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Review

Strategies and Research Progress of Chinese Medicine in Prevention and Treatment of Diabetic Peripheral Neuropathy*

YANG Dan and LIANG Xiao-chun

ABSTRACT Diabetic peripheral neuropathy (DPN) seriously affects the quality of life in patients with type 2 diabetes mellitus. This paper reviews the role of Chinese medicine in the main treatment goal of DPN, including protecting pancreatic β-cells, in the use of antioxidation therapy to delay disease progression, and in the endpoint of neural repair and regeneration. We propose that protecting the body from injury caused by high glucose and oxidative stress, and promoting repair and regeneration of nerves should be the research direction for the prevention and treatment of DPN.

KEYWORDS diabetic peripheral neuropathy, pancreatic β-cell, anti-oxidative stress, neural repair and regeneration, Chinese medicine

Diabetic peripheral neuropathy (DPN) is considered one of the most prevalent chronic complications of diabetes mellitus (DM). DPN manifests in several forms, including sensory, motor, and autonomic neuropathies, and has a significant negative impact on health-related quality of life. Therefore, prevention of disease progression before serious complications occurrence plays an important role. The first and foremost is protection of pancreatic β-cells. Secondly, antioxidant treatment is necessary to slow down progression of DPN. Moreover, injured nerves need repair and regeneration. The objective of the present review is to summarize strategies and research progress of Chinese medicine (CM) in prevention and treatment of DPN.

Protecting Pancreatic β-Cells

Insulin resistance (IR) and a progressive decline in functional β-cell mass are characteristics of type 2 DM (T2DM). The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated no significant impact of intensive glycemic control on the risk of ongoing decline in β-cells function. It was reported that as the patients with T2DM were diagnosed, the function of β-cells was significantly impaired and the rate of β-cell failure was similar regardless of dietary intervention or treatment with metformin or sulfonylurea.[1,2] Moreover, clinical trials have demonstrated that glucagon-like peptide-1 (GLP-1) receptor agonists and inhibitors of GLP-1-degrading enzyme dipeptidyl peptidase Ⅳ improved β-cell function, increased insulin secretion, and improved blood glucose control effectively in patients with T2DM.[3-6]

The efficacy of CM alone or a combination therapy of CM and Western medicine (WM) in protecting pancreatic β-cells and treating T2DM is under investigation. Cai, et al[7] reported that Jinlida Granule (津力达颗粒, composed of *Ginseng Radix et Rhizoma*, *Poria*, *Ophiopogonis Radix*, *Rehmanniae Radix*, *Polygonati Rhizome*, *Atractylodes lancea*, *Sophorae Flavescentis Radix*, *Polygoni Multiflori Radix*, *Cornus Officinalis*, *Eupatorii Herb*, *Coptidis Rhizome*, *Anemarrhena*, *Lycii Cortex*, *Epimedii Folium*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Puerariae Lobatae Radix*, and *Litchi Semen*) could decrease the level of serum nesfatin-1 and correct the dysfunction of glucose metabolism in patients with pre-diabetes, and effectively improve the function of islet β-cells. After 4-week treatment with CMs (composed of *Astragali Radix*, *Rhizoma Dioscoreae Persimilis*, *Radix Codonopsis*

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Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Translational Medicine Center, Chinese Academy of Medical Sciences, Beijing (100730), China
Correspondence to: Prof. LIANG Xiao-chun, Tel: 86-10-69155331, E-mail: xcliang@vip.sina.com

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pilosula, *Atractylodis Macrocephalae Rhizoma*, *Radix Trichosanthis*, *Rehmanniae Radix*, *Scrophularia Ningpoensis*, *Coptidis Rhizome*, *Gypsum fibrosum, Pueraria Lobata*, *Angelicae Sinensis Radix*, *Cornus Officinalis*, and *Schisandra Chinensis*) combined with an insulin pump, the islet β-cell function of patients with T2DM was evaluated using a hyperglycemic clamp technique.[8] The study demonstrated that CMs combined with insulin pump could control plasma glucose well in the treatment of T2DM, and the mechanism might be related to the recovery of islet β-cell sensitivity to glucose stimulation and the improvement in IR.[8]

Another study evaluated the effects of Modified Liujunzi Decoction (加味六君子汤, MLJZ) on improving islet β-cell function of T2DM patients with the syndrome of Pi (Spleen)-deficiency and phlegm-stagnation.[9] A total of 72 patients with were selected and randomly divided evenly into a treatment group and a control group. Both groups were given the same dosage of metformin hydrochloride tablets and acarbose. The treatment group was additionally given oral MLJZ 200 mL, thrice daily for 3 months. The results showed that MLJZ combined with WM improved islet β-cell function of T2DM patients with the syndrome of Pi-deficiency and phlegm-stagnation better than WM alone.

Wu, et al[10] observed the effect of Compound Shengjin Granule (复方生津颗粒, CSJ, composed of *Radix Trichosanthis*, *Coptidis Rhizome*, *Puerariae Lobatae Radix*, *Pseudostellariae Radix*, *Schisandra Chinensis*, and *Paeoniae Radix alba*) on protection of pancreatic β-cells and serum resistin in patients with T2DM. Sixty T2DM patients with the syndrome of qi-deficiency and yin-deficiency were randomly divided into a treatment group and a control group. They were treated with a combination of conventional drugs and CSJ or with conventional drugs alone, respectively. After 6 months of treatment, the fasting blood insulin and resistin decreased substantially, postprandial C-peptide increased and the homeostasis model assessment for IR decreased.

Zhu, et al[11] found that integrative CM (*Astragali Radix*, *Angelicae Sinensis Radix*, *Rhizoma Dioscoreae Persimilis*, *Mori Cortex*, *Morus alba*, *Ramulus Mori*) and WM could improve the islet β-cell function of patients with latent adult autoimmune DM. Additional studies reported that Compound Shenqi Granule (参芪复方颗粒),[12] Mudan Granule (木丹颗粒),[13] and Xiaoketing Capsule (消渴停胶囊)[14] could inhibit the apoptosis of islet β-cells and promote their regeneration.

Radix Astragali is one of the most pivotal qi-tonifying herbs and is among the highest ranked CMs in the treatment of T2DM patients with syndrome of qi-deficiency and yin-deficiency. It was reported that astragalus polysaccharides (APS) increased insulin secretion of rats with T2DM, promoted the fat cells to take up glucose and undergo cell differentiation, and increased the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) mRNA. The effects of APS were similar to rosiglitazone.[15,16]

Psidium guajava, one genus of *Psidium Linn*, belongs to the family of *Myrtacea*. Pharmacological study suggests that its leaves possess several bioactivities, such as antioxidant, scavenging free radicals, anti-diabetic, and anti-hyperlipidemic effects. Guavenoic acid (GA) could improve the proliferation of insulinoma (INS-1) cells and promote the insulin synthesis and secretion of INS-1 cells. GA could decrease the levels of blood glucose in diabetic rats.[17] Mori Folium total flavonoid (MFTF) could inhibit apoptosis of pancreatic islet β cells in diabetic rats induced by injection of streptozotocin (STZ) and intake of high fat-high sucrose diet. The anti-apoptotic protein Bcl-2 and apoptotic protein Bax in islet tissue were detected by immunohistochemistry. The mechanism of inhibiting apoptosis was found to be related to the up-regulation of bcl-2/Bax.[18,19]

Flavonoids from *Potentilla Discolor* Bunge (PDB), for clinical treatment of syndrome of excessiveness of Wei (Stomach)-fire of T2DM, especially with the symptoms of swift digestion with rapid hungering, had the effects of cleaning heat, detoxification, and cooling blood. PDB at medium and high doses showed some success in promoting repair of pancreatic islet β-cells and regeneration of pancreatic tissue.[20,21] The pancreatic pathology of diabetic rats induced by STZ was studied with hematoxylin-eosin and terminal oxynucleotidyl transferase mediated dUTP biotin nick end labeling (TUNEL) staining. Polygona-polysaccharose (50, 100, 150 mg/kg) could effectively inhibit islet cell apoptosis and protect the cell structure of T2DM rats. The possible mechanism related to lowering caspase-3.[22] Berberine,[23] salidroside[24] and *Salvia miltiorrhiza* Bge. f. alba[25] could ameliorate the hyperglycemia by protecting β-cell survival, with

Chin J Integr Med 2018 Oct;24(10):794-800

increased β-cell proliferation and decreased β-cell apoptosis.

Antioxidation Therapy and Slowing Disease Progression

Brownlee[26] has proposed a 'unifying mechanism' of hyperglycemia-induced damage in DM, a common pathogenesis of diabetic chronic complications, which is oxidative stress. The imbalance of several metabolic pathways including the activation of protein kinase C, polyol pathway, accumulation of advanced glycation end products (AGEs), and the inflammatory pathway result in oxidative stress, which promotes the occurrence and progression of diabetic chronic complications including DPN.[26,27] Antioxidant treatment is expected to provide a new strategy for treatment of diabetic chronic complications, leading to great interest in the development of antioxidant drugs.

Alpha lipoic acid (ALA) is a powerful antioxidant. The protective mechanisms of ALA in treatment of DPN include an increase of endoneurial blood flow and the Na^+-K^+ ATPase activity in nerve, improvement of nerve conduction velocity, inhibition of lipid peroxidation, resistance of inflammation, and protection of endothelial function.[28] The SYDNEY2 study demonstrated that patients' neuropathic sensory symptoms and pathophysiology improved after receiving oral ALA (600 mg/d).[28] The study enrolled patients with DM and with a deficit in both motor and sensory nerve conduction. They were treated orally with ALA 600 mg and superoxide dismutase (SOD) 140 IU/day. After 4-month treatment, Bertolotto, et al[29] observed that the patients' electroneurographic parameters improved and their pain was relieved significantly. Best improvements were observed in sensory nerve conduction. Another studies showed that ALA could prevent peripheral nerve injury caused by hyperglycemia-induced oxidative stress in STZ-induced diabetic rats. The following pathways were suggested: treating endothelial malnutrition, increasing endoneurial blood flow and sensory nerve conduction, regulating the level of nicotinamide adenine dinucleotide (NAD+)/reduced nicotinamide adenine dinucleotide phosphate (NADH) in the mitochondria of nerve cells, improving Na^+-K^+ ATPase activity, and inhibiting the exhaustion of glutathione (GSH).[30,31]

Taurine is one of the main free amino acids in mammalian spinal cord and brain, which are rich in neurons, neurogliocytes, and nerve terminals. The effects of taurine on improving nerve injury may be achieved by removing free radicals, reducing lipid peroxidation, and up-regulating the expression of nerve growth factor (NGF) mRNA.[32] Jinmaitong Capsule (筋脉通胶囊, JMT, composed of *Cuscutae Semen*, *Ligustri lucidi Fructus*, *Cinnamomi Ramulus*, *Corydalis Rhizoma*, *Hirudo*, *Asari Herba*, etc.) had the effects of Shen (Kidney)-nourishing, blood-activating, and warming the channels. And it was found to be remarkably effective in clinical treatment of DPN.[33,34] After intragastric administration with JMT for 16 weeks, levels of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase p22-phox subunit, inducible nitric oxide synthase (iNOS), and nitro tyrosine protein in the sciatic nerve of STZ-induced diabetic rats with DPN were significantly decreased.[35] The mRNA and protein levels of cytochrome C and caspase-3 decreased, as did the apoptosis in dorsal root ganglion (DRG) neurons. The mRNA and protein levels of Bcl-2 increased. JMT-medicated serum can down-regulate the expressions of iNOS protein and NADPH oxidase p22-phox subunit mRNA of Schwann cells (SCs) cultured in high-glucose medium.[36] The levels of superoxide anion decreased and the levels of mitochondrial membrane potential increased in DRG neurons.[37-39] In high glucose-cultured rat SCs treated with JMT, both the expression of specific markers of DNA oxidative damage (eg, 8 hydroxy deoxyguanosine) and the mRNA and protein levels of factors involved in apoptosis (such as active caspase-3) decreased.[40,41] JMT can antagonize high glucose-induced oxidative stress and activate the mitochondrial pathway and apoptosis, suggesting that JMT could be used to prevent and treat T2DM with DPN.[35-41]

Modified Bugan Decoction (加味补肝汤, MBG, composed of *Lycii Fructus*, *Chaenomeles sinensis*, *Angelica sinensis*, *Rhizoma Chuanxiong*, *Radix Rehmanniae Preparata*, *Radix Paeoniae Alba*, *Herba Taxilli*, *Radix Ophiopogonis*, *Radix Salviae Miltiorrhizae*, *Radix Trichosanthist*, etc.) treatment on diabetic rats by intragastric administration for 8 weeks decreased the content of serum alondialdehyde (MDA) and increased the level of serum GSH. It also inhibited the transcription of caspase-3 mRNA and activation of caspase-3. Positive expression of p38 mitogen-activated protein kinase (p38 MAPK) in the DRG neurons of the diabetic rats and the serum MDA were decreased in the MBG group. The neuronal protection

was possibly related to eliminating lipid peroxide and inhibiting the p38 MAPK pathway.[42,43]

Tangluoning (糖络宁, TLN, composed of *Astragali Radix*, *Cornus Officinalis*, *Dipsacus asperoides*, *Cibotii Rhizoma*, *Salviae Miltiorrhizae Radix et Rhizoma*) has the effect of tonifying qi and yin, nourishing Gan (Liver) and Shen, and promoting blood. Clinical research suggests that TLN improves both the symptoms and nerve conductive velocity of patients with DPN. TLN extract significantly decreased the concentration of MDA in serum and sciatic nerve, increased activity of SOD in serum and sciatic nerve, and decreased the expressions of active proteins p-p38 MAPK, p-p46 c-Jun N-terminal kinase (JNK) and p-extracellular regulated protein kinases (ERK)1/2 in DRG, resulting in inhibition of oxidative stress.[44-46]

Neural Repair and Regeneration

DPN is the result of combination of multiple factors, including dysfunction of blood vessels, nerves and the immune system. Whatever the cause might be, the result eventually is the degeneration of nerve fibers and necrosis of nerve cells. Therefore, the treatment of DPN should focus on repair and regeneration of the peripheral nerves, a very complex process. Once nerve damage occurs, a series of nerve repair and regeneration mechanisms are initiated in the body. SCs, also known as the nerve membrane cells, are unique glial cells in the peripheral nervous system. They express and secrete neurotrophic factors to maintain the survival of neurons and the normal structure and function of nerve fibers. The neurotrophic factors can promote axonal regeneration and myelination of regenerated axons. There was dysfunction of nerve regeneration and repair in patients with DPN, although effective intervention strategies are presently lacking. However, studies have shown that neurotropin, a nonprotein material with biological activity extracted from the skin of rabbits inoculated with cowpox virus vaccine, had positive effects in the treatment of diabetic neuralgia and numbness. Its mechanism might involve the inhibition of peripheral nerve regeneration and repair.[47,48]

Tangbikang (糖痹康, composed of *Astragali Radix*, *Ligustri Lucidi Fructus*, *Cinnamomi Ramulus*, *Scutellariae Radix*, *Coptidis Rhizome*, etc.) is beneficial to injured diabetic peripheral nerve repair. It has been shown to promote the expressions of brain-derived neurotrophic factor protein and mRNA of sciatic nerves in DPN rats. It could also inhibit the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway and down-regulate pro-apoptotic factors and caspase-3 protease.[49,50]

Studies have shown that JMT could promote proliferation of SCs and the expressions of various neurotrophic factors and their receptors. JMT could up-regulate the expressions of ciliary neurotrophic factor (CNTF) and NGF in the sciatic nerve.[51] The mRNA expression levels of NGF and CNTF were also increased by JMT.[52,53] The expressions of NGF receptor, p75 neurotrophin receptor, and tyrosine kinase A of sciatic nerve in the JMT groups were significantly enhanced when compared with the control DM groups.[54,55] Serum containing JMT could promote proliferation of SCs cultured in high-glucose medium and up-regulate the expression levels of NGF, CNTF and CNTF mRNA.[56-58]

Liu, et al[59] explored the protective effect of *Astragali Radix*, *Salvia miltiorrhiza* Bunge, *Dioscoreae Rhizoma* and their compound on apoptosis of SCs co-cultured with rat endothelial cells in high glucose. The SCs apoptotic rates in the CM herb intervention groups were significantly decreased compared with the high glucose control group. Among the CM herb intervention groups, the compound intervention group had the highest protective effect.

Wu, et al[60] observed changes in the activity and proliferation of cultured SCs under the high-glucose conditions and showed that allyl glycoside (AG) extracted from *Herba Rhodiolae* could significantly reverse the decrease of SCs proliferation induced by high glucose. Expression of vascular endothelial growth factor in the sciatic nerves of diabetic rats with diabetic neuropathy was increased after treatment with MBG.[61] Other research reported that taurine could reduce the apoptosis of SCs by inhibiting the transcription of caspase-3 mRNA and the activation of caspase-3.[62]

Evaluation and Expectation

The pathogenesis of DPN is not yet fully understood, and it is impossible to completely prevent or reverse the occurrence and development of its complications. Therapies based on a single pathogenesis of DPN (such as aldose reductase inhibitor) play a limited role. Even considering the unified mechanism of oxidative stress, anti-oxidative treatment does not show satisfactory efficacy in clinical trials or practice. An ideal drug should be an agent acting on multiple targets related to its

pathogenesis, that is right the superiority of CM.

Study suggested that the homeostasis of energy and metabolism in pancreatic islet β-cells was the key to maintaining normal function. Excessive nutrients are oxidized and utilized in the mitochondria of pancreatic β-cells in T2DM, and a certain amount of reactive oxygen species (ROS) are produced simultaneously, leading to a decrease in the antioxidative capacity of β-cells. In addition, islet β-cells are very sensitive to ROS, and their antioxidative capacity is weak, which further aggravates the injury of islet β-cells.[63]

Clinical studies described above mostly focused on the expression of certain factors or proteins, but the influencing factors were ignored. For example, hyperglycemia triggers the body to produce oxidative stress reaction that is throughout multiple metabolic process of DPN, but most of the studies focused on the observation of intermediary indicators about eliminating free radicals and improving antioxidant ability.

There are few comprehensive and systematical studies. Many exploratory studies have examined how to prevent the degeneration and dysfunction of neurons, and to promote the regeneration and repair of neurons. Most of the studies focused on SCs that are involved in the process of repair and regeneration of DPN through a variety of pathways, especially the activated SCs. Multiple cytokines and signaling pathways participate in the process above. However, most studies were just aimed at the role of SCs in repair and regeneration of peripheral nerve in one or several aspects. Further research about some specific molecular mechanisms in each aspect is needed.

There are relatively few studies on single CM herb and the exact mechanisms of action. While research on CM has been about a single pathway or just to detect some indirect indicators, coherent systematic research has been lacking. The advantages of multi-targeting of CM prescription have not been fully realized. Other limitations include the unclear complex mechanism of herb-herb interaction in CM compound prescription, the different dosages of each herb in the compound prescription, the different microenvironments between *in vitro* and *in vivo*, and unsatisfactory linking between animal experiments and clinical trials. Further, well-run studies can identify the drugs, including those from CMs mentioned above, that can protect the body from injury caused by high glucose and oxidative stress and promote repair and regeneration of nerves. If CM is found to promote islet β-cells proliferation and differentiation and decrease apoptosis, it might prevent the occurrence of DPN and even reverse the course of T2DM.

Conflict of Interest

The authors claimed no potential conflicts of interest relevant to this article.

Author Contributions

Liang XC drafted the Chinese manuscript. Yang D translated the Chinese manuscript into English and edited the present review. Both authors read and approved the final manuscript.

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