

## Advances in the treatment of diabetic peripheral neuropathy by modulating gut microbiota with traditional Chinese medicine

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### Abstract

Diabetic peripheral neuropathy (DPN) is one of the strongest risk factors for diabetic foot ulcers (neuropathic ulcerations) and the existing ulcers may further deteriorate due to the damage to sensory neurons. Moreover, the resulting numbness in the limbs causes difficulty in discovering these ulcerations in a short time. DPN is associated with gut microbiota dysbiosis. Traditional Chinese medicine (TCM) compounds such as Shenqi Dihuang Decoction, Huangkui Capsules and Qidi Tangshen Granules can reduce the clinical symptoms of diabetic nephropathy by modulating gut microbiota. The current review discusses whether TCM compounds can reduce the risk of DPN by improving gut microbiota.

**Key Words:** Diabetes; Peripheral neuropathy; Traditional Chinese medicine; Gut microbiota; Diabetic foot ulcer; Treatment

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**Core Tip:** Diabetic peripheral neuropathy (DPN) is associated with gut microbiota dysbiosis. Traditional Chinese medicine (TCM) compounds such as Shenqi Dihuang Decoction, Huangkui Capsules and Qidi Tangshen Granules can reduce the clinical symptoms of diabetic nephropathy by modulating gut microbiota. In this review, the authors discuss whether TCM compounds can reduce the risk of DPN by improving gut microbiota.

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## INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the commonest complications in patients with diabetes and the prevalence of DPN is as high as 50% and maybe even higher, which is also one of the main contributors of the high mortality in patients with diabetes. The duration of DPN is long with poor outcomes[1,2]. DPN is a heterogeneous disease and it has different symptoms which primarily includes neurological disorders such as limb numbness, usually symmetrical, stabbing pain and muscle weakness. Inappropriate treatment of DPN may lead to ulcers and gangrene, which probably results in limb loss and seriously affects quality of life in this population[3,4].

DPN is common in both type 1 and type 2 diabetes. The majority of preclinical and clinical studies focus on the pathogenic cause of hyperglycemia because prettily good control of blood glucose can delay the progression of DPN. Studies using diabetic animal models have confirmed several potential mechanisms to produce glucotoxicity and damage to the nervous system including post-translational modifications of proteins with glycans, aldose reductase, glycolysis and increased glucose metabolism through other pathways for the catabolism of glucose. However, it is becoming increasingly evident that factors except for hyperglycemia may also cause the occurrence, development and severity of neuropathy and neuropathic pain[5,6]. For example, peripheral nerves contain insulin receptors that transduce the neurotrophic and neurosupportive properties of insulin, independent of systemic glucose regulation, while it has becoming a focus of concern that the detection of neuropathy and neuropathic pain in patients with metabolic syndrome and poor glycemic control to protect against the pathogenic role of dyslipidemia in patients with type 2 diabetes and neuropathy[7-9].

DPN usually affects the sensory neuropathy and sensorimotor neuropathy. The sensory neuropathy is the most common form of DPN in patients with diabetes in clinical practice. It is characterized by gradual loss of nerve fibers of different sizes. In this progressive disease, the distal portions of the nerves in hands and feet are first affected with retraction of sensory axons at the end of the peripheral nervous system. This phenomenon is usually called “stocking & glove neuropathy”, which reflects damage to the longest sensory axons and thus is considered as a length-dependent neuropathy[10,11]. The reduction in the sensation and feeling is one of the commonest and earliest patterns of DPN and these symptoms occur gradually including tingling on the toes, pain and loss of feeling.

Clinical evidence for motor dysfunction is a little unusual in patients with diabetes and the symptoms only appear in 1% to 6% patients, usually in those confirmed with DPN. In the animal models of diabetes, early decreased motor nerve conduction velocities can be easily discovered. However, in both animal models and human studies, it has been proved that compound muscle action potential amplitude and muscular strength are reduced[12-15]. Although hyperglycemia is one of the factors that induce the development of nerve injury, recently, evidence has demonstrated that damage to the small fibers of the peripheral nervous system may occur in individuals with impaired glucose tolerance independent of the diagnosis of hyperglycemia and diabetes[16]. In addition, keeping blood glucose under control can partly prevent and/or postpone the occurrence of DPN in patients with type 1 diabetes. However, it hardly benefits patients with type 2 diabetes. Hence, other diseases besides hyperglycemia may have an influence on the occurrence and development of DPN in type 2 diabetes. The multitude clinical manifestations of DPN including pain in 15% to 30% patients makes the identification of pathophysiology and treatment of DPN challenging[17-20].

## ASSOCIATION BETWEEN GUT MICROBIOTA AND DPN

Risk factors for DPN include duration of diabetes, age, hemoglobin A1c (HbA1c), diabetic retinopathy, smoking and body mass index. A successful way of managing DPN involves exercise in combination with altered lifestyle and targeted diets as well as medication intervention. Studies showed that the occurrence of diabetes and its complications are associated with dysbiosis of the gut microbiota. The development of these disease are mainly related to the increased intestinal permeability, for which bacterial by-products can enhance inflammation by permeating the leaky intestinal barrier[21-23]. Species such as *Lactobacillus fermentans*, *Akkermansia muciniphila*, *Bacteroides fragilis*, and *Enterococcus rosenbergii* have been discovered to be associated with insulin sensitivity and glucose metabolism[24-26]. Gut bacteria *Akkermansia* may impact the effects of metformin on glucose metabolism. *Bifidobacterium* and *Lactobacillus spp.* play a predominant role in the repair of the intestinal mucosal barrier. *Bifidobacterium spp.* that is discovered to be capable of producing bacteriocins is negatively associated with inflammation, hyperglycemia, and insulin resistance through preventing mucosal adhesion and maintaining intestinal barrier function. Probiotics and yogurt or milk containing *Bifidobacterium* and *Lactobacillus* can reduce fasting blood glucose and HbA1c in patients with diabetes. Based on this, we can come to a conclude that *Bifidobacterium* and *Lactobacillus* can inhibit the potential intestinal pathogens and enhance intestinal antioxidant capacity and digestive enzyme activities. Fecal microbiotas, kinds of Gram-negative bacteria, are negatively associated with HbA1c and can increase intestinal synthesis of glucagon like peptide-1, peptide YY, acetate and butyrate, and maintain blood glucose homeostasis[27].

## MODULATING GUT MICROBIOTA WITH TRADITIONAL CHINESE MEDICINE FOR DPN

According to traditional Chinese medicine (TCM), DPN belongs to the field of “Xiaoke Disease”. It is induced by the protracted course of not cured diabetes, poor glycemic control and erosion of the nerve cells. It is generally agreed that “internal heat” oriented pathogenesis of “deficiency of Yin and Jin and excess of dryness and heat” induced by congenital deficiency, long established inappropriate diet, long period of emotional disorder and overstrain associated disorder of internal organs are probably cause of diabetes. Lung, spleen and especially kidney are most affected locations. Gut microbiota dysbiosis will result in intestinal microbial imbalance and insulin resistance, which in further weaken one’s physical defenses against infection providing a chance for the six evils to attack the human body. TCM have the potential to lessen the symptoms of DPN by modulating gut microbiota which is out of balance. TCM compounds follow the compatibility principle of “monarch, minister, assistant, and guide”, which means herbs interact and restrict each other to achieve the optimally holistic effect through multiple targets, levels multiple pathways. For example, Shenqi Dihuang Decoction can regulate the spleen and stomach consequently building a healthy gut microbiome and constructing an integrated intestinal mucosal barrier[28].

Moreover, Huangkui Capsule’s pharmacological effects, such as anti-inflammatory, antiviral, antibacterial, *etc.* can modulate the balance of gut microbiota from the perspective of inflammation treatment. Studies showed that adding Huangkui Capsule to the experimental group achieved decrease in 24 hours urine albumin-creatinine ratio and blood urea nitrogen content and increase in the number of Gram positive and negative bacteria in the intestine compared with the control group, indicating Huangkui Capsule can relieve the clinical symptoms of diabetic nephropathy[29]. Other studies demonstrated that Qidi Tangshen Granules can improve gut microbiota composition, reduce serum total bile acid level to alleviate the clinical symptoms of diabetic nephropathy[30]. In addition, TCM compounds such as Gegen Qinlian Decoction, Bupi Yishen formular, Baoshen formular, Qinshi Shenshu Capsules, Sanhuang Yishen Capsules and Fuzi Lizhong Pills also can improve the microorganism environment of intestines and stomach by modulating gut microbiota, suppressing the proliferation of harmful bacteria and increasing good bacteria in the gut. Studies[31,32] found those TCMs with effectiveness characterized by tonifying spleen, nourishing Qi, lifting Yang and Qi and harmonizing the stomach and intestines, and dredging Fu organs and sinking turbidity can actively alleviate nerve pain, repair damaged nerves and regulate the generation of inflammatory mediators through modulating gut microbiota. Meanwhile, the gut microbiota and its metabolic products can regulate glucose metabolism slowly, mediate immune response, regulate and promote the release of various signaling factors and facilitate recovery from DPN.

Diabetes is a multi-factor caused disease and its onset and development are thought to be profoundly influenced by the environment and hereditary factors. It is the main cause of Renal failure, cardiovascular disease, and retinopathy. A great microbial ecosystem lives in the human digestive tract and it co-evolves with human beings to realize mutual benefits, maintain human health and prevent diseases. According to the “gut-kidney axis” hypothesis, gut microbiota dysbiosis is associated with diabetes and there is a mutual causality relationship between them. Gut microbiota can activate immune cells with its metabolic products and other constituents to trigger inflammatory reaction and accelerate the progression of complications in diabetes. Gut microbiota community derived antigens can induce conventional T cells differentiate into multiple effector cells such as Th2 cells, Th17 cells and T cells (Tregs) to regulate autoimmune response and immune homeostasis and have an impact on the onset and development of DPN. More and more evidence showed that changes in gut microbiota composition and function are associated with the increased risks for the onset and development of diabetes and its complications. Some studies investigating the influence of probiotic administration on blood glucose control and renal function in patients with diabetic nephropathy found that the use of probiotics (*Bifidobacterium*, *Lactobacillus acidophilus*, and *Streptococcus thermophilus*) can modulate gut microbiota in these patients, improve blood glucose control, and reduce fasting blood glucose, 2 hours postprandial serum glucose, HbA1c and microalbuminuria/creatinine (mAlb/Cr) levels with boosting therapeutic potential in the clinical practice[33-35]. The mechanism of its blood glucose lowering is probiotics can promote gut microbiota to yield insulinotropic polypeptide and glucagon-like peptide-1, which stimulate muscle glucose uptake and by this way reduce blood glucose.

Microbiome symbiosis plays a crucial role in regulating metabolism and reducing the risks for diabetes. However, the underlying mechanism has not been well understood[36,37] (Table 1). According to TCM, imbalance of spleen Qi’s lifting and sinking function will further affect the intestine’s digestion, absorption and elimination work. When Zhuo-Du (turbid-toxin) accumulates in the intestines, it is apt to cause gut microbiota dysbiosis with reduced number of beneficial microbe and overrun of harmful microbe. Gut microbiota dysbiosis and the imbalance of microecology will affect liver, spleen and kidney[38-40]. Studies showed that Huangkui Capsules can regulate the blood glucose level, elevate the distribution and subsets of gut microbiota and improve kidney function in patients with diabetic nephropathy[24].

## CONCLUSION

Above all, DPN is associated with gut microbiota dysbiosis in diabetes. TCM compounds with the effectiveness of gut microbiota dysbiosis modulation such as Shenqi Dihuang Decoction, Huangkui Capsules and Qidi Tangshen Granules can reduce the relevant clinical symptoms of DPN. With diagnosis and treatment on the basis of an overall analysis of the illness and the patient’s condition, TCM can modulate the species and amounts of gut microbiota to realize the balance and diversity of gut microbiota. In the further, TCM’s role in modulating gut microbiota will gain increasing attention in the clinical practice. Relevant researches are warrant to profoundly investigate various TCMs’ therapeutic efficacy for the complications of diabetes.

Table 1 Microbiome symbiosis plays a crucial role in regulating metabolism and reducing the risks for diabetes

Item	Role of microbiome symbiosis in regulating metabolism and reducing the risks for diabetes
1	Gut microbiota dysbiosis results in the production of short chain fatty acids such as butyric acid, propionic acid, and acetic acid, which will ruin the intestinal barrier integrity, activate inflammatory signaling cascade response and cause damage to multiple organs
2	Trimethylamine nitrogen oxide produced by the gut microbiota will increase the accumulation of cholesterol, which will lead to insulin resistance and raise the risk for diabetes
3	It is demonstrated that changes in the gut microbiota groups have an effect on intestinal permeability and inflammation in diabetes

## FOOTNOTES

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