

Combing and exploring the origin and development of diabetic nephropathy based on the theory of collateral disorders

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Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81860836), Lin Dan inheritance studio project of national famous and old traditional Chinese medicine expert (No. State Administration of Traditional Chinese Medicine (2016) No. 42) and Hainan Natural Science Foundation (No.2019CXTD407).

Citation

Xie YR, Ma TP, Lin D, Yu YC, Xie YQ. Combing and exploring the origin and development of diabetic nephropathy based on the theory of collateral disorders. *Hist Philos Med.* 2022;4(1):5. <https://doi.org/10.53388/HPM20220101005>.

Executive editor: Na Liu.

Received: 19 October 2021; Accepted: 29 November 2021; Available online: 02 December 2021.

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Abstract:

By searching TCM disease names "Xiao Shen", "Shen Xiao" and "Xin Xiao", which are considered higher degree of coincidence with diabetic nephropathy according to study. And combined with the theory of collateral disorders, sort out the classic literature of traditional Chinese medicine and modern experts' works in chronological order. To make a preliminary exploration of the origin of diabetic nephropathy based on the theory of collateral disorders. Hope to provide reference for TCM theory and clinical research on treating diabetic nephropathy from the theory of collateral disorders in the future.

Keywords: diabetic nephropathy; the theory of collateral disorders; classic literature

Diabetic nephropathy (DN), also known as diabetic glomerulosclerosis, is a glomerulopathy that is mainly caused by systemic microvascular damage. It is one of the most common systemic microvascular complications of diabetes, and is also one of the main causes of end-stage chronic renal failure. If having diabetes for a long time, it can easily affect the microvessels of the eye, kidneys, peripheral nervous system, and the large vessels of the heart, brain and lower extremities.

This disease belongs to the categories of "edema", "Shenxiao", "Xiaoshen", "Xiaodan", "Nidu", "Xiaoke", "Guange" and "Neixiao" in the theory of traditional Chinese medicine. Since the first mention of "Xiaoke" [1] in the *Huangdi Neijing* and the introduction of the name of diabetic nephropathy in western medicine, most doctors have classified this disease into diabetes and named it "Xiaoke". This disease belongs to the typical "collateral disorders due to the long illness" and "kidney disorders due to the long illness". In recent years, with the continuous deepening of research on diabetic nephropathy and the continuous development and improvement of the theory of collateral disorders, remarkable progress has been made in the treatment of this disease from the theory of collateral disorders. Diabetic nephropathy, however, is a modern disease name. The theory of treating diabetic nephropathy from collateral disorders theory is scattered in traditional Chinese medicine literature and has not been systematically organized. According to the statistical data of relevant literature, the majority of modern experts reached agreement on the conformity degree between "Xiao Shen", "Shen Xiao", "Xiao Xiao" and diabetic nephropathy [2]. Xiaoke generally refers to diseases characterized by drinking more, eating more, urinating more, losing weight, or sweet urine in the theory of traditional Chinese medicine. This disease is called "Xiao Dan" in *Huangdi Neijing*. Thirsty for water is "Shang Xiao", which means diabetes involving the upper warmer. Easy to be hungry is "Zhong Xiao", which means diabetes involving the middle warmer. Urinate immediately after drinking is "Xia Xiao", which means diabetes involving the lower warmer. The above three kinds are collectively referred to as "Xiaoke", also known as Three Xiao. Therefore, this subject used the three words as key words to explore the source and course of treatments of diabetic nephropathy from the theory of collateral disorders, combing and searching its origin and development process.

Origin

The beginning of diabetic nephropathy is in the kidney. From the perspective of collateral disorders, the kidney collateral should be to blame. The theory of collateral disorders was first seen from the early Qin Dynasty to the Warring States period, originated in *Huangdi Neijing*, which put forward the concept of "collateral" for the first time and laid the foundation of collateral disorders theory. The chapter 17 of the *Methods of Pulse Examination* said "The meridians are the internal, the branches are the collateral, and the other branches are the minute collateral." The etiology and pathogenesis of diabetic nephropathy in traditional Chinese medicine are congenital insufficiency or acquired diet disorder, emotional disorder, excessive labor, Yin deficiency fire and fluid depletion. It has long been harmful to qi and jin, resulting in injuries both of qi and Yin deficiency. The course of disease is long, with the righteousness deficiency. The final pathological changes are the spleen and kidney deficiency or yin-yang deficiency, which will lead to the deficiency of kidney collateral and cause phlegm turbidity, congestion and other pathological products block, over time phlegm and blood stasis mutual knot, stagnation form. The formation of accumulation is discussed in Chapter 66 of *Lingshu*: "deficiency and evil invade human also start from the skin... Stay but don't go away, pass it away from the intestines and stomach, collect the original, stay in the pulse, stay but don't go away, and rest to form accumulation. Or attach to the minute collaterals, or collaterals..." Which has pointed out the pathological changes of the accumulation and stagnation information is that body's positive deficiency lasts for a long time, while the evil Qi remains in the collaterals and don't go. In the same chapter says "if the collateral injury of the intestines and

stomach, the blood overflows outside the intestines, there is cold outside the intestines, and the juice foam fights with the blood, then it is combined, condensed and accumulated." It is pointed out that due to evil invading the collaterals of the intestines and stomach, the collaterals are damaged and the blood overflows outside the intestines. If there is cold outside the intestines, the juice foam and the overflowing blood gather and coagulate together without dissipation, that is, the accumulation of body fluid and blood is formed by the cold coagulation. Because blood flows in collaterals, body fluid and blood stagnation should belong to collaterals.

Modern medical research holds that the nephron composed of renal corpuscle and renal tubules is the basic unit of renal structure and function, and the capillaries in the renal corpuscle come from the branches of renal artery. Each primary branch of renal artery protrudes into the renal capsule from the blood vessel pole and then branches to form a reticular capillary loop, which is similar to the structural characteristics of horizontal separation and layer by layer subdivision of renal collateral branches. It is identical with the concept of collaterals in traditional Chinese medicine. A significant clinical manifestation of diabetic nephropathy is glomerular microangiopathy. Along with the progression of the disease, the mesangial matrix increased and the basement membrane thickened and the arteriolar hyaline transformation developed. Finally, it developed to glomerulosclerosis, which was consistent with the pathological changes of peripheral vessels caused by the accumulation of phlegm and blood stasis.

Development

Han Dynasty

In the *Treatise on Cold Damage and Miscellaneous Diseases* of Han Dynasty, Zhang Zhongjing first put forward the concept of "vein and collaterals" and the pathogenesis of "Ying-qi and Wei-qi are blocked, blood unable to flow" [3]. In the *Synopsis of Golden Chamber*, he set up articles such as edema, arthralgia syndrome, jaundice, liver obstruction and consumptive disease, discussed the diseases and syndromes related to the pathogenesis of "blood stasis in the collaterals" [4], connecting the past and the future, and opened the precedent of the method of activating blood circulation, removing blood stasis and dredging the collaterals and the method of searching and clearing the collaterals by insects and ants, which laid the foundation of syndrome and treatment of collateral disease theory [5]. In the *Synopsis of Golden Chamber*, although it is not clear that drugs for activating blood circulation to remove blood stasis and dredge collaterals are used to treat diabetes, but it is effective for diabetic nephropathy according to the research of later generations, especially the Didang Decoction and the Dahuang Zhechong Pill (DZP). Duhang Decoction is composed of rhubarb, peach kernel, gadfly and leech. It is a classic recipe for breaking blood and removing blood stasis in the treatment of blood stasis in the lower energize syndrome. It has the effects of breaking blood and removing blood stasis, promoting blood circulation and dredging collaterals. The subjects were treated with the decoction to prevent the pathological changes of diabetic kidneys, improve the renal function and inhibit the expression of ICAM-1 in the renal cortex. The experimental results prove that the decoction can protect the kidneys of diabetic nephropathy. The mechanism may reduce the inflammatory response by inhibiting the expression of ICAM-1, thereby reducing the urinary protein and slowing down the progression of diabetic nephropathy [6]. Dahuang Zhechong pill is composed of cooked rhubarb, leech, soil Zhechong, grub, gadfly, peach kernel, dry paint, bitter almond, *Scutellaria baicalensis*, *Rehmannia glutinosa*, white peony, licorice, etc. according to modern pharmacological analysis, it can improve microcirculation and reduce blood viscosity. The main components of it is Zhechong, which can inhibit platelet aggregation and reduce adhesion rate. Gadfly and leech have antithrombin effect, can inhibit blood coagulation and platelet aggregation, and have effect on peripheral blood vessel occlusion and stenosis, as well as the main factors causing pathological changes, and the metabolic disorder of sugar, fat and

protein [7]. Zhang Zhongjing, according to the theory of yin and Yang in *Su Wen*, "To distinguish between Qi and blood, those with excess blood use the method of purging blood, and those with deficiency of Qi use the method of ascending and tonifying blood". He developing and initiating the method of promoting blood circulation, removing blood stasis and dredging collaterals, which is one of the most important methods for clinical treatment of diabetic nephropathy and kidney disease.

Tang Dynasty

Wang Tao of Tang dynasty recorded the disease name of "Shenxiao Disease" in *Arcane Essentials from the Imperial Library* [8]. When discussing the name of the disease, he quoted the *Gu Jin Lu Yan Fang* written by Zhen Liyan of Sui Dynasty, "There are three diseases of Xiao Ke... Thirsty and can't drink much, urinate a few, Yin is weak, but the legs are swollen and the feet are thin first, it is Shenxiao disease." [9] The description of Xiao Ke disease related symptoms is similar to that of diabetic nephropathy.

Song Dynasty

Northern Song Dynasty Wang Huaiyin and others in the Northern Song Dynasty wrote *Taiping Shenghui Fang*. In volume 53, the prescriptions for treating and eliminating the Shenxiao and white turbid urine said, "urinating immediately when drinking water, the urine tastes sweet and white, and the waist and legs are thin, it is Shenxiao." "Urine is as white as fat is Shenxiao. This is caused by fatigue and injury to the kidney, which is also due to kidney qi deficiency and cold. The kidney governs water, while the opening of the orifices is in Yin. Yin is the way of urination. Because bladder cold and kidney injury, so urine is white and like fat, or like bran." "The same article discusses the prescriptions for treating and eliminating Shenxiao: "Xiaoshen are kidney deficiency and fatigue, bladder cold and damage, spleen and stomach qi failure, exopathogen heat and toxin turn fierce hot. Even if you eat food, you can't nourish your skin. Your legs and shins are thin, your joints are sore, and your urine is frequent, so it's called Xiaoshen. A person who usually indulges without restraint, when kidney qi is weak in old age, the disease occurs. Being afraid of not having sexual intercourse when in young age, so take more Shi San to help to get fun. Excessive use leads to exhaustion of Qi, isolation of Wei Qi and wasted body. The mouth is dry, the semen is discharged by itself, or the urine is white and turbid, the stool is dry and difficult to discharge, and the food you eat turns into urine, which consumes kidney qi, so it is called Xiaoshen." Which pointed out the disease name, etiology and pathogenesis of Xiaoshen [10]. In volume 59 of *General Medical Collection of Royal Benevolence*, it pointed out that the kidney collaterals are damaged, the opening and closing function of the kidney is abnormal, and the essence cannot be absorbed. The urine sugar increases and proteinuria appears when it is excreted with the urine. "People suffering from Xiaoshen have excessive sexual intercourse and take Shi San when they are young, which lead to depletion of blood essence and dry of kidney water. Feeling Thirsty and drinking water, water flows down into the bladder, leading to urination increases, legs are thin and joints are sore. So it's called Xiaoshen." Volume 52 records the treatment of Xiaoshen: "It can cure kidney deficiency, urinate more, weak joints, and become thinner and thinner day by day, which called Xiaoshen. Cistanche Pill includes Cistanche deserticola (remove chapped skin, roasted with wine), aconite (cracked and navel peeled), Tribulus terrestris (fried, remove horn), mulberry cuttlebone (fried two liang for each), Schisandra chinensis (fried), keel (grind, one liang for each), Astragalus membranaceus (file, fried), dodder powder, Dendrobium (remove root, one and a half liang for each). The above nine drugs are crushed into powder and added honey to synthesize the bolus like the volume of Wutong seed. Take 20 pills with saline at a time on an empty stomach [11]. Tang Shenwei put forward the method of treating the Xiaoshen with a single drug of pilose antler in *Classified Materia Medica*: "Tang Shenwei put forward the method of eliminating the kidney with a single drug of pilose antler in *Classified Materia Medica*: "treat the Xiaoshen and excessive urination. Usin one

antler, scorch and sift. Take a square cun spoon with wine, and gradually add it to one and a half spoon." [12]

Southern Song Dynasty Yang Shiyong of the Southern Song Dynasty describe the name of the disease in the *Effective Recipes from Renzhai House*: "When the heat is latent in the lower part, the legs and knees are skinny, the joints are sore, the essence is lost and bone is marrow emptiness. Drinking water to save himself, but unable to drink too much. Then drown in low part, urinate more and turn to turbid. The disease belongs to lower energizer, which is called Xiaoshen." [13] Zhu duanzhang's *Weisheng Jiabao Fang* points out that edema can occur with a long course of disease, and the condition is serious: "Long term illness will lead to edema, or back sores, or foot and knee have leakage sores, which may cause death." He also said, "for a long time, the symptoms change to frequent urination, its color like thick oil, there is a floating membrane on it, its taste is sweet as honey, attract all insects gather to eat. It is also a crisis, which is named Xiaoke." [14] It is pointed out a critical syndrome that if urine turbidity occurs. Zhang Rui's *Jifeng Puji Fang* records Ejiao Decoction to treat deficiency heat, excessive urination, or feeling the wind-cold, appear beriberi, Xiaoke and Xiaoshen, the pulse is thin and weak. Take this decoction and the symptoms will be relieved immediately. It includes donkey hide gelatin (half liang), dried ginger (seven liang), pockmarked seeds, Polygala tenuifolia (one and a half liang for each), aconite (one). The above drugs are ground into coarse powder. Each time take three qian of water, fry two to one zhan and then take it. If urinate more, dozens or more times day and night, take the White Poria cocos Pill recorded in the *Ben Cao Jian Yao Fang* frequently. It includes white Poria cocos, raspberry, trichosanthes root, Coptis chinensis, trichosanthes root, ginseng, Radix Rehmanniae and Radix Scrophulariae (one liang for each), Dendrobium and Fructus Cnidii (seven qian and five fen for each), thirty chicken stomachs (light stir-frying). The above drugs grind into the powder, add honey and synthesize bolus like wutong seed. Take 30 pills at a time with Cishi Decoction. It can cure the thinning of legs, the weakness of waist and feet caused by Xiaoshen [15].

Jin Dynasty

Liu Wansu of the Jin Dynasty put forward in the *Three Xiao Lun* that "those who drink more and eat more are Xiaoke, those who eat more are Xiaozhong, those who has muscle wasting and urinate with fat liquid are Xiaoshen. These are Three Xiao diseases. Although it is not recorded, according to the *Huangdi Neijing*, it is also dryness-heat." [16] It is pointed out that those who has Xiaoshen often have fat liquid in their urine.

Ming Dynasty

The *Mi Zhuuan Zheng Zhi Yao Jue Ji Lei Fang* of Ming Dynasty records the etiology and pathogenesis of Xiaoshen: "Xiaoshen is a very serious disease. In ancient times, it was called Qiangzhong. It is also called Neixiao. Mostly because of wanton lust and abuse of drugs. Kidney qi is weak, shi qi is independent with no nutrient. Therefore, the kidney yang is deficient, there is no semen, urination is frequent, mouth and lips are dry." [17] Li Shizhen's *Compendium of Materia Medica* records Walnut Pill: "It can cure Xiaoshen caused by lacking moderation of sexual behavior and abusing drugs, or emotional disorder hurts kidney. Which can lead to weak water and strong fire, dry mouth and tongue, uncontrolled ejaculation of semen, or deep-coloured urine, dry and solid stool, or urinate a lot without thirst. Four Liang walnut meat, four Liang white Poria cocos and one liang aconite (peeled and sliced). Ginger juice and clam powder are baked at the same time to powder. Add honey and synthesize bolus like wutong seed. Take 30 pills at a time with rice soup (*Puji Fang*)." [18] According to the *Yi Fang Lei Ju* compiled in the 25th year of Emperor Li Yi, the emperor Shizong of Korea, the disease belongs to lower energizer. "The unctuous strangury occurs at the beginning, which means urinate like cream. With the development of the disease, the face becomes swarthy, the body is thin, the auricles are parched, and the urine is turbid and greasy. The treatment method is to nourish blood to purge and distinguish the clear and turbid, then the disease will heal itself." [19]

It provides a new idea for the treatment of Shenxiao disease from "blood stasis" [20].

Qing Dynasty

Feng Chuzhan's *Secret record of Feng's brocade bag* in the Qing Dynasty contains that "those who has Xiaoshen, shows dry heat and thirst, thin and weak, black face, turbid urine, and fat liquid likes ointment." [21] Among them, leg swelling, urine, turbidity and lipid fluid are all seen in diabetic nephropathy. Ding Yaochen's *Miraculous and Simple Prescription* records the treatment method of Xiaoshen: "those who has Xiaoshen shows unctuous strangury at the beginning, which means urinate like cream. With the development of the disease, the face becomes swarthy, the body is thin, the auricles are parched, and the urine is turbid and greasy. Blood nourishing therapy should be used to distinguish the clear and turbid, and the disease will heal itself." [22] It is recorded in *Incisive Light on the Source of Miscellaneous Disease* that Bawei pill and Schisandra chinensis are used to boost source of fire for eliminating abundance of yin, and Bawei pill and Schisandra chinensis and Rehmannia glutinosa are used to strengthen governor of water for restraining hyperactivity of yang to treat Xiaoshen [23]. *Gu Songyuan's Medical Mirror* contains its treatment: "the symptoms of Xiaoshen are thin bones and painful legs. It is appropriate to nourish the kidney-fluid. Take Eucommia ulmoides and Cortex Phellodendri as the monarch drug, asparagus, ginseng, Anemarrhena, Schisandra chinensis and dry yam as the adjunctive drug, and take these with Siwu Decoction." [24] Yu Chang's *Medical Laws* advocates the method of needle shooting and pricking the collaterals and oral administration of meridian guiding drugs to treat the syndrome of pathogen invading meridian and collateral [25]. Wang Qingren's *Corrections on the Errors of Medical Works* [26] combined Qi tonifying and blood activating and collaterals dredging to create the method of Replenishing Qi and Promoting Blood Flow to Remove Obstruction in Collaterals [27]. Buyang Huanwu Decoction is a famous prescription for the treatment of qi deficiency and blood stasis syndrome, which comes from *Corrections on the Errors of Medical Works*. It has the effects of promoting blood circulation, removing blood stasis and dredging collaterals. According to modern pharmacological research, the compatibility of herbs in Buyang Huanwu Decoction can effectively reduce blood viscosity, improve microcirculation, and has a good therapeutic effect on diabetic nephropathy [28].

Up to the Qing Dynasty, Ye Tianshi creatively integrated the content of "collaterals" in the Internal Classic into the theory of internal injuries and miscellaneous diseases. The *Clinic Guideline of Medical Records* clearly puts forward the academic views of "chronic diseases transform to collaterals" and "prolonged pain involve collaterals": "All meridians dominate Qi, collaterals dominate blood, and long-term illness leads to blood stasis." "At the beginning, Qi knot in the meridians, and long-term blood will hurt the collaterals." "If the disease does not heal for a long time, the blood collaterals will be injured certainly." "The chronic disease will always be in the collaterals." "Chronic pain into blood collateral." [29] Which reveals the evolution law of disease from shallow to deep, from Qi to blood, widely applies this theory to clinical practice, and establishes various methods of using pungent and aromatic drugs to dredge collaterals, thus forming a more systematic theoretical system of "prolonged diseases involve collaterals".

As a branch of the meridians, collaterals are finely differentiated layer by layer like branches. Collaterals are narrow and widely distributed in a network along the meridians. The *Su Wen* says, "when the disease is in the blood, it needs to regulate collaterals." Collateral blood comes from the viscera and meridians. After circulation, it flows to the meridians and transports the blood to all parts of the body. Due to the numerous branches of collaterals and narrow collaterals, Qi, blood and body fluid flow in them, which is easy to stagnation. Once the diseases of meridians and viscera last for a long time, the evil of meridians and viscera will be introduced into the collaterals, or the Qi spread to blood and will injure the collaterals, which will affect the normal distribution of Qi, blood and body fluid in the collaterals, resulting in pathological changes such as Qi stagnation, blood stasis and phlegm coagulation, which is also the development of the disease

from shallow to deep. The "collaterals" in the theory of traditional Chinese medicine are identical to the microvessels in modern medicine to a certain extent. Because the blood flow of kidney collaterals is characterized by slow blood flow, large blood flow, collateral dispersion, end connection, fluid blood exchange, two-way flow and functional regulation, so the disease pathogens are easy to hurt kidney collaterals, forming the characteristics of collateral pathogenesis of "easy stagnation, easy blood stasis, easy entry and difficult exit, easy accumulation and formation" [30]. In the course of diabetic nephropathy, the disease starts in the liver and kidney, Qi and yin deficiency, stasis of the kidney collateral. The clinical manifestations are frequent urination, polyuria, turbid urination and sweet urination. The course of the disease is long will hurt yin and Yang, lead to spleen and kidney deficiency, water retention and overflow skin. It can be seen that skin edema, cold chills limbs, and even pleural effusion and ascites. If the disease persists and does not heal, it will lead to late renal failure, the decline of Qi, blood, yin and Yang, the retention of turbid poison, the spread of heart and lung. Symptoms like palpitation, shortness of breath, suffocation, inability to lie flat, oliguria or no urine may occur. Throughout the whole process of the occurrence and development of diabetic nephropathy, its characteristics and clinical manifestations are consistent with Ye Tianshi's theory of "chronic diseases transform to collaterals" and "prolonged pain involve collaterals".

Development status

From the late Qing Dynasty to the founding of new China, due to specific historical reasons, the research on collateral disease theory did not find relevant literature, and the development of collateral disorders theory was interrupted. In modern times, Professor Wu Yiling established the modern theory of collaterals and collateral disorders on the basis of summarizing the previous experience. Since then, the systematic theory of collaterals disorders has been formed for the first time. Professor Wu Yiling put forward the theory of "three-dimensional network system" on collateral disorders, and summarized the collateral system of the whole body from three specific angles of time, space and function: Collaterals are a network system of meridians separated horizontally, subdivided layer by layer, crisscrossed, distributed all over the body, inside and outside, and widely distributed among viscera and tissues, forming a spatial distribution law of ((body surface - floating collaterals, Yang collaterals) one (between muscles - meridians) one (viscera collaterals, Yin)), distributing Qi, blood and body fluid according to a certain speed and frequency, so as to play the role of "promoting qi and blood and managing Yin and Yang". Its physiological function is to maintain life activities and maintain the stability of human internal and external environment [31]. Professor Tong Xiao Lin found that when clinical diabetes was treated according to the syndrome differentiation and treatment of Xiaoke, it is often hard to match the syndromes and prescriptions, or have the syndrome type without prescriptions. The clinical efficacy is poor. Based on the theory and clinical research of collateral disease, the name of diabetes in TCM is named "Sugar Collateral Disease" [33], and summarize its characteristics and clinical outcome. According to the theory of traditional Chinese medicine, blood stagnation runs through the pathological process of diabetic nephropathy. The deficiency of Qi and Yin and deficiency of kidney collateral can produce phlegm, blood stasis and other pathological products blocking kidney collaterals. This is consistent with the pathological changes of blood viscosity and hypercoagulability caused by diabetic nephropathy in the theory western medicine.

Summary

Diabetes is not healed for a long time, and easily causes other diseases, involving the microvasculature and large vessels in all parts of the body, such as diabetic nephropathy. The concept of collaterals is in fact similar to the concept of microvasculature in modern medicine. Microvessels and collaterals in the kidney have similar structural and

functional characteristics. According to the characteristics of diabetic nephropathy and the changes of syndromes, it covers the collateral vessels, namely, microvascular lesions. Therefore, this disease should be responsible for the kidney collateral and the kidney collateral damage, namely the abnormal microvasculature of the kidney, leading to the occurrence of diabetic nephropathy. It can be seen that diabetes and its complications related to vascular diseases concern collaterals. Collateral disorders can be regarded as one of the basic pathological bases of diabetic nephropathy. This topic uses modern literature search and related references to identify three Chinese medicine ancient books, namely, "Shenxiao, Xiaoshen and Neixiao" as the search term, combing the relevant ancient books and modern experts' works, sorting out and exploring the origin and development of diabetic nephropathy from collateral disorders theory in chronological order. Hope that it will provide a reference for the theory and clinical research of diabetic nephropathy in the future.

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