension can activate the TGF-β signaling pathway, inducing excessive deposition of glomerular matrix.[47] It also promotes fibroblast activation and proliferation, increasing extracellular matrix production.[48] These processes ultimately lead to fibrosis of the glomeruli and tubulointerstitium, impairing renal filtration function and promoting irreversible renal damage. Vascular damage and narrowing are specific manifestations of hypertension.[49] Hypertension causes endothelial cell damage and dysfunction, increasing vascular permeability and promoting inflammatory responses.[50] Damaged endothelial cells trigger smooth muscle cell proliferation and vascular wall thickening, leading to vascular narrowing and renal ischemia. Reduced blood flow and ischemia further damage tubules and

glomeruli. In hypoxic conditions, oxygen supply diminishes, leading to tissue hypoxia and damage. Hypertension exacerbates renal damage not only through direct vascular injury but also by promoting inflammatory responses. Endothelial cells release pro-inflammatory mediators, such as IL-6 and TNF-α, under hypertensive conditions, activating inflammatory cells and triggering a cascade of inflammatory responses. These responses cause further damage to glomeruli and tubules and exacerbate fibrosis, worsening renal function.[51] Hypertension is closely associated with RAAS activation. RAAS activation leads to vasoconstriction and elevated blood pressure, increasing intraglomerular pressure. RAAS also promotes TGF-β release, inducing excessive deposition of glomerular matrix and leading to renal fibrosis.[52] Furthermore, RAAS activation causes sodium and water retention, increasing blood volume and pressure, further burdening the kidneys.[53]

Dyslipidemia

Dyslipidemia is a major factor in the development of DKD, with complex and diverse mechanisms. Dyslipidemia refers to abnormal lipid levels, including elevated low-density lipoprotein (LDL), free fatty acids, abnormal lipoproteins, and ceramides. These abnormal lipids negatively impact the kidneys through multiple pathways.[54] Firstly, dyslipidemia targets proximal tubular epithelial cells, podocytes, and tubulointerstitial tissue through biochemical changes. Abnormal lipids, especially LDL and free fatty acids, bind to cell membrane receptors and enter renal cells, promoting lipid accumulation. Excess lipid accumulation leads to cellular dysfunction and death.[55] LDL and ceramides, in particular, generate ROS and induce lipid peroxidation through biochemical reactions, increasing oxidative stress. ROS and lipid peroxidation products directly damage renal cells and induce inflammatory responses, further exacerbating renal damage and fibrosis.[56] Secondly, high cholesterol and triglyceride levels promote atherosclerosis, impairing renal blood supply. Atherosclerosis causes renal vascular narrowing and reduced blood flow, leading to renal ischemia and hypoxia. Hypoxia triggers stress responses that damage glomeruli and tubular epithelial cells, promoting glomerulosclerosis and tubulointerstitial fibrosis.[57] Additionally, dyslipidemia exacerbates renal damage by modulating multiple signaling pathways. For example, hyperlipidemia activates the NF-κB signaling pathway, promoting the expression of inflammatory cytokines and increasing renal inflammation.[58] Inflammatory cells, such as monocytes and macrophages, infiltrate the kidneys and release pro-inflammatory factors like IL-6 and TNF-α, further aggravating renal damage and fibrosis.[59]

Routine Treatment Methods

The treatment strategies for DKD encompass a range of approaches aimed at controlling blood glucose and blood pressure, reducing proteinuria, slowing the progression of kidney function decline, and improving overall health outcomes for patients.

Blood Glucose Control

Effective blood glucose control is fundamental in the prevention and management of DKD. Diabetic patients must maintain their blood glucose levels within a reasonable range to alleviate the burden on the kidneys. Common oral hypoglycemic agents include metformin, sulfonylureas, and DPP-4 inhibitors, each working through different mechanisms to lower blood glucose levels. For instance, metformin lowers blood glucose by inhibiting hepatic glucose production and enhancing insulin sensitivity in peripheral tissues.[60] Sulfonylureas control blood glucose by stimulating insulin secretion.[61] For patients with T1D and some with T2D, insulin is an indispensable treatment.[62] Recently, the use of SGLT2 inhibitors such as dapagliflozin and empagliflozin has become more widespread. These drugs not only lower blood glucose by reducing renal glucose reabsorption but also offer unique renal protective effects.[63]

GLP-1 receptor agonists (such as liraglutide and semaglutide) and SGLT2 inhibitors not only effectively control blood glucose but also show significant benefits for weight loss and cardiovascular health.[64] These medications work through different mechanisms: GLP-1 receptor agonists reduce blood sugar levels and help with weight loss by suppressing appetite and enhancing the feeling of fullness, while also significantly lowering the risk of cardiovascular events.[65] On the other hand, SGLT2 inhibitors promote weight loss by increasing glucose excretion through urine and reduce the risk of heart failure and chronic kidney disease progression. Widely used in diabetic patients with cardiovascular risk, these two classes of drugs offer multiple health benefits beyond blood sugar management.[66]

Blood Pressure Control

Hypertension is a significant risk factor for DKD, making blood pressure control crucial for kidney protection. Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARBs) are commonly used antihypertensive drugs that effectively lower blood pressure and protect the kidneys by reducing intraglomerular pressure and proteinuria.[67] Calcium channel blockers like amlodipine and beta-blockers like metoprolol are also used to manage hypertension, helping to reduce blood pressure and cardiovascular risk through different mechanisms.[68] Research indicates that strict blood pressure control can significantly slow the progression of DKD and reduce the risk of cardiovascular diseases in patients.[69]

Reduction of Proteinuria

Reducing proteinuria is a vital goal in the treatment of DKD. Proteinuria not only signals kidney damage but also contributes to further renal function deterioration. ACEI and ARBs are the primary drugs for reducing proteinuria by lowering intraglomerular pressure and thus decreasing protein leakage.[70] Additionally, mineralocorticoid receptor antagonists like spironolactone can further reduce proteinuria. Studies have shown that the combined use of these drugs can significantly decrease proteinuria and slow the rate of renal function decline.[71]

Lipid Control

Dyslipidemia is a key factor in the progression of DKD, making the management of lipid levels vital for both cardiovascular and renal health. Statins, such as atorvastatin, are widely recommended for diabetic patients, especially those who are older or have additional cardiovascular risk factors, regardless of their initial cholesterol levels. The benefits of statins extend beyond simply lowering LDL cholesterol; they also help stabilize atherosclerotic plaques, reduce inflammation, and improve overall vascular health, thereby significantly decreasing the risk of cardiovascular events like heart attacks and strokes.[72] This comprehensive role in cardiovascular prevention makes statins a cornerstone in managing diabetic patients, who are inherently at higher risk for cardiovascular complications.

Furthermore, controlling lipid levels is crucial for kidney protection. Statins not only reduce cholesterol but also limit lipid accumulation in the kidneys, alleviating inflammation and slowing down the progression of DKD.[73] Fibrates, such as fenofibrate, complement this effect by targeting elevated triglycerides, further enhancing lipid profiles and providing additional protection. Numerous studies support the approach of strict lipid management to reduce cardiovascular risks and protect renal function in patients with DKD, underscoring the importance of comprehensive lipid control as part of an integrated strategy to address both heart and kidney health.[74]

Anti-Inflammatory and Antioxidant Therapy

Inflammation and oxidative stress are key players in the pathogenesis of DKD. Antioxidants like vitamins E and C can neutralize free radicals and reduce oxidative stress-induced kidney damage.[75] Research on anti-inflammatory drugs is ongoing, with some novel anti-inflammatory agents showing potential efficacy in treating DKD. These drugs work by inhibiting the production and release of pro-inflammatory cytokines, thereby mitigating inflammatory responses and protecting renal function.[76]

Diet and Lifestyle Interventions

Healthy diet and lifestyle modifications are crucial in managing DKD. A low-protein diet can reduce the metabolic burden on the kidneys and slow the decline in renal function.[77] A low-salt diet helps control blood pressure and reduce proteinuria.[78] Smoking cessation is important for reducing kidney damage and improving overall health.[79] Additionally, moderate exercise aids in controlling blood glucose and blood pressure, improving cardiovascular function and enhancing quality of life.[80] Through healthy diet and lifestyle interventions, patients can better manage DKD and delay disease progression.

Other Treatment Methods

With ongoing medical research, new treatment methods are emerging, offering more options for patients with DKD. Renoprotective drugs like fingolimod protect the kidneys through various mechanisms, reducing inflammation and fibrotic responses.[81] Gene therapy and cell therapy are also under investigation and may provide revolutionary treatment options for DKD in the future. Stem cell therapy, which has shown promising results in preliminary studies, aims to repair damaged kidney tissues and improve renal function.

Personalized Treatment

Personalized treatment plans are essential for DKD patients, as individual characteristics significantly influence the effectiveness and safety of therapy.

Consideration of Comorbidities

Patients often have various comorbidities, such as hypertension, cardiovascular disease, or other metabolic issues, which can affect treatment choices.[82] For instance, patients with cardiovascular disease may benefit more from medications that offer cardiac protection, such as SGLT2 inhibitors or GLP-1 receptor agonists.[83] For those with hypertension, drugs that simultaneously control blood pressure and improve kidney function are more suitable Therefore, treatment plans should be tailored based on the patient's comorbidities to enhance therapeutic outcomes and minimize adverse effects.

Impact of Age

Age is a crucial factor when designing a personalized treatment plan. Older patients may face a higher risk of drug-related side effects, making it important to choose safer medications and avoid potential drug interactions.[84] Additionally, since kidney function may decline with age, medication dosages need to be adjusted according to renal function to prevent toxicity from drug accumulation.

Changes in Renal Function

As DKD progresses, kidney function may deteriorate significantly, affecting the metabolism and excretion of medications. Treatment plans should be personalized based on the patient's eGFR and other renal function indicators.[85] For example, some antidiabetic medications may need to be reduced or discontinued in cases of impaired renal function,[86] whereas SGLT2 inhibitors can still provide renal protection within certain eGFR levels.[87]

Regular Monitoring and Treatment Adjustments

To ensure the safety and efficacy of treatment, it is crucial to regularly monitor the patient's condition, including blood glucose levels, blood pressure, and eGFR. Based on these monitoring results, treatment plans may need to be dynamically adjusted. For instance, medication changes or dose adjustments may be necessary as the disease progresses or new comorbidities emerge. Regular monitoring also allows for the early detection of adverse effects, enabling timely treatment modifications to reduce risks.

In summary, personalized treatment plans should take into account the patient's individual characteristics and be adjusted according to changes in the patient's condition to improve outcomes and ensure long-term safety.

Acupuncture Treatment

Acupuncture is a traditional Chinese medicine therapy that involves inserting fine needles into specific points on the body to regulate the flow of qi and blood, restore the balance of yin and yang, and thereby treat diseases and promote health. Acupuncture has multiple effects, including promoting blood circulation, alleviating pain, and improving organ function. Modern medical research has found that acupuncture exerts its therapeutic effects by regulating the nervous, immune, and endocrine systems. Due to its non-pharmacological nature and fewer side effects, acupuncture has been widely used in the management of various chronic diseases and pain, including DKD.

Mechanism of Acupuncture in Treating Diabetic Kidney Disease

Regulating Blood Glucose

Acupuncture treats DKD by regulating blood glucose levels, primarily through stimulating specific acupoints such as Zusanli (ST36), Spleen Shu (BL20), and Pancreas Shu (BL23), enhancing insulin secretion, and improving insulin sensitivity.[88] When these acupoints are stimulated by acupuncture, the nervous system transmits signals to the pancreas, promoting the restoration and enhancement of β-cell function. This stimulation can activate insulin secretion, increasing its concentration in the blood. Insulin is a key hormone in regulating blood glucose, responsible for transporting glucose from the blood into cells for metabolism, and its increased secretion can significantly lower blood glucose levels.

Zusanli is an important acupoint on the stomach meridian, located 1.5 cun below the kneecap on the anterior lateral side of the tibia. Traditionally, Zusanli is widely used to enhance spleen and stomach function, boost immunity, and improve overall health. It is considered a key point for regulating the digestive system and helps harmonize qi and blood.[89] Studies indicate that stimulating Zusanli can improve kidney function, potentially by increasing renal blood flow and promoting the excretion of metabolic waste, thereby playing a beneficial role in treating DKD.[90] Additionally, Zusanli can alleviate symptoms associated with DKD, such as fatigue and digestive issues, thereby enhancing the patient's quality of life.

Shenshu is a major acupoint on the bladder meridian, located 1.5 cun lateral to the lumbar spine. This acupoint is closely associated with kidney function and is traditionally used to treat conditions related to kidney qi deficiency, such as fatigue, sexual dysfunction, and edema. In traditional Chinese medicine, the kidneys are regarded as the "foundation of life", intimately connected to growth, development, metabolism, and reproductive processes.[91] Acupuncture at Shenshu can enhance kidney function and improve overall metabolic capacity, playing a positive role in the treatment of DKD. By improving renal blood supply and metabolism, needling Shenshu can slow the progression of kidney damage and promote the recovery of renal function.[92]

Additionally, acupuncture affects systemic metabolic pathways, particularly by improving peripheral tissue sensitivity to insulin, enabling cells to utilize and absorb glucose more effectively. Specifically, acupuncture may enhance the expression and function of insulin receptors, boost insulin signal transduction, and make major metabolic organs such as muscles, fat, and the liver more responsive to insulin. This promotes glucose uptake and utilization, helping to reduce blood glucose concentrations and prevent persistent hyperglycemia.[93] By stabilizing and lowering blood glucose levels, acupuncture helps reduce glucose fluctuations, which is crucial in preventing long-term hyperglycemia-induced kidney damage. Regulating blood glucose through acupuncture not only directly lowers blood glucose levels but also indirectly reduces glomerular and tubular damage, protecting renal function.

Yihui G[94] explored the effects of electroacupuncture on T2D mice and non-alcoholic fatty liver disease (NAFLD) mice. The results showed that electroacupuncture significantly lowered fasting blood glucose, insulin, total cholesterol, and triglyceride levels while increasing hepatic glycogen content. Metabolomics analysis identified 47 metabolites, eight of which changed significantly after electroacupuncture treatment. Pathway analysis suggested that electroacupuncture modulates amino acid metabolism, energy metabolism, and oxidative stress, thereby intervening in glucose and lipid metabolism disorders. The study concluded that electroacupuncture can regulate liver metabolic patterns in T2D and NAFLD mice, reducing hepatic glucose and lipid accumulation, providing new insights and theoretical foundations for acupuncture treatment of glucose and lipid metabolism-related diseases.

Xihui Q[95] investigated the effects of acupuncture on fibroblast growth factor 21 (FGF21) and related adipokines in obese T2D rats. The study found that acupuncture significantly alleviated the histopathological changes in visceral fat, restored body weight, fasting blood glucose (FBG), and insulin resistance index levels. Acupuncture treatment significantly reduced triglyceride and LDL-C levels while increasing high-density lipoprotein cholesterol, FGF21, adiponectin (ADP), and C-peptide levels. Moreover, acupuncture significantly increased the mRNA expression levels of FGF21, ADP, and AMPK, and upregulated the expression levels of multiple proteins such as FGFR3, ERK, and AMPK. The study demonstrated that acupuncture improves metabolic disorders in obese T2D rats by regulating the FGF21 signaling pathway and related adipokines, reducing FBG and body weight, and enhancing insulin sensitivity.

Improving Renal Blood Flow and Microcirculation

Acupuncture treats DKD by improving renal blood flow and microcirculation, primarily involving the stimulation of specific acupoints such as Shenshu (BL23) and Mingmen (DU4).[96] Acupuncture at these points can effectively dilate renal blood vessels, increase blood flow to the kidneys, and enhance the microcirculation of the glomeruli and tubules. Increased blood flow not only provides more oxygen and nutrients to help kidney cells recover and repair but also helps remove metabolic waste and toxins, reducing the burden on the kidneys.

Specifically, acupuncture regulates blood flow through neural reflexes and local effects. On one hand, acupuncture stimulation at acupoints sends signals through neural reflex arcs, regulating the autonomic nervous system, causing renal vasodilation, and improving overall blood supply. On the other hand, acupuncture induces a series of biochemical reactions locally, releasing various vasoactive substances such as nitric oxide (NO) and prostaglandins. These substances act directly on the renal vascular walls, causing relaxation of the vascular smooth muscle, dilating the vessels, and increasing blood flow.[97]

This improvement in blood flow and microcirculation has multiple positive effects on the treatment of DKD. Firstly, increased blood flow can alleviate hyperperfusion and hyperfiltration in the glomeruli, reducing intraglomerular pressure and thus decreasing mechanical damage to the glomeruli. Secondly, improved microcirculation can effectively prevent and mitigate renal ischemia and hypoxia, protecting glomerular and tubular epithelial cells from further damage. Additionally, good microcirculation can promote kidney repair processes, reduce inflammation and fibrosis, and thus protect renal function and slow the progression of DKD.[98]

A study[99] explored the effects of electroacupuncture stimulation at Zusanli (ST36) on experimental renovascular hypertension. The results showed that 30 minutes of daily electroacupuncture treatment for five days significantly lowered the mean arterial pressure in hypertensive hamsters and increased the nitric oxide (NO) concentration around small arteries. Molecular biology analysis further revealed that the expression of endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) was significantly reduced under hypertensive conditions, while electroacupuncture treatment not only prevented this reduction but also significantly increased eNOS and nNOS expression levels, particularly in gastric and cheek pouch tissues associated with the stomach meridian. Electroacupuncture exerts its antihypertensive effects through multiple mechanisms. Firstly, electroacupuncture promotes the production and release of NO, a potent vasodilator, which helps to dilate blood vessels and improve blood flow, thereby lowering blood pressure. The study found that electroacupuncture activated eNOS and nNOS, increased NO bioavailability, and significantly raised NO concentrations in blood vessels. Secondly, electroacupuncture may affect the renin-angiotensin system. Hypertension is often accompanied by elevated Ang II, which raises blood pressure by causing vasoconstriction. Electroacupuncture treatment showed a reduction in Ang II, alleviating its vasoconstrictive effects and further helping to lower blood pressure. Additionally, electroacupuncture may influence other molecules and pathways involved in blood pressure regulation. Studies have shown that electroacupuncture can modulate endothelial function, reduce oxidative stress, and inflammatory responses, all of which are crucial factors in hypertension development. By comprehensively regulating these molecular mechanisms, electroacupuncture significantly improved blood pressure levels and vascular function in hypertensive hamsters. This study indicates that electroacupuncture significantly lowers blood pressure in experimental hypertension through multiple mechanisms, including increased NO production, regulation of the renin-angiotensin system, and improved endothelial function, providing scientific evidence and theoretical support for acupuncture treatment of hypertension.

Antioxidant and Anti-Inflammatory Effects

Acupuncture treats DKD through antioxidant and anti-inflammatory effects, mainly by stimulating specific acupoints such as Shenshu (BL23) and Zusanli (ST36) to reduce oxidative stress and inflammatory responses. Firstly, acupuncture can increase the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase. These enzymes neutralize excess ROS in the body, reducing oxidative damage to kidney cells. By reducing ROS production, acupuncture effectively lowers hyperglycemia-induced oxidative stress, protecting glomerular and tubular epithelial cells and preventing further structural and functional damage.[90] Secondly, acupuncture can modulate the immune system and inhibit the release of pro-inflammatory cytokines. Hyperglycemic conditions trigger inflammatory responses, releasing

large amounts of pro-inflammatory cytokines such as IL-6 and TNF-α. These inflammatory cytokines activate inflammatory cells in the kidneys, leading to damage to the glomeruli and tubules. Acupuncture reduces the release of IL-6 and TNF-α and inhibits the activation of inflammatory signaling pathways, thereby alleviating renal inflammation.[100]

By combining these effects, acupuncture can effectively protect kidney cells, reducing oxidative stress and inflammatory responses, and slowing the decline in renal function. Specifically, reducing oxidative stress helps maintain cell membrane integrity, preventing lipid peroxidation and protein damage;[101] reducing inflammatory responses helps prevent glomerular basement membrane thickening and tubulointerstitial fibrosis.[102]

YingGao Q[103] explored the effects of acupuncture and moxibustion on the expression of Fas and Fas ligand (FasL) in the kidneys of diabetic rats with contrast-induced nephropathy (CIN) to understand their protective mechanisms. The results showed that combined acupuncture and moxibustion significantly reduced UN and creatinine levels, decreased malondialdehyde content in the kidneys, significantly downregulated the expression of Fas and FasL mRNA and proteins in the kidneys, and significantly upregulated the levels of NOS, SOD and total antioxidant capacity in the kidneys. Histopathological and ultrastructural observations indicated that combined acupuncture and moxibustion significantly alleviated pathological damage to the glomeruli and tubules. These results suggest that acupuncture and moxibustion protect against CIN in diabetic rats by regulating the expression of Fas and FasL genes and proteins, reducing oxidative stress and kidney damage, with combined treatment being more effective than acupuncture or moxibustion alone.

A study[104] aimed to determine the mechanisms and efficacy of electroacupuncture (EA) in alleviating inflammation induced by DKD. Mice were injected intraperitoneally with streptozotocin (STZ, 50 mg/kg) for five consecutive days, and blood glucose levels (>300 mg/dL) were measured after 12 weeks. The results showed that EA treatment significantly reduced serum levels of IL-1β and IL-6 in DKD mice and protected the kidneys from damage. Further research found that EA exerts anti-inflammatory effects by inhibiting the HMGB1/NLRP3/NF-κB pathway. Specifically, EA inhibited the expression of HMGB1, which in turn inhibited the activation of the NLRP3 inflammasome and NF-κB signaling pathway, reducing the release of pro-inflammatory cytokines. Inhibition of HMGB1 enhanced EA's anti-inflammatory effects by inhibiting the NLRP3/NF-κB pathway, while activation of HMGB1 weakened EA's anti-inflammatory effects by inducing the NLRP3/NF-κB pathway. The study demonstrates that EA protects DKD mice from inflammatory damage by inhibiting the NLRP3 inflammasome and NF-κB signaling pathway and reducing the production of pro-inflammatory cytokines.

Modulating Gut Microbiota

Acupuncture treats DKD by influencing the gut microbiota, primarily through modulating the composition and function of intestinal microorganisms to improve overall gut health. Acupuncture at specific acupoints such as Zusanli (ST36) and Hegu (LI4) can promote the growth of beneficial bacteria like Bifidobacterium and Lactobacillus while inhibiting the proliferation of harmful bacteria such as Escherichia coli and Clostridium, thereby restoring the balance of the gut microbiota. A healthy gut microbiota significantly impacts host metabolism, immune regulation, and inflammatory responses.

Specifically, a balanced gut microbiota can reduce the production of intestinal toxins like endotoxins. Excessive endotoxins can penetrate the gut barrier and enter the bloodstream, triggering systemic inflammatory responses and increasing the burden on the kidneys. By modulating the gut microbiota, acupuncture can decrease gut permeability, reduce endotoxin release and absorption, and thus lower systemic inflammation levels. Additionally, a healthy microbiota can synthesize short-chain fatty acids such as butyrate, which possess anti-inflammatory properties that inhibit the production of pro-inflammatory cytokines, further mitigating inflammatory responses.

Acupuncture can also influence the enteric nervous system and the endocrine system, improving intestinal motility and digestive function, promoting nutrient absorption, and enhancing the immune barrier function. These regulatory effects help maintain the ecological balance of the gut, improve host metabolic status, and reduce kidney damage caused by metabolic disorders.

Linhui C[105] explored the effects of EA at Zusanli (ST36) on the gut microbiota and plasma metabolites in mice with T2D. The results showed that EA treatment significantly reduced fasting blood glucose and insulin levels, alleviated pathological damage in the liver and colon, and increased the richness and diversity of the gut microbiota. Specifically,

EA decreased the relative abundance of Clostridium and increased the relative abundance of Lactobacillus. Additionally, EA reduced plasma levels of fructose.[106]

Ting P[107] conducted a study to investigate the mechanisms by which EA alleviates insulin resistance in T2D mice. In this study, diabetes was induced in mice by intraperitoneal injection of STZ, and EA treatment was administered for 4 weeks, 12 weeks after diabetes induction. The results showed that EA significantly improved blood glucose levels, reduced serum levels of inflammatory cytokines IL-1β and IL-6, and protected renal function. Further research revealed that EA exerts anti-inflammatory effects by inhibiting the HMGB1/NLRP3/NF-κB signaling pathway. Specifically, EA inhibited the expression of HMGB1, thereby preventing the activation of the NLRP3 inflammasome and the NF-κB signaling pathway, reducing the release of pro-inflammatory cytokines. By modulating the gut microbiota, increasing the abundance of Firmicutes and Actinobacteria, and increasing the content of bile acids such as cholic acid and ursodeoxycholic acid, EA enhanced the expression levels of TGR5 and GLP-1 proteins in the small intestine, further promoting insulin secretion and improving insulin sensitivity. These results suggest that EA improves insulin resistance and metabolic disorders in T2D mice through multiple mechanisms, including gut microbiota regulation, bile acid metabolism modulation, and inhibition of inflammatory pathways.

Regulate the Central Nervous System

Acupuncture stimulates specific acupoints, activating the peripheral nervous system and influencing the central nervous system. When acupuncture targets specific points, it activates peripheral nerves, which transmit signals to the spinal cord and brain.[108] Research indicates that this stimulation prompts the release of various neurotransmitters, including endorphins, norepinephrine, and dopamine. These neurotransmitters play a crucial role in regulating pain perception, as well as affecting mood, stress, and overall bodily function.[109]

Acupuncture alters the pathways of pain signal transmission through its effects on the spinal cord and brain. This mechanism is explained by the "gate control theory", which posits that acupuncture can inhibit pain signals by enhancing the transmission of non-pain signals. Consequently, acupuncture can stimulate sensory nerves, change the activity of spinal neurons, and reduce the transmission of pain signals, thereby alleviating the patient's perception of pain. Additionally, acupuncture enhances the body's natural analgesic capacity by promoting the release of endogenous pain-relieving substances that bind to specific receptors in the central nervous system.[110]

Furthermore, acupuncture plays a significant role in regulating the hypothalamic-pituitary-adrenal axis. By lowering the secretion of stress hormones, such as cortisol, acupuncture alleviates pressure on the kidneys and improves their metabolic and excretory functions. Studies have shown that acupuncture effectively mitigates chronic stress responses, thereby protecting renal function.[111] This comprehensive mechanism of action highlights acupuncture's unique advantages in the treatment of DKD, as it not only alleviates pain and discomfort but also enhances the overall health status of patients.

Conclusion

The treatment of DKD encompasses various strategies, including pharmacological interventions, dietary adjustments, and lifestyle modifications. Despite advancements in controlling the disease and slowing its progression, many patients still progress to ESRD, requiring dialysis or kidney transplantation. Current research is focused on elucidating the molecular mechanisms of DKD and exploring new therapeutic targets and methods, including anti-inflammatory treatments, antifibrotic therapies, and cell-based therapies. Future research directions also include personalized medicine, aiming to tailor treatment plans based on the specific conditions and genetic backgrounds of patients to improve their prognosis.[112] In response to this situation, current treatment strategies include the use of ACE inhibitors and SGLT2 inhibitors, which are widely recommended for the treatment of DKD. ACE inhibitors reduce intraglomerular hypertension and proteinuria, demonstrating effectiveness in lowering the risk of ESRD. Meanwhile, SGLT2 inhibitors provide renal protection through mechanisms such as decreasing intraglomerular pressure and improving hemodynamics. However, despite the significant impact of these drugs in slowing disease progression, many patients still progress to ESRD after treatment. This indicates limitations in the current therapeutic approaches, especially in advanced stages of the disease or among patients with additional comorbidities. Therefore, further research and new treatment strategies are needed to address these gaps and improve long-term outcomes for patients.[113]

Acupuncture, a traditional Chinese medicine therapy, has demonstrated multiple advantages in the treatment of DKD. Firstly, acupuncture helps control the disease by regulating blood glucose levels and improving insulin sensitivity. Secondly, acupuncture can enhance renal blood flow and microcirculation, alleviating hyperperfusion and hyperfiltration in the glomeruli, thus protecting renal function. Additionally, acupuncture exhibits antioxidant and anti-inflammatory effects, reducing oxidative stress and inflammation-induced kidney damage. By modulating the gut microbiota and promoting the growth of beneficial bacteria, acupuncture also improves metabolic status, offering positive effects for DKD patients.

In terms of diet, acupuncture can help improve digestive function, thereby enhancing nutrient absorption. When combined with dietary recommendations for low salt and low protein, this approach can effectively manage blood sugar levels and reduce the burden on the kidneys.[114] Additionally, acupuncture promotes metabolism, which aids in weight management—an important factor for improving kidney health.

Regarding medication, acupuncture can be used alongside conventional treatments. Research indicates that acupuncture can enhance the efficacy of medications while reducing side effects. For example, acupuncture may alleviate gastrointestinal discomfort caused by medications, thereby improving patient adherence. This integrated treatment strategy not only enhances kidney function but also improves the overall quality of life for patients.[115]

Overall, acupuncture, with its minimal side effects and holistic approach, serves as a valuable adjunct in the comprehensive treatment of DKD.[116]

However, acupuncture has its drawbacks. Firstly, the efficacy of acupuncture varies among individuals, with different patients exhibiting different responses. Secondly, acupuncture treatment requires professional practitioners, and the process is complex, necessitating long-term adherence by patients to achieve noticeable effects. Moreover, the mechanisms of acupuncture are not fully understood, and further scientific research is needed to provide robust evidence supporting its efficacy.[89]

During acupuncture treatment, the interaction between healthcare providers and patients can offer psychological support, helping patients better understand and manage their conditions. Additionally, acupuncturists can provide health education during treatment, imparting self-management techniques to patients, such as strategies for coping with the stress and anxiety associated with their illnesses. This approach enhances overall patient care by addressing both physical and emotional aspects of health.

This integration of psychological support and health education is vital in fostering a holistic treatment environment, promoting better health outcomes and improving patients' quality of life.

In summary, acupuncture shows significant advantages in the treatment of diabetic nephropathy, alleviating clinical symptoms, slowing disease progression, and improving the quality of life through multiple mechanisms. Nevertheless, acupuncture also has limitations that necessitate more scientific research and clinical trials to validate its effectiveness and safety. Combining the strengths of modern medicine and traditional Chinese medicine, an integrated treatment approach may prove to be an effective pathway for managing diabetic nephropathy in the future.

Abbreviations

DKD, diabetic kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; T1D, type 1 diabetes; T2D, type 2 diabetes; BUN, blood urea nitrogen; hypoalbuminemia, decreased blood protein levels; HbA1c, glycated hemoglobin; ROS, reactive oxygen species; AGEs, advanced glycation end-products; LDL, low-density lipoprotein; RAAS, renin–angiotensin–aldosterone system; FBG, fasting blood glucose; ADP, adiponectin; eNOS, endothelial nitric oxide synthase; nNOS, nitric oxide synthase; SOD, superoxide dismutase; FasL, Fas and Fas ligand; NO, nitric oxide; CIN, contrast-induced nephropathy; EA, electroacupuncture; STZ, streptozotocin; ACEI, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin II Receptor Blockers; Scr, serum creatinine.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by Natural Science Foundation of Heilongjiang Province Project [No. LH2019H112]; Heilongjiang Province Traditional Chinese Medicine Research Project [No. ZYW2024-119].

Disclosure

The authors report no conflicts of interest in this work.

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