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Exploration on the Relationship between Intestinal Microbiota and Diabetic Kidney Disease Based on the Theory of the Correlation between the Spleen and Kidney

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Abstract: *Diabetic Kidney Disease (DKD) is a major microvascular complication of diabetes. Its pathogenesis is complex and involves multiple factors such as metabolic disorders, inflammatory responses, and intestinal microbiota dysbiosis. This article takes the traditional Chinese medicine (TCM) theory of "the correlation between the spleen and kidney" as the core, systematically explores the role of the intestinal microbiota in the occurrence and development of DKD, and proposes a pathological model of the "spleen-kidney-intestinal microbiota axis". By integrating the physiological functions of TCM, namely "the spleen governing transportation and transformation, and the kidney governing water metabolism", with the metabolic regulation and immune-inflammatory mechanisms mediated by the intestinal microbiota in Western medicine, this article reveals the molecular pathways through which deficiency of both the spleen and kidney leads to intestinal microbiota dysbiosis, intestinal barrier damage, and the accumulation of uremic toxins. It provides new ideas for the integrated treatment of DKD combining traditional Chinese and Western medicine.*

Keywords: *Theory of the Correlation between the Spleen and Kidney; Intestinal Microbiota; Diabetic Kidney Disease; Intestine-Kidney Axis; Integration of Traditional Chinese and Western Medicine*

1. Introduction

Diabetic nephropathy (DN) is a diabetes-induced microvascular complication of the kidney, characterized pathologically by glomerulosclerosis and mesangial matrix expansion, with clinical manifestations including persistent proteinuria, edema, hypertension, and progressive decline in glomerular filtration rate (GFR). Epidemiological studies estimate that approximately 30%–40% of diabetic patients worldwide progress to DN [1]. The gut microbiota plays a pivotal role in maintaining host homeostasis through multifaceted mechanisms. First, it exerts protective functions by preventing pathogen colonization, enhancing nutrient digestion and absorption, and synthesizing essential vitamins (e. g. , vitamin K, B12) and amino acids. Second, microbial communities modulate systemic inflammation via anti-inflammatory signaling pathways, regulate lipid metabolism through bile acid transformation, and critically shape immune system development, particularly in early life [2]. Third, microbiota-derived metabolites—including short-chain fatty acids (SCFAs), bile acids (BAs), lipopolysaccharide (LPS), and trimethylamine N-oxide (TMAO)—serve as key mediators of host-microbe crosstalk, influencing cellular processes ranging from energy metabolism to epigenetic regulation. Dysbiosis, characterized by reduced microbial diversity, compositional shifts (e. g. , decreased SCFA-producing taxa), and functional alterations, disrupts this equilibrium. Pathological consequences include diminished SCFA production, accumulation of uremic toxins (e. g. , indoxyl sulfate), aberrant activation of the renin-angiotensin system (RAS), chronic low-grade inflammation, and maladaptive immune responses, collectively exacerbating tissue injury and metabolic dysfunction [3].

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2. The Core Connotations of the Theory of the Correlation between the Spleen and Kidney in Traditional Chinese Medicine

2.1 The Physiological Functions and Pathological Correlations of the Spleen and Kidney

As the largest lymphoid organ in the human body, the spleen harbors abundant lymphocytes such as B cells and T cells. Immunoglobulins (e. g. , IgM, IgG) secreted by B cells form antibody-antigen complex cascades, playing a central role in humoral immune responses [4]. The "Spleen-Kidney Correlation Theory" originated in the Qin-Han period, as evidenced in the Huangdi Neijing: Suwen. The chapter On the Generation of the Five Zang Organs states, "The kidney governs bones, manifests in hair, and is regulated by the spleen, " while On the Jade Mechanism and True Viscera notes, "If untreated, spleen disease transmits to the kidney, " establishing a foundational framework for the physiological interdependence and pathological transmission between these organs [5]. By the Eastern Han dynasty, Zhang Zhongjing expanded this theory through clinical insights. In Treatise on Cold Damage Diseases, he proposed that spleen yang deficiency could progress to kidney yang deficiency, advocating dual reinforcement of both organs' yang qi. His Synopsis of the Golden Chamber emphasized prioritizing spleen and kidney tonification in chronic diseases, introducing methods like "regulating the spleen, nourishing the kidney, and warming yang with sweet-tonic herbs, " thereby formalizing the principle of dual spleen-kidney supplementation. During the Jin-Yuan period, the Yishui School, led by Zhang Yuansu, focused on the depletion of spleen and kidney essence as central to disease pathogenesis. Li Dongyuan's "Spleen-Stomach Theory" elevated the spleen's role as the "source of life, " asserting that "impairment of the spleen-stomach breeds all ailments, " and highlighted pathological interactions where spleen dysfunction propagates to the kidney. The Ming-Qing era witnessed further refinement. Influenced by the Yishui School, physicians such as Zhang Jingyue, Xue Ji, Zhao Xianke, and Li Zhongzi emphasized deficiency syndromes and pioneered warm-tonification therapies. Xue Ji identified mutual causation in spleen-kidney deficiency syndromes, advocating simultaneous spleen fortification and kidney warming. Li Zhongzi crystallized the theory by declaring, "The kidney is the congenital foundation, and the spleen the acquired foundation, " stressing their codependence: "A robust kidney stabilizes the spleen; a healthy spleen nourishes the kidney. " Cheng Guopeng delineated therapeutic priorities: "Tonify the spleen if it weakens alone; strengthen the kidney if it fails singly; dual deficiency demands combined treatment. "In 1988, Professor Deng Tietao's "Five Zang Interrelation Theory" integrated these concepts into a mature framework. The spleen-kidney relationship became a cornerstone, encapsulating their physiological synergy, pathological interplay, and therapeutic reciprocity [6]. As Yizong Bidu summarizes: "The kidney, rooted in water, is the origin of life; the spleen, grounded in earth, nourishes all beings. "

2.2 Diagnosis and Treatment of Diabetic Nephropathy (DN) Based on the Theory of "the Correlation between the Spleen and Kidney"

Diabetes corresponds to the TCM syndrome of Xiao-Ke (wasting-thirst syndrome), with its renal complication termed Xiao-Ke Nephropathy in modern contexts. The disease is rooted in Yin deficiency with secondary dry-heat, wherein pathological interactions among the lung, spleen, and kidney culminate in systemic dysfunction: lung dryness disrupts fluid distribution, depriving the spleen and kidney of nourishment; stomach heat consumes lung Yin and kidney essence; kidney Yin deficiency fuels pathogenic fire, further damaging the lung and stomach. TCM interventions targeting Yin nourishment, heat clearance, and viscera harmonization demonstrate efficacy in alleviating symptoms, reducing proteinuria, and delaying renal deterioration. For instance, modified Shenqi Dihuang Decoction effectively treats Qi-Yin deficiency-type diabetic nephropathy, improving clinical manifestations, preserving renal function, mitigating chronic microinflammation, and restoring gut microbiota balance, highlighting its multi-target therapeutic potential [7].

3. Research Progress in Western Medicine on the Intestinal Microbiota and Diabetic Kidney Disease

3.1 Characteristics of Intestinal Microbiota Dysbiosis

The human gastrointestinal tract harbors a highly complex microbial ecosystem, comprising approximately 100 trillion microorganisms, including bacteria, fungi, viruses, phages, and archaea [8]. At the phylum level, the gut microbiota is predominantly composed of six major groups: Bacteroidetes,

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Firmicutes Verrucomicrobia,Proteobacteria,Actinobacteria,and Fusobacteria,with Bacteroidetes and Fir micutes collectively constituting over 90% of the total microbial biomass . The stability of this microbial community is critically linked to host health, where dysbiosis—characterized by shifts in taxonomic composition or functional capacity—has been implicated in the pathogenesis of metabolic, inflammatory, and immune-mediated disorders [9].

3.2 The Action Mechanism of the Intestine-Kidney Axis

The gut microbiome is a complex system that maintains dynamic metabolic and ecological balance. In adults, there are approximately 100 trillion bacteria, with 80% residing in the gut—about tenfold the number of human cells [10]. The gut microbiome encodes genes 150 times the size of the human genome, comprising over 5, 000 microbial strains and 1, 000 microbial communities. Dominated by anaerobic bacteria, it also includes viruses, protozoa, archaea, and fungi. Bacteroidetes and Firmicutes are the primary phyla, while Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia exist in relatively smaller quantities [11]. Early-life stress, such as maternal separation or prenatal stress, induces microbiota changes that may become risk factors for stress-related diseases in adulthood. For example, maternal separation reduces lactobacilli in (juvenile mice) feces within three days, causing long-term effects, while prenatal stress decreases Bifidobacterium and Lactobacillus in rhesus monkeys. The gut microbiota performs diverse functions: it forms an intestinal barrier, promotes epithelial cell regeneration,and nourishes the mucosa via short-chain fatty acids (SCFAs) [12]; stimulates innate immunity in early life to drive the maturation of gut-associated lymphoid tissue and activate adaptive immunity; synthesizes and metabolizes nutrients, hormones, and vitamins while aiding drug and toxin clearance; maintains a state of "low-grade physiological inflammation" for rapid pathogen defense; and inhibits pathogen growth through competitive exclusion, limiting their access to nutrients and cellular sites. These roles highlight its critical importance for human health [13]. The gut microbiota influences the brain not only via the nervous system—specifically through the neuroanatomical pathways of the gut-brain axis—but also through the endocrine, immune, and metabolic systems. The bidirectional communication between the gut and the brain is termed the gut-brain axis [14]. The origin of uraemic toxins in chronic kidney disease (CKD) is multiple. The importance of toxins generated by intestinal microbial metabolism is increasingly recognized. Intestinal bacteria degrade proteins reaching the colon into various metabolites like ammonium, amines, thiols, phenols and indoles. Some of these are absorbed and usually eliminated by the kidney, but accumulate in CKD. Intestinal flora play a significant role in producing toxins related to CKD, such as phenols (including p-cresol and its derivatives), indoles (like indoxyl sulfate), amines and polyamines. This shows a close connection between intestinal flora and the kidney, as the abnormal metabolism of intestinal flora can lead to the accumulation of toxins that impact the kidney's function and the progression of CKD [15].

4. The Theory of the Correlation between the Spleen and Kidney and the Intestinal Microbiota

4.1 The Biological Basis of Intestinal Microbiota Dysbiosis Caused by Spleen Deficiency

In individuals with spleen qi deficiency, dysfunction in digestion and absorption often leads to gastrointestinal discomfort or even diarrhea. Altered intestinal permeability triggers widespread gut microbiota dysbiosis, which in turn exacerbates spleen qi deficiency, forming a vicious cycle. Therapeutic approaches focusing on invigorating spleen qi can regulate the gut microbiota, aiding in the restoration of the physiological functions of the five zang-organs (heart, liver, spleen, lung, kidney) in traditional Chinese medicine theory [16]. Dysbiosis of the gut microbiota can lead to spleen dysfunction in transportation and transformation (a key physiological function in traditional Chinese medicine) and abnormal metabolism, triggering mineral metabolic disorders. This process further impairs kidney qi (vital energy), ultimately affecting renal function.

4.2 The Vicious Cycle Between Kidney Deficiency and Uremic Toxins

In the progression of chronic kidney disease (CKD), a tightly linked vicious cycle emerges between kidney deficiency—a core concept in traditional Chinese medicine (TCM)—and the retention of uremic toxins, which exacerbate renal damage. Uremic toxins are toxic substances that accumulate in the body due to the kidneys' impaired ability to excrete waste products in urine. Among these, the enterogenic uremic toxins p-cresyl sulfate (PCS) and indoxyl sulfate (IS) are prototypical examples [17]. Primarily generated by intestinal microbial metabolism, these toxins promote the progression of renal fibrosis and

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deteriorate renal function, forming a bidirectional pathological loop with kidney deficiency. From a TCM perspective, "kidney deficiency" encompasses insufficient renal qi (vital energy), which governs the body's water metabolism and detoxification processes. In modern medical terms, this aligns with declining renal functions such as reduced glomerular filtration rate (GFR) and impaired tubular secretion. Normally, the kidneys efficiently clear PCS and IS, which are produced when gut microbiota metabolize dietary amino acids (e. g. , tyrosine and tryptophan). However, as kidney deficiency progresses—manifesting as weakened "qi transformation" in TCM or dysfunctional renal excretion in biomedicine—the clearance of these toxins is severely compromised. Accumulated PCS and IS then exert direct toxic effects on renal tissues: they induce injury in renal tubular epithelial cells, promote the activation of fibroblasts, and accelerate the deposition of extracellular matrix proteins, leading to irreversible renal interstitial fibrosis. Concurrently, these toxins trigger inflammatory and oxidative stress responses in the kidneys, further damaging glomeruli and accelerating the decline of renal function. The cycle operates in two interdependent directions. On one hand, kidney deficiency—whether due to qi deficiency, yin deficiency, or other patterns—undermines the kidneys' ability to filter and eliminate uremic toxins, allowing PCS and IS to accumulate. This "toxin retention" is both a consequence of weakened renal qi and a driver of further renal injury. On the other hand, the toxic effects of PCS and IS disrupt renal cellular homeostasis: they interfere with mitochondrial energy metabolism, dysregulate epigenetic modifications (e. g. , DNA methylation), and activate pro-fibrotic signaling pathways (such as the TGF-β/Smad pathway) [18].

5. New Strategies for the Treatment of Diabetic Kidney Disease (DKD) with the Integration of Traditional Chinese and Western Medicine

5.1 Development of Traditional Chinese Medicine Compound Prescriptions Based on Microbiota Regulation

In the current medical field, the development of traditional Chinese medicine (TCM) compound prescriptions based on microbiota regulation has great potential. As we know, many kinds of traditional Chinese medicines and their compound prescriptions have a prebiotic-like effect, which can effectively promote the proliferation of intestinal bacteria and also have a good bidirectional regulatory ability. From the perspective of traditional Chinese medicine, intestinal microbiota imbalance can be differentiated into various syndrome types such as qi deficiency of the spleen and stomach, intense heat-toxin, and internal retention of damp-heat. For different manifestations of different syndrome types, different kinds of drugs such as qi-tonifying agents, heat-clearing agents, and spleen-invigorating and water-draining agents are used for treatment respectively, which can achieve comprehensive conditioning. For example, in the treatment of patients with chronic liver diseases complicated with intestinal microbiota imbalance, He Jinxiang added ecological preparations or lactulose preparations on the basis of conventional liver-protecting, enzyme-lowering and fluid-replacing treatments, and combined with traditional Chinese medicine therapies such as clearing heat and detoxifying, activating blood circulation and removing blood stasis, or invigorating the spleen and replenishing qi, and purging the bowels to achieve good curative effects [19]. In addition, in the study by Yang Chunjia et al. , it was found that the combined use of honeysuckle and prebiotics had a better effect than the use of honeysuckle or prebiotics alone, which coincided with the treatment principle of combining attacking and tonifying in traditional Chinese medicine. It can be seen that the development of traditional Chinese medicine compound prescriptions based on microbiota regulation is expected to bring new breakthroughs for the treatment of diseases related to intestinal microbiota [20].

5.2 Microbiota Transplantation and Personalized Treatment

Microbiota transplantation aims to treat diseases by transplanting the intestinal microbiota of healthy donors into the intestines of patients to re-establish the balance of the patients' intestinal microecology. With the deepening of research, microbiota transplantation technology has been continuously improved, evolving from traditional fecal microbiota transplantation to the current standardized preparation process, and has achieved remarkable efficacy in clinical applications [21]. The rise of the concept of personalized medicine has further promoted the development of microbiota transplantation. Each patient has differences in intestinal microbiota composition, disease status, genetic background, and lifestyle. Therefore, it is crucial to conduct precise microbiota transplantation treatment based on individual patient characteristics. Comprehensive analysis of patients' intestinal microbiota using technologies such as metagenomics and metabolomics can provide in-depth understanding of the patients' microbiota

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characteristics, thereby enabling the selection of suitable donors and the formulation of personalized transplantation plans to enhance the effectiveness and safety of treatment [22]. While modern medicine continues to explore microbiota transplantation and personalized medicine, the strategy of integrating traditional Chinese and Western medicine offers new perspectives for the development of this field. In traditional Chinese medicine theory, the "spleen and stomach" of the human body share many similarities with the functions of the intestinal microbiota. The holistic concept and the ideology of syndrome differentiation and treatment emphasized in traditional Chinese medicine coincide with the concept of personalized medicine. During the process of microbiota transplantation, traditional Chinese medicine syndrome differentiation methods can be integrated to identify the constitution of patients, and appropriate treatment timings and adjuvant therapies can be selected according to different constitution types. For example, for patients with spleen and stomach deficiency, traditional Chinese medicine can be used for conditioning before and after microbiota transplantation to improve the function of the spleen and stomach, enhance the intestinal adaptability to the transplanted microbiota, and improve the treatment effect [4]. In addition, external treatment methods of traditional Chinese medicine, such as acupuncture and tuina, can also regulate the flow of qi and blood in the meridians of the human body, improve the intestinal microecological environment, and work synergistically with microbiota transplantation. The strategy of integrating traditional Chinese and Western medicine is also reflected in the rehabilitation management of patients after microbiota transplantation. Traditional Chinese medicine emphasizes the regulation of diet, emotions, and other aspects. By guiding patients to maintain a reasonable diet, avoid foods that damage the spleen and stomach, and keep a pleasant mood, it can promote the colonization and growth of the transplanted microbiota in the patients' intestines. At the same time, combined with the function of traditional Chinese medicine in strengthening the body's resistance, it can enhance the patients' immunity and prevent the recurrence of diseases.

Microbiota transplantation and personalized medicine represent important advancements in modern medicine, and the strategy of integrating traditional Chinese and Western medicine injects new vitality into their development. By integrating the advantages of traditional Chinese and Western medicine, there is hope to further improve the efficacy of microbiota transplantation and bring the promise of recovery to more patients. In the future, with the continuous deepening of research, the model of microbiota transplantation, personalized medicine, and the integration of traditional Chinese and Western medicine will play an important role in the treatment of more diseases and promote innovation and development in the medical field.

6. Discussion and Prospect

Clinical efficacy validation is a cornerstone of therapeutic optimization, playing a pivotal role in advancing medical treatments from theoretical concepts to practical applications. In the realm of microbiota transplantation and personalized medicine, particularly when integrating traditional Chinese medicine (TCM) and Western medicine, the validation of clinical efficacy becomes even more crucial. The "microbiota-guided" integrated TCM-Western medicine approach, while demonstrating unique and significant advantages in addressing complex diseases, currently faces a notable limitation—the absence of robust, high-quality evidence-based medical validation. This gap hinders its widespread adoption and integration into mainstream medical practices. The lack of comprehensive validation primarily stems from the complexity of this interdisciplinary approach. The interplay between TCM theories, Western medical techniques, and the dynamic nature of the gut microbiota creates a multifaceted system that is challenging to evaluate using traditional clinical trial methods. Moreover, the subjective nature of TCM syndrome differentiation and the diverse range of biomarkers involved in microbiota and metabolic studies further complicate the process of establishing clear, objective efficacy metrics. To overcome these challenges, future research endeavors should embrace innovative and adaptive clinical trial designs. Implementing graded intervention groups within these trials can offer a more nuanced understanding of the treatment's efficacy. For instance, different subgroups could receive varying intensities or combinations of TCM therapies, Western medical interventions, and microbiota transplantation procedures. This approach allows researchers to dissect the individual and synergistic effects of each component, providing valuable insights into the optimal treatment strategies. In the context of diabetic kidney disease (DKD) patients, a prime focus should be on evaluating multiple outcome measures. Beyond the conventional clinical endpoints, assessing improvements in TCM syndrome scores can capture the holistic changes in a patient's condition from a TCM perspective. Renal function indices, such as estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR), remain essential markers for evaluating the progression and treatment response of DKD. Additionally, quantifying the gut microbiota α-diversity can offer insights into the restoration of the gut

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microecological balance, which is closely linked to the overall health and disease management of DKD patients. Simultaneously, the development of efficacy prediction models based on microbial metabolic functions holds great promise. By leveraging advanced bioinformatics and machine learning techniques, researchers can analyze the vast amount of data generated from metagenomic and metabolomic studies. These models can identify key microbial metabolites and metabolic pathways associated with treatment responses, enabling the prediction of individual patient outcomes. Such predictive capabilities not only enhance the precision of treatment but also facilitate personalized medicine approaches, where treatments can be tailored to the specific needs and characteristics of each patient. The integration of metabolomics and metagenomics has indeed breathed new life into DKD research. Metabolomics, which focuses on the comprehensive analysis of small-molecule metabolites in biological samples, provides a snapshot of the physiological state of an organism. When combined with metagenomics, which explores the genetic material of microbial communities, it offers a more complete picture of the complex interactions between the host and its microbiota. Constructing three-dimensional correlation models of "TCM syndromes-characteristic microbiota-differential metabolites" represents a significant leap forward in understanding DKD. These models enable researchers to systematically analyze the biological processes underlying disease progression, uncovering the intricate relationships between TCM syndromes, the composition and function of the gut microbiota, and the metabolic profiles of patients. By precisely interpreting the interactive network among "syndromes-microbiota-metabolites, " these models can help identify novel biomarkers and therapeutic targets. This new understanding also has far-reaching implications for TCM. By understanding how specific microbial communities and metabolites influence disease progression, researchers can design more effective treatment regimens that target the gut microbiota. This could involve the use of prebiotics, probiotics, or even customized microbiota transplantation protocols tailored to the unique microbiota profiles of DKD patients. In conclusion, the integration of advanced research methodologies, innovative clinical trial designs, and interdisciplinary approaches is essential for validating the clinical efficacy of the "microbiota-guided" integrated TCM-Western medicine approach. By addressing the current gaps in evidence-based validation and leveraging the power of metabolomics and metagenomics, this approach can be transformed into a more precise, effective, and reliable therapeutic strategy, heralding a new era of precision medicine in the treatment of DKD and potentially other complex diseases.

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