

# Discussion on the Etiology and Pathogenesis of Diabetic Nephropathy based on Chen's Three-cause Theory

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**Abstract:** *The etiological theory of traditional Chinese medicine began in the Yellow Emperor's Neijing, was based on the Jinkui Yaolu, and became an important part of the entire theoretical system of Chinese medicine. Diabetic nephropathy is one of the most important chronic microvascular complications of diabetes and a common cause of end-stage renal disease. TCM treatment can reduce proteinuria and delay the progression of kidney disease. Based on the "Three Causes Theory" and related theories of traditional Chinese medicine, this paper expounds the etiology and pathogenesis of diabetic nephropathy, and puts forward the diagnosis and treatment idea of "internal repair, external control, and insulated moderation". The purpose of this paper is to help readers better understand and apply the theory of "Three Causes" and apply it to diabetic nephropathy, and to demonstrate the Chinese medicine ideas contained in the "Three Causes Theory" and its significance to the prevention and treatment of modern diseases.*

**Keywords:** Three-cause theory, Diabetic nephropathy, Etiology, Pathogenesis.

## 1. Introduction

Diabetic Kidney Disease is a glomerulosclerosis caused by diabetes, the most common complication of diabetes and one of the leading causes of renal dialysis in developed countries [1]. Characterized by proteinuria, impaired renal function, or both, it affects over 840 million people worldwide [2]. Approximately 40% of type 2 diabetes (T2D) patients and 30% of type 1 diabetes (T1D) patients develop DKD. With the rising global prevalence of diabetes, DKD cases are expected to increase by nearly 50% in the next 24 years, reaching 783 million [3]. Prolonged diabetes leads to the production of advanced glycation end products, activation of the growth factors, hemodynamic and hormonal changes, increased release of reactive oxygen species and inflammatory mediators, resulting in glomerular basement membrane thickening, diffuse and nodular mesangial expansion, podocyte injury, and glomerulosclerosis. These pathological changes are often accompanied by significant tubulointerstitial inflammation and fibrosis [4]. Western medical interventions primarily focus on controlling blood glucose, blood pressure, and inhibiting the renin-angiotensin system. Treatment recommendations include targeting a glycated hemoglobin concentration <7% and blood pressure <140/90 mmHg, with RAS blockers as the cornerstone therapy [4], aiming to slow renal failure progression and reduce associated high cardiovascular risks. However, blood glucose and blood pressure control alone have been shown insufficient to completely prevent DKD progression to end-stage renal disease [5]. Numerous studies indicate that traditional Chinese medicine (TCM) can improve proteinuria, protect renal function, and delay disease progression [6–7].

The "Three-Cause Theory" was proposed by Chen Wuzhe of the Song Dynasty as a classification of disease etiology, dividing causes into internal, external, and non-internal-non-external categories, forming the foundation of TCM etiology. Historical physicians held varying interpretations of this theory, but this paper primarily focuses

on Chen Wuzhe's Three-Cause Theory. The author briefly analyzes the "Three-Cause Theory" and related TCM principles, combining them with DKD's pathological features, clinical characteristics, and research progress to propose the TCM treatment principle of "Internal Cultivation, External Defense, and Moderation", discussing its etiology, pathogenesis, and therapeutic strategies to improve the health and quality of life of DKD patients.

## 2. Explanation of the Three-Cause Theory

The Three-Cause Theory first appeared in Su Wen·Tiao Jing Lun: "The birth of pathogenic factors may originate from yin... yin-yang, joy, and anger." It linked etiology to the location of disease onset, clarifying the classification of yin and yang. Later, Ling Shu Jing·Bai Bing Shi Sheng stated: "The onset of all diseases... arises from three types of qi, each injuring differently," proposing a tripartite classification of etiology. By the Eastern Han Dynasty, Zhang Zhongjing summarized it in Jin Gui Yao Lue: "Countless diseases do not exceed three categories: first, meridians and collaterals affected by pathogens entering the zang-fu organs... third, injuries from sexual indulgence, weapons, or insect/animal bites." This marked the inception of the "Three-Cause" concept. In the Song Dynasty, Chen Wuzhe expanded upon Nei Jing and Jin Gui Yao Lue, pioneering the "Three-Cause Theory" as a systematic classification of etiology. He established a TCM diagnostic framework centered on etiology, with pulse, disease, syndrome, and treatment as its pillars. Chen's theory categorized causes as:

Internal Causes: The seven emotions—anger, joy, worry, pensiveness, grief, fear, and fright. External Causes: The six climatic pathogens—wind, summer heat, dampness, cold, dryness, and fire. Non-Internal-Non-External Causes: Factors outside the first two categories, such as dietary irregularities, overexertion, trauma, or insect/animal bites—essentially external causes violating normal physiological limits. His book San Yin Fang further elaborated: "The six climatic

pathogens are the normal qi of heaven... classified as external causes; the seven emotions are the normal nature of humans... classified as internal causes; while dietary excess or hunger," shouting injuring qi... are non-internal-non-external causes. This emphasized that each etiology has unique pathways of invasion and pathogenesis. Chen emphasized etiology, basing the Three-Cause Theory on "diagnosis via etiology" and "syndrome differentiation to trace causes." By integrating clinical symptoms, syndrome patterns, and pathological mechanisms, the theory delves into disease origins to guide treatment—summarized as "differentiate the three causes, unify in treatment." As stated, "Treatment methods must first examine the three causes; once clarified, the approach will invariably target the root." This highlights the theory's significance in clinical practice: without understanding etiology, disease origins remain obscure. The Three-Cause Theory's classification method, combining pathogenic factors and disease pathways, refined TCM etiology. It encompassed Nei Jing's yin-yang dichotomy while advancing Jin Gui Yao Lue's reverse-pathology approach, offering enduring guidance for clinical syndrome differentiation [8].

### 3. Applying the Three-Cause Theory to DKD

The Three-Cause Theory divides complex diseases into three categories — internal, external, and non-internal-non-external — each with diagnostic and therapeutic frameworks. By analyzing disease origins, pulse, and syndromes, it identifies causes, infers pathological mechanisms, summarizes syndrome patterns, and guides treatment [9].

DKD arises from prolonged diabetes-induced kidney damage, involving external invasions, dietary imbalances, emotional disturbances, and overexertion. Per the Three-Cause Theory: Internal Causes: The seven emotions. External Causes: The six climatic pathogens.

Non-Internal-Non-External Causes: Dietary and lifestyle excesses (excluding trauma/insect bites). These causes interact, generating pathological products like phlegm-turbidity, blood stasis, and turbid toxins that exacerbate DKD.

#### 3.1 Internal Causes of DKD

Emotional activities are normal physiological responses, but their pathological impact depends on individual psychological resilience [10]. Abnormal emotions thus contribute to DKD. The Three-Cause Theory specifies internal injuries from the seven emotions: anger, joy, worry, pensiveness, grief, fear, and fright. DKD falls under TCM categories like "lower wasting," "kidney wasting," or "kidney decline," resulting from chronic diabetes damaging the zang-fu organs, ultimately depleting kidney yin/yang and life-gate vitality [11]. Its pathogenesis involves spleen-kidney deficiency as the root and phlegm-stasis as the branch—a deficiency-excess complex [12]. Morphologically, the spleen is deficient while the kidney is excessive; functionally, the spleen is excessive while the kidney is deficient, with emotional factors persisting throughout [13]. Emotions remain harmless when balanced ("tranquil spirit"), but excess ("agitated emotions") induces disease [14]. Qing Dynasty's Huang Yanyu noted in *Si Sheng Xin Yuan*: "Wasting-thirst is a foot jueyin disorder... liver qi stagnation forces improper discharge, disrupting

ministerial fire's storage." This highlights the liver's role in diabetes pathogenesis via qi dysregulation. Ling Shu·Wu Bian states: "A rigid heart breeds anger, driving qi upward... leading to wasting-thirst," linking stubbornness and anger to diabetes. Lin Zheng Zhi Nan Yi An [15] adds: "Melancholy ignites internal fire, causing wasting-thirst," implicating chronic stress in yin-blood consumption and fluid depletion. Diabetic patients often endure lifelong treatment, fostering tension, anxiety, and fear, which impair liver qi dispersion, disrupt zang-fu functions, and manifest as edema, proteinuria, hypertension, or renal dysfunction [16]. Su Wen·Ben Shen states: "Fearful overthinking injures the spirit... chronic fear damages essence, causing bone weakness and spontaneous emissions." Emotional extremes injure organs, precipitating disease. In DKD: Overthinking harms the heart-spirit, leading to emaciation and fatigue.

Excessive worry knots spleen qi, causing abdominal distension and poor appetite, impairing blood production. Grief damages the liver's ethereal soul, triggering irritability and headaches; liver-blood deficiency dries the eyes and stiffens sinews.

Rage injures the kidney's will, causing confusion, lumbar weakness, and proteinuria; kidney-water dysfunction yields edema. The sequence of emotional damage in DKD begins with liver stagnation overwhelming the kidneys (via Wood overacting on Water), spleen-earth failing to control water, and heart-fire failing to warm kidney-water—culminating in kidney decline. Damaged zang-fu organs further disrupt emotions, as Su Wen·Ben Shen notes: "Liver qi deficiency causes fear, excess causes anger; heart qi deficiency causes grief, excess causes incessant laughter." Emotional factors primarily drive DKD via liver qi stagnation, disrupting qi-blood harmony, gradually weakening the heart-spleen, and ultimately the kidneys [13]. Qi stagnation also induces water retention and blood stasis. The emotion-DKD relationship is bidirectional: emotional disorders cause diabetes progressing to DKD, while DKD exacerbates emotional instability, indirectly affecting glucose metabolism via qi-blood-fluid imbalances [17], accelerating DKD progression [18]. Modern medicine confirms that stress and anxiety aggravate DKD [19].

#### 3.2 External Causes of DKD

The external causes are the six climatic pathogens, which transform from normal "six qi" (wind, cold, summer heat, dampness, dryness, fire) when excessive or untimely, overwhelming the body's adaptability. Ling Shu·Bai Bing Shi Sheng states: "Wind, rain, cold, and heat... cannot injure alone." Su Wen·Ping Re Lun adds: "Where pathogens gather, qi must be deficient." Chronic diabetes weakens zang-fu organs, making them susceptible to external pathogens, which further deplete healthy qi, disrupt qi-blood balance, and impair kidney qi, culminating in DKD. This aligns with modern virology: infections (e.g., enteroviruses) trigger type 1 diabetes via cross-reactive immunity, exacerbating autoimmunity and DKD [20]. Clinically, DKD patients experience worsened renal function after exposure to pathogen [21]. Dong Yuan Shi Shu·Xiao Ke Lun notes: "External cold pathogens, after three days, deplete grains and fluids, transmitting inward to cause wasting-thirst,"

describing how pathogens invade the lungs, transform into heat, attack the spleen-stomach, and generate lung-dryness/stomach-heat, progressing to kidney yin depletion and DKD. Key pathogens in DKD include wind, fire/heat, and dryness, which readily consume fluids and qi, causing “triple wasting.” External pathogens induce diabetes, which damages kidney qi, while diabetes weakens zang-fu organs, facilitating infections—a vicious cycle accelerating DKD.

### 3.3 Non-Internal-Non-External Causes of DKD

These primarily involve dietary irregularities and overexertion/inactivity. Su Wen·Qi Bing Lun states: “Sweet mouth disease arises from five qi overflow... due to overeating rich foods... progressing to wasting-thirst,” linking diet to diabetes.

**Dietary Excess:** Rich, spicy, or sweet foods damage the spleen-stomach, generating heat that dries fluids, causing diabetes. Latent heat later injures the kidneys, impairing essence retention and leading to DKD. Modern studies confirm poor diet as a key DKD factor [22]. **Overexertion:** Sexual Overindulgence: Depletes kidney essence, unbalancing water-fire dynamics, drying kidney yin, and worsening proteinuria [23]. **Physical Overwork:** Su Wen·Ju Tong Lun states: “Strain depletes qi,” injuring lung-spleen qi, depleting fluids, and causing yin-deficient heat. **Prolonged Inactivity:** Su Wen·Xuan Ming Wu Qi warns: “Prolonged sitting damages flesh; prolonged lying damages qi,” causing qi stagnation, phlegm-dampness, and blood stasis that injure the kidneys [24].

## 4. Treatment Principles for DKD Based on the Three-Cause Theory: “Internal Cultivation, External Defense, and Moderation”

Given DKD’s complex etiology, treatment remains challenging. The proposed principles aim to improve renal function and delay progression.

### 4.1 Internal Cultivation

Emotional disorders cause qi stagnation, organ dysfunction, and yin-yang imbalance, leading to diabetes and DKD. Modern biopsychosocial models emphasize psychological factors. Thus, “Internal Cultivation” involves mental serenity, moral refinement, and emotional balance. **Clinician/Family Role:** Provide counseling to alleviate stress and foster optimism. **Self-Regulation:** Techniques like mindfulness, music therapy, cognitive-behavioral methods, qigong, Tai Chi, or emotion-countering therapies (e.g., laughter for grief) show clinical efficacy [25-26]. Zhang Fengying et al. [27] found emotional interventions enhance medication adherence, self-management, and quality of life in DKD patients.

### 4.2 External Defense

Since external pathogens exacerbate DKD, “External Defense” combines prevention and treatment. **Harmonizing with Nature:** Adapt to seasonal changes (“time-place-person” triad) to avoid pathogens. **Strengthening Healthy Qi:** As Su Wen states: “With healthy qi intact, pathogens cannot invade.” Qi must be sufficient, unblocked, and harmonized to resist disease, repair

tissues, and adapt to stressors [28].

### 4.3 Moderation

Dietary therapy is central to DKD management, improving metabolism and quality of life [29]. **Dietary Guidelines:** Balance glucose control, renal function, and nutrition.

Reduce carbohydrates/fats; adopt low-sugar, low-protein diets. Avoid alcohol, smoking, and stimulants (e.g., coffee, strong tea). Modern studies confirm dietary therapy slows DKD progression [30]. Guo Zongcheng et al. [31] showed low-protein diets improve  $\beta$ -cell function, reduce oxidative stress, and modulate gut microbiota/mTOR pathways. Le Nina [32] demonstrated internet-based personalized diets enhance glycemic control and renal function in stage III–IV DKD. Han Kun [33] and Hu Yuanni [34] reported dietary interventions improve nutrition, stabilize glucose, and elevate quality of life. **Activity Balance:**

**Avoid Sexual Overindulgence:** Preserve kidney essence to prevent premature aging and DKD.

**Exercise Moderately:** Neither overwork (injuring qi) nor inactivity (causing stagnation). Follow the golden mean — “labor without exhaustion,” aligning with TCM’s harmony philosophy.

## 5. Conclusion

The Three-Cause Theory’s categories are interconnected, jointly influencing DKD’s onset and progression. As a chronic disease, understanding its internal, external, and non-internal-non-external causes enables better prevention. Thus, the “Internal Cultivation, External Defense, and Moderation” principles offer a TCM framework to: Regulate emotions and nurture the spirit. Defend against external pathogens via holistic adaptation. Moderate diet, activity, and lifestyle excesses. Applying the Three-Cause Theory in modern clinics preserves TCM heritage while improving DKD management, broadening therapeutic perspectives.

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