Study on the TCM Pathogenesis of Angiopathic Complications of Type II Diabetes

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Excess production of reactive oxygen species (ROS) of mitochondrion mediated by hyperglycemia is the common pathogenesis of angiopathic complications of diabetes. TCM holds that the damp from the dysfunction of spleen, kidney and liver is the causative factor of complications of diabetes. This is similar to the mechanism of ROS resulting in angiopathic complications of diabetes. When the angiopathic complications of type II diabetes mellitus (T2DM) are differentiated as caused by turbid damp in TCM can be explained as ROS. Since the obstruction of pathogenic damp in channels and collaterals is said to be the main pathogenesis, the treating principle should be dissolving the damp to remove the obstruction.

At present, it is held by researches on the pathogenesis of angiopathic complications of diabetes that oxidation stress is the common pathogenesis of angiopathic complications of type II diabetes mellitus (T2DM). In accordance with the principle of ‘treatment based on symptoms and prescription corresponding to symptoms’, the clinical observation on the treatment of phlegm-damp type of T2MD by modified prescriptions of Lei’s Fangxiang Huazhuo Fa (雷氏芳香化浊法 Lei’s Method of Eliminating Damp with Aromatics) was done. Based on its good therapeutic effect, the animal experiment from the angle of oxidation stress was conducted. The authors have learned that the TCM concept of pathogenic damp has certain relations with the oxidation stress of angiopathic complications of T2DM. A discussion follows.

Oxidation Stress and Angiopathic Complications

Oxygen element is the main source of energy supply for organism, and also the essential substance for the synthesis of ATP and hormone. During the oxidizing reaction of organism, the oxygen element itself also has reductive reaction, forming the reactive oxygen species (ROS). ROS are the atoms, atomic groups and molecules, which possess an odd number of electrons, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH). At normal times, the ROS is the instant product of biochemical reaction of body, which is eliminated quickly by the anti-oxidation defensive system, not accumulated inside the body. However, oxidation stress induced by ROS may occur, if there is too much production of ROS or decreased antioxidation ability of the body, leading to a series of damages to the tissues and cells. The antioxidation defensive system includes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione (GSH).

The NADH formed through the process of gluolysis of the intracellular glucose undergoes oxidative phosphorylation by means of the mitochondrial electron transport respiratory chain. Under the condition of diabetes, the glucose oxidation will increase, and when it surpasses the dealing ability of the respiratory chain, there may appear single-electron transport and increased production of ROS in the mitochondrion. ROS can induce the break of DNA chain and activate poly (ADP-ribose) polymerase (PARP). PARP can make ADP ribose
Polymer gathers to key enzyme in glycolysis, glyceraldehyde phosphate dehydrogenase (GAPDH) and make the latter lose its activity. When GAPDH is deactivated, the pass for glucose to be thoroughly oxidated into carbon dioxide and water through tricarboxylic acid cycle will be blocked, and the formation of polybasic alcohol, advanced glycosylation end products (AGEs), protein kinase C (PKC) and hexosamine will be activated, leading to angiopathic complications of diabetes. The activation of the above-mentioned can, in turn, promote the occurrence of oxidation stress, forming a vicious cycle. Thus, it can be seen that the over production of ROS on the mitochondrial electron transport chain mediated by hyperglycemia is the key link in the development of angiopathic complications of diabetes.

**TCM Knowledge about Oxidation Stress Leading to Angiopathic Complications of Diabetes**

T2DM is a disease caused by the interaction between gene and the environment, with the latter playing the main role. For this, TCM has already had its statements. For instance, in *Miraculous Pivot* (灵枢), it is said that ‘those with weak five zang organs are easily to have Xiaodan (diabetes)’. Plain Questions (素问) says: “This disease often occurs in fat people, who often eat sweet and fatty food. The fatty food causes internal heat, while the sweet food causes fullness in the middle-jiao, leading to upward flow of qi developing into Xiaoke (diabetes)”. And Medical Records as a Guide to Practice (临证指南医案) says: “Mental depression with burning of internal fire contributes to the severe diabetes”. The location of Xiaoke (diabetes) is in the spleen, kidney and liver. Over intake of fatty and sweet food and eating and drinking too much at one meal can injure the spleen-qi, resulting in dysfunction of the spleen in transforming and transporting water-damp or essence of water and grain, and water accumulation to form damp. The kidney dominates water. Congenital deficiency (such as premature labor), indulgence of sexual activities, and strain and stress can all injure the kidney and make it dysfunctional in opening and closing, leading to water accumulation. Mental depression can injure the liver to cause stagnation of the liver-qi, unsmooth flow of qi, and disturbance of functional activity of qi in tri-jiao, thus obstruction of water due to qi stagnation. All the above-mentioned factors can cause formation of pathogenic-damp, and the damp accumulation leads to Xiaoke (diabetes). In recent years, the action of obesity and fat endocrine in T2DM has become the hot topics in researches. TCM has the saying that ‘fat people often have phlegm’. It has been shown by Liu Yanjiao’s research about the inter-relationship between phlegm-damp constitution of obesity people and diabetes that among the Chinese people who have T2DM, the incidence of those with phlegm-damp constitution is 64.96%, in which the incidence of those fat people with phlegm-damp constitution is 98.93%, suggesting that fat people are most likely to have phlegm and damp, and phlegm-damp constitution is the main constitutional type of T2DM accompanied with obesity. After studying on the syndrome characteristics of diabetics with varying duration of diabetes, Xu Zhengzheng puts forward that the syndrome of damp stagnation has universality in diabetics, and the intractability of diabetes is most likely related with the deep accumulation of pathogenic damp in the body, and therefore, it is necessary for TCM treatment of diabetes to take pathogenic-damp into consideration at any time. In mid 1990s of last century, the particularity of obesity in T2DM had been already noticed. The corresponding studies showed that a large number of T2DM patients accompanied with obesity were believed to have phlegm-damp in syndrome differentiation of TCM. The treatment with modified Lei’s Fangxiang Huazhuo Fa could yield the effect of lowering the blood sugar and regulating blood-lipid. The basic researches later also proved that the prescriptions to dissolve damp modified according to Lei’s Fangxiang Huazhuo Fa could decrease the AGEs expression of renal cortex of diabetic rats, raise the activity of SOD, and decrease...
the content of toxic metabolite of lipid peroxide, malondialdehyde (MDA). And their inhibiting AGEs and oxidation stress did not rely on the blood sugar lowering. The above is sufficient to indicate that damp is one of the basic pathogenic characters of T2DM.

Pathogenic damp is the pathologic product of dysfunction of the spleen, kidney and liver, which further becomes the causative factor of complications of Xiaoke (diabetes). Accumulation of damp obstructing the channels and collaterals is the basic pathologic change of angiopathic complications of T2DM. If the damp obstructs the brain collaterals, there may appear apoplexy (wind-stroke); if it obstructs the heart vessels, there may appear precordial pain due to obstruction of qi in the chest (coronary heart disease); if it obstructs in the lower limb, there may appear gangrene of toe (arteriosclerotic obliteration of the lower limb, thromboangiitis obliterans); if it obstructs the eyes, there may appear diabetic eye diseases (diabetic retinopathy); if it obstructs the kidney vessels, making water overflowing in the muscles and skin, there may appear edema (diabetic renal diseases); and if it obstructs in the limbs, muscles and skin, there may appear numbness of the extremities and sensory disturbance (diabetic neuropathy). The pathologic mechanism of the above-mentioned pathologic changes is similar, in many aspects, to that of the diabetic angiopathic complications caused by the generation of ROS; and the only difference is the varying expressions of Chinese and western medical concepts. Therefore, the writers think that if, according to the TCM differentiation, the pathogenesis for the angiopathic complication of T2DM is pathogenic damp, it can be understood and explained as ROS.

**TCM Differential Treatment for Pathogenic Damp**

Diagnosis and treatment based on an overall analysis of symptoms and signs are the core of TCM theory and the essence of Chinese clinical medicine. The annotation of TCM concepts is aimed at developing the TCM theory and raising the therapeutic effects. There are various kinds of angiopathic complications of T2DM. No matter what kind of complication it is, if the pathogenesis is differentiated as pathogenic damp, the treatment should be given based on syndrome-differentiation.

For such patients accompanied with fat body figure, lassitude and asthenia, abdominal distention and poor appetite, shortness of breath with disinclination to talk, pale tongue with sticky coating, and deep-slow pulse, the treating principle should be strengthening the spleen and eliminating damp. The modified Shenling Baizhu San (Ginseng-Poria-Atractylodes Powder) and Xiangsha Liujunzi Tang (Decoction of Cyperus and Amomum with Six Noble Ingredients) can be used. For those with soreness and weakness of the waist and knee joints, dizziness and blurred vision, tinnitus and lassitude, heaviness of the limbs, pale tongue with white-sticky coating, and deep-slow pulse, the treating principle should be nourishing the kidney and promoting diuresis. The modified Jinkui Shenqi Wan (Pills for Restoring the Function of the Kidney Recommended by Synopsis of Prescriptions of the Golden Chamber) and Yougui Wan (Yang-Restoring Pill) can be used. For mental depression, anxiety and restlessness, hypochondriac distending pain, sticky sensation in the mouth, red tongue with sticky coating, and wiry pulse, and the treating principle should be soothing the liver and resolving damp. The modified Xiaoyao San (Carefree Powder) can be used. Long-term accumulation of pathogenic damp may turn into heat, leading to damp-heat, for which the severity of each should be differentiated. The symptoms of heavy sensation of the head like being wrapped by cloth, heavy sensation of the body and weakness of the limbs, epigastric fullness, white-sticky tongue coating, and slow pulse may indicate heavy damp but light heat, which can be treated by the modified Sanren Tang (Decoction for Dispelling Dampness and Clearing Heat with Three Kinds of Kernels). The symptoms of flushed face and
excessive thirst, profuse eating but easily getting hungry, heavy sensation of the body and gastric fullness, yellow-sticky tongue coating, and slippery-rapid pulse may indicate heavy heat but light damp, which can be treated by the modified Baihu Tang (白虎汤 White Tiger Decoction) plus Cangzhu Tang (苍术汤 Atractylodes Decoction). The symptoms of flushed face and thirst, gastric and abdominal fullness, lassitude of the limbs, yellow and scanty urine, yellow-sticky tongue coating, and slippery pulse may indicate the same heaviness of the heat and damp, which can be treated by the modified Ganlu Xiaodu Dan (甘露消毒丹 Universal Antitoxic Pill).

Damp accumulation can lead to disturbance of water passage in the tri-jiao, and the treating principle should be removing obstruction and promoting free flow of qi and blood and dredging passages in the tri-jiao. For dispersing the upper-jiao, Sang Ye (桑叶 Folium Mori), Qian Hu (前胡 Radix Peucedani), and Pi Pa Ye (枇杷叶 Folium Eriobotryae) can be used; for promoting transportation in the middle-jiao, Huo Xiang (藿香 Herba Agastachis), Pei Lan (佩兰 Herba Eupatorii), and Hou Pu (厚朴 Cortex Magnoliae Officinalis) can be used; and for promoting diuresis in the lower-jiao, Tong Cao (通草 Medulla Tetrapanacis), Ze Xie (泽泻 Alismatis), and Da Huang (大黄 Radix et Rhizoma Rhei Palmati) can be used. For damp stagnation in the tri-jiao, which makes dysfunction of the bladder, and characterized by chest stress and gastric fullness, nausea, vomiting and acid regurgitation, short and scanty urine, sticky tongue coating, and slippery pulse, the treating principle should be eliminating heat and promoting diuresis, and the modified Wendan Tang (温胆汤 Decoction for Clearing Away Gallbladder-Heat), or herbs such as Xing Ren (杏仁 Semen Armeniacae Amarum), Hou Pu (厚朴 Cortex Magnoliae Officinalis) and Fu Ling (茯苓 Poria) can be used. For pathogenic damp obstructing the chest, characterized by gastric and abdominal fullness, hypochondriac distending pain, sticky-white tongue coating like a layer of powder, dark-red or purple-red tongue, herbs should be used for soothing the chest, and the modified Lei’s Xuantou Muyuan Fa (雷氏宣透医学法 Lei’s Method of Dispersing the Chest) can be used.

In Clinic, for treating T2DM differentiated as pathogenic damp type, we often use Lei’s Fangxiang Huachuo Fa. The prescription contains Huo Xiang (藿香 Herba Agastachis), Pei Lan (佩兰 Herba Eupatorii), Chen Pi (陈皮 Pericarpium Citri), Qing Ban Xia (清半夏 Rhizoma Pinelliae), Hou Pu (厚朴 Cortex Magnoliae Officinalis), Da Fu Pi (大腹皮 Pericarpium Arecae), and He Ye (荷叶 Folium Nelumbinis). This prescription originated from Lei Feng’s Treatise on Seasonal Diseases (时病论) of the Qing Dynasty, which was indicated for May mycotic damp, and syndrome of clogging of the upper and middle qi systems. Later, it was used by people for treating damp-warm diseases with heavy damp and light heat obstructing the middle-jiao, belonging to the treatment for external damp. In the prescription Huo Xiang (藿香 Herba Agastachis) and Pei Lan (佩兰 Herba Eupatorii) can not only disperse the pathogenic damp, but also strengthen the spleen and regulate the stomach to promote transformation and transportation in the middle-jiao; and when combined with Hou Pu (厚朴 Cortex Magnoliae Officinalis), they can promote smooth flow of qi of the spleen and stomach. When smooth flow of qi in the middle-jiao is ensured, the pathogenic damp will not generate and accumulate, hence the satisfactory therapeutic effect of the prescription in treating the internal damp. In clinical practice, in regard to the pathogenesis of pathogenic damp obstructing the collaterals, medicines for promoting free flow of qi and blood in the channels and collaterals can be used, such as Dang Gui (当归 Radix Angelicae Sinensis), Di Long (地龙 Phereetima Aspergillum), Si Gua Luo (丝瓜络 Retinervus Luffae Fructus), and Luo Shi Teng (络石藤 Caulis Trachelosperm). ‘Wind can prevail over dampness’, Some medicines for eliminating wind can also be added, such as Jing Jie (荆芥 Herba
Schizonepetae), Fang Feng (防风 Radix Saposhnikoviae), and Qiang Huo (羌活 Rhizoma seu Radix Notopterygii). If there is the tendency of damp turning into heat or there is already heat, Chan Tui (蝉蜕 Periostracum Cicadae) can be added. ‘Excessive damp injures yang-qi’. Damp is a yin pathogenic factor, which tends to injure yang-qi. Therefore, even for the mixture of damp and heat, the heat-eliminating should be limited, i.e. medicines of extreme cold in nature should be avoided.

From the above, the authors think that pathogenic damp is closely related with ROS, and its accumulation obstructing the channels and collaterals is the common pathogenesis of angiopathic complications of T2DM. The accumulation deep in the channels and collaterals makes the condition protracted and intractable. The principle of treatment should be dissolving the damp and dredging the channels and collaterals. When damp is eliminated and the channels and collaterals are smooth, the occurrence of terminal events can be decreased.

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