

Theoretical Mechanisms of Acupuncture in Improving Type 2 Diabetes Mellitus Complicated with Peripheral Neuropathy

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Abstract: With the development of traditional Chinese medicine (TCM), acupuncture has demonstrated distinct advantages in the treatment of type 2 diabetes mellitus complicated with peripheral neuropathy. This paper aims to systematically elaborate on the clinical efficacy and theoretical mechanisms of acupuncture in the clinical management of type 2 diabetes mellitus complicated with peripheral neuropathy by collecting relevant clinical studies published in recent years. Additionally, it provides a systematic discussion on the TCM disease nomenclature, syndrome differentiation and classification of diabetic peripheral neuropathy (DPN), as well as the acupoint selection principles for acupuncture treatment.

Keywords: Acupuncture; Diabetic peripheral neuropathy; Traditional Chinese Medicine

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1. Introduction

Acupuncture, an important component of traditional Chinese medicine (TCM), is a conventional therapeutic approach that takes the meridian and acupoint theory as its core. It regulates Qi and blood, balances Yin and Yang, and prevents and treats diseases by stimulating specific parts of the human body through needling or moxibustion. With the construction of the Belt and Road Initiative in the new era of China, acupuncture therapy has been promoted and applied worldwide, and gained extensive recognition both at home and abroad. Benefiting from the favorable international environment, acupuncture has made considerable progress in such aspects as clinical application, therapeutic methods, theoretical basis, operational standards, mechanism of action and theoretical construction, and is gradually stepping onto the world stage^[1].

2. The theoretical basis and clinical application of acupuncture in the treatment of type 2 diabetes mellitus complicated with diabetic peripheral neuropathy

The origin of acupuncture is closely related to the production and living practices of early human beings. In the primitive society, people accidentally discovered that when a certain part of the body was pricked or pressed during labor, the

original pain or discomfort would be relieved, thus gradually accumulating the experience of “selecting acupoints according to the location of pain”^[2]. The record in *Classic of Mountains and Seas* that “there exists a stone as smooth as jade, which can be made into needles” is exactly a description of primitive acupuncture instruments. In the Shang and Zhou dynasties, the development of metal smelting technology promoted the innovation of acupuncture needles; bronze needles and iron needles emerged one after another, and the therapeutic scope of acupuncture was consequently expanded. During the Spring and Autumn, Warring States, Qin and Han dynasties, the emergence of *Huangdi Neijing* (Yellow Emperor’s Internal Classic), a classic work of traditional Chinese medicine, systematically elaborated on the meridian doctrine, acupoint theory and acupuncture treatment principles for the first time. It explicitly put forward the proposition that “meridians are the pathways that determine life and death, treat various diseases, and regulate deficiency and excess, and thus must remain unobstructed”, laying the theoretical foundation for acupuncture and moxibustion science and marking a new stage where acupuncture evolved from empirical medicine to theoretical medicine^[3].

The therapeutic theory of acupuncture is guided by the core concepts of TCM, and is supported by three main pillars: the meridian and acupoint theory, the Qi-blood-body fluid doctrine, and the Yin-Yang and five-element doctrine. Meridians are pathways that circulate Qi and blood, connect the Zang-Fu organs, and communicate the internal and external parts of the body, running through the upper and lower, left and right, interior and exterior regions of the human body. The twelve regular meridians and the eight extraordinary meridians constitute the main body of the meridian system. Acupoints, on the other hand, are special sites where the Qi and blood of the meridians infuse into the body surface, they serve as both the reaction sites of diseases and the stimulation sites for acupuncture. By stimulating acupoints, acupuncture can regulate the circulation state of Qi and blood in the meridians, thus achieving the therapeutic purpose of “free flow of Qi and blood ensures the absence of pain”^[4]. The Qi-blood-body fluid doctrine serves as the functional basis of acupuncture treatment. TCM holds that “disharmony of Qi and blood gives rise to various diseases”, and the tonic and reducing techniques of acupuncture can harmonize Qi and blood, nourish body fluids, and restore the normal physiological functions of the body. The Yin-Yang and five-element doctrine provides a theoretical basis for syndrome differentiation and treatment in acupuncture. The essence of disease lies in the imbalance between Yin and Yang. By selecting specific acupoints and adopting corresponding techniques, either tonifying or reducing, warming or clearing, acupuncture promotes the body to achieve a balanced state of “Yin-Yang equilibrium”. Meanwhile, based on the laws of generation and restriction among the five elements, it indirectly regulates the functions of the Zang-Fu organs. In addition, acupuncture treatment follows the principles of syndrome differentiation and treatment, acupoint selection along meridians, and the combination of local and distal acupoint selection, so as to ensure the pertinence and effectiveness of the treatment^[5].

In terms of clinical application, acupuncture boasts an extremely wide therapeutic scope, covering diseases in multiple clinical departments such as internal medicine, surgery, gynecology, pediatrics, and otorhinolaryngology. It exhibits unique advantages especially in treating painful diseases, neurological diseases, metabolic diseases, and functional disorders. In the field of pain management, acupuncture exerts a significant analgesic effect on diseases such as cervical spondylosis, lumbar disc herniation, migraine, and arthritis^[6-9]. In the treatment of neurological diseases, acupuncture can effectively improve motor and sensory functions in patients with stroke sequelae, facial paralysis, and Parkinson’s disease. By stimulating meridians and acupoints, it promotes the repair and regeneration of damaged nerves^[10-12]. In recent years, the application of acupuncture in metabolic diseases and psychosomatic diseases has attracted considerable attention. For instance, acupuncture can regulate blood glucose and lipid levels, improve body fat metabolism in patients with obesity, and alleviate emotional disorders such as insomnia, anxiety and depression. Its mechanism of action is closely associated with the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and the improvement of autonomic nervous system dysfunction^[13]. In gynecological diseases, acupuncture can be used for treating dysmenorrhea, menstrual irregularities, polycystic ovary syndrome, and other conditions^[14]. It exerts therapeutic effects on gynecological disorders by harmonizing Qi and blood as well as regulating the thoroughfare and conception vessels.

The clinical application forms of acupuncture are also constantly innovating. In addition to the traditional filiform needle acupuncture and moxibustion, therapies such as electroacupuncture, warm acupuncture, acupoint catgut embedding,

and auricular acupuncture have gradually become popular. Electroacupuncture combines needling with electrical stimulation, which enhances the stimulation intensity and duration, and is thus suitable for the treatment of chronic pain and neurological diseases^[15]. Acupoint catgut embedding achieves long-acting stimulation by implanting absorbable sutures into acupoints, making it convenient for patients with chronic diseases such as obesity and chronic gastrointestinal disorders to receive long-term treatment^[16].

With its characteristics of being simple, convenient, cost-effective and efficacious, as well as the advantages of being green, non-invasive and having minimal side effects, acupuncture not only occupies an important position in domestic clinical practice, but also serves as one of the representative therapies of TCM. It has remarkable clinical efficacy and deserves to be promoted and applied worldwide, thus providing a distinctive treatment option for the cause of human health.

3. Pathogenesis of diabetic peripheral neuropathy

Pathogenesis of Diabetic Peripheral Neuropathy (DPN): DPN is one of the most common chronic complications of diabetes mellitus^[17]. Its pathogenesis is complex and is currently considered to be the result of the combined action of multiple factors. The core mechanisms can be summarized into the following four categories.

3.1. Mechanism of metabolic disorder

Hyperglycemia and hyperlipidemia are regarded as independent risk factors for neuropathy and are considered the initiating factors of DPN. It is generally accepted that glucose and lipid metabolic disorders are closely associated with insulin resistance. Pancreatic β -cell failure is the core factor underlying the progression of insulin resistance to hyperglycemia and diabetes. When β -cells fail to overcome insulin resistance and thus maintain physiological glucose levels, the non-enzymatic glycosylation of extracellular matrix components, such as collagen, myelin proteins, laminin in the Schwann cell basement membrane, and the basement membrane surrounding vascular endothelial cells, can impair the regeneration of nerve fibers, cause thickening of the vascular basement membrane and changes in its permeability, further exacerbating nerve conduction disorders^[18,19].

3.2. Mechanism of oxidative stress and inflammatory response

Vincent et al proposed that under the state of oxidative stress in diabetes, excessive production of reactive molecules in the body can not only directly cause oxidative damage to biomacromolecules such as DNA, proteins, and lipids, resulting in structural and functional disorders of neurons and vascular endothelial cells^[20]. But also, oxidative stress can activate multiple cellular signal transduction molecules through four classic hyperglycemia-induced injury pathways, namely advanced glycation end products (AGEs) formation, protein kinase C (PKC) pathway activation, polyol pathway metabolism, and hexosamine pathway. Eventually, this leads to changes in intracellular gene expression and protein function, dysfunction of endothelial cells and neurons, and cell apoptosis.

3.3. Mechanism of microangiopathy

Elevated blood glucose levels in diabetes lead to insulin resistance and obesity, which in turn inhibit the browning of white adipose tissue. This subsequently induces glucose and lipid metabolic disorders, exacerbates such disorders, and promotes inflammatory responses, thereby causing microangiopathy^[21]. This is also an important cause of symmetrical distal sensorimotor neuropathy in DPN.

3.4. Mechanism of neurotrophic factor deficiency

Neurotrophic factors can improve insulin resistance in diabetic patients, regulate blood glucose metabolism, balance lipid and energy metabolism, and thus exert their anti-diabetic effects effectively. In contrast, the deficiency of neurotrophic

factors combined with sustained hyperglycemia can induce metabolic disorders, abnormal cellular secretory functions, and further aggravation of neurotrophic factor deficiency in the body. These impairments will subsequently lead to structural and functional damage of neural tissues, and the two factors (hyperglycemia and neurotrophic factor deficiency) interact with each other ^[22].

4. Theoretical basis of acupuncture in the treatment of diabetic DPN

Acupuncture therapy for Diabetic DPN takes the meridian theory and Zang-fu syndrome differentiation theory of TCM as the core, and combines the understanding of nerves and blood circulation in modern medicine, thus forming a distinctive theoretical system for treatment.

4.1. TCM meridian syndrome differentiation theory

In the context of TCM, DPN falls into the categories of “blockage syndrome (Bi Zheng)” and “flaccidity syndrome (Wei Zheng)” ^[23]. Its core pathogenesis is that a prolonged course of diabetes leads to Qi-Yin deficiency, blood stasis obstructing collaterals, and malnutrition of tendons and vessels. A prolonged course of diabetes consumes Qi and Yin. Deficiency of Qi leads to failure in promoting blood circulation, while Yin deficiency results in sluggish blood flow. Eventually, blood stasis blocks the meridians, causing numbness, pain, and hypoesthesia of the limbs. Acupuncture treatment follows the principles of dredging meridians, promoting blood circulation to remove blood stasis, and replenishing Qi to nourish Yin. By selecting acupoints such as Zusanli (ST36), Sanyinjiao (SP6) and Taixi (KI3) to replenish Qi and nourish Yin, and acupoints including Xuehai (SP10) and Geshu (BL17) to promote blood circulation for removing blood stasis, combined with local Ashi points as well as acupoints of the Yangming and Taiyin meridians of the hands and feet, acupuncture dredges the Qi and blood in the meridians, restores the nourishment of tendons and vessels, and thus achieves the therapeutic effect of “no pain when the meridians are unobstructed”.

4.2. Zang-Fu correlation theory

In TCM, diabetes is believed to be located in the lung, spleen and kidney, and the occurrence of DPN is particularly closely related to spleen-kidney deficiency. The spleen governs transportation and transformation as well as blood control; spleen deficiency leads to insufficient production of Qi and blood, resulting in malnutrition of the limbs. The kidney governs essence storage; kidney essence deficiency fails to nourish the muscles and bones. By stimulating the back-shu acupoints such as Pishu (BL20) and Shenshu (BL23), acupuncture regulates Zang-Fu functions, replenishes Qi, blood and body fluids from the root, and improves the state of neural malnutrition.

4.3. Theory of action mechanism based on modern medicine

From the perspective of modern medicine, the mechanism of acupuncture in the treatment of DPN can be summarized as follows: it regulates nerve conduction function by stimulating nerve endings through acupuncture needling; acupuncture can also promote the release of endogenous vasoactive substances, optimize vasodilation function, improve microcirculation in the lesion area, dilate blood vessels, increase blood flow, and alleviate ischemia and hypoxia in nerve tissues ^[24,25]. Meanwhile, it can reduce the level of oxidative stress, increase acetylcholine concentration, inhibit apoptosis in hippocampal neurons, decrease the expression of apoptosis-related genes and proteins, and promote the repair and regeneration of damaged nerve fibers ^[26].

5. Acupuncture point combination schemes for diabetic DPN of different syndrome types

In clinical TCM practice, DPN is commonly classified into 4 syndrome types: Qi-Yin deficiency complicated with blood

stasis, Yang deficiency with cold congelation, liver-kidney insufficiency, and damp-heat invasion. The acupoint matching is based on basic acupoints as the core and modified according to the characteristics of different syndrome types, as detailed below.

Qi-Yin Deficiency Complicated with Blood Stasis (Core Pathogenesis): A prolonged course of diabetes consumes Qi and injures Yin, leading to Qi deficiency with blood stasis and malnutrition of tendons and vessels. Main Symptoms: Limb numbness, dull pain, accompanied by mental fatigue and weakness, dry mouth and throat, heat in the palms and soles, pale purple tongue with little coating, and thready and unsmooth pulse. Basic Acupoints: Zusanli (ST36), Sanyinjiao (SP6), Xuehai (SP10), Taixi (KI3). Syndrome-Differentiated Additional Acupoints: Pishu (BL20), Geshu (BL17), Taiyuan (LU9).

Yang Deficiency with Cold Congelation (Core Pathogenesis): Insufficiency of kidney Yang leads to cold pathogen congelation and meridian obstruction. Main Symptoms: Limb cold pain, numbness and insensitivity, aggravated by cold exposure, accompanied by fear of cold and cold limbs, soreness and weakness of waist and knees, pale tongue with white coating, and deep and slow pulse. Basic Acupoints: Zusanli (ST36), Sanyinjiao (SP6), Yanglingquan (GB34), Ashi Points. Syndrome-Differentiated Additional Acupoints: Shenshu (BL23), Mingmen (GV4), Guanyuan (CV4) (with moxibustion).

Liver-Kidney Insufficiency (Core Pathogenesis): Liver-kidney Yin deficiency leads to failure in nourishing tendons and vessels, and insufficiency of the marrow sea. Main Symptoms: Limb numbness, contracture pain, accompanied by dizziness, tinnitus, soreness and pain of waist and knees, blurred vision, red tongue with little coating, and thready and wiry pulse. Basic Acupoints: Taixi (KI3), Sanyinjiao (SP6), Yanglingquan (GB34), Hegu (LI4). Syndrome-Differentiated Additional Acupoints: Ganshu (BL18), Shenshu (BL23), Xuanzhong (GB39).

Damp-Heat Invasion (Core Pathogenesis): Accumulation of damp-heat descends to the limbs and blocks the meridians. Main Symptoms: Limb numbness, burning pain, accompanied by heavy sensation of the limbs, dryness and bitterness in the mouth, yellowish and reddish urine, red tongue with yellow greasy coating, and slippery and rapid pulse. Basic Acupoints: Zusanli (ST36), Yanglingquan (GB34), Bafeng (EX-LE10), Baxie (EX-UE9). Syndrome-Differentiated Additional Acupoints: Yinlingquan (SP9), Quchi (LI11), Taichong (LR3).

6. Conclusion

To sum up, as an important therapy of TCM, acupuncture is supported by the core theories including meridian and acupoint theory, Qi-blood-body fluid theory and Yin-Yang and five elements theory. Relying on the advantages of being simple, convenient, economical and effective, it has achieved remarkable curative effects in the clinical treatment of diseases across multiple departments. Moreover, it has been globally promoted along with the advancement of the Belt and Road Initiative. Diabetic DPN, as a common chronic complication of diabetes, is closely associated with metabolic disorders, oxidative stress and inflammatory responses, microangiopathy, and neurotrophic factor deficiency. In the context of TCM, it falls into the categories of “Bi Zheng (blockage syndrome)” and “Wei Zheng (flaccidity syndrome)”, and its core pathogenesis is characterized by Qi-Yin deficiency and blood stasis obstructing the meridians. Acupuncture for the treatment of DPN has established a unique theoretical system integrating TCM and Western medicine. From the TCM perspective, it follows the principles of dredging meridians and promoting blood circulation to remove blood stasis, and selects acupoints based on meridian syndrome differentiation and Zang-Fu correlation theory. From the perspective of Western medicine, it can regulate nerve conduction, improve microcirculation, alleviate oxidative stress and promote the repair of damaged nerves. In clinical treatment, adhering to the principle of combining channel-based acupoint selection, local acupoint selection and syndrome-differentiated acupoint matching, basic acupoints are combined with syndrome-specific additional acupoint schemes to targetedly improve various DPN symptoms. With definite curative effects, this therapy provides a unique and effective treatment option for DPN, which is worthy of further promotion and application.

Disclosure statement

The authors declare no conflict of interest.

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