Therapeutic effects of modified Danggui Sini Decoction on plasma level of advanced glycation end products in patients with Wagner grade 0 diabetic foot: a randomized controlled trial

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Background: Many studies have demonstrated association between advanced glycation end products (AGEs) and diabetic angiopathy. There are certain advantages of traditional Chinese medicine (TCM) therapy in treatment of these diseases.

Objective: To evaluate the therapeutic effects and safety of modified Danggui Sini Decoction, a compound traditional Chinese herbal medicine for nourishing blood to warm meridians, on plasma level of AGEs in patients with Wagner grade 0 diabetic foot ulcers of blood stasis or/and kidney yang deficiency syndrome.

Design, setting, participants and interventions: A random and positive control method was adopted. Seventy-two cases of Wagner classification of grade 0 diabetic foot ulcers with blood stasis or/and kidney yang deficiency syndrome were randomly divided into treatment group and control group. There were thirty-six cases in each group. All the patients were collected from Maoming Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine. Patients received oral and written information about the clinical procedures before giving their written informed consent. The study was approved by the Ethics Committee of Maoming Hospital of Traditional Chinese Medicine. The patients in the treatment group were treated with modified Danggui Sini Decoction, and the patients in the control group were treated with cilostazol. A course of treatment was 14 days, and the patients in the two groups were treated for 3 courses.

Main outcome measures: The changes of clinical symptoms, ankle-brachial index (ABI), electromyography, lower extremity arteries measured by ultrasonic Doppler, fasting blood glucose, hemoglobin A1c, fibrinogen, and plasma level of AGEs were detected in the two groups before and after treatment. The safety of modified Danggui Sini Decoction was assessed by laboratory data and adverse events.

Results: There were statistical differences in clinical efficacy, ABI, lower extremity arteries hemodynamics, and nerve conduction velocity between the two groups (P<0.05, P<0.01). The plasma level of AGEs after treatment was significantly decreased in the two groups, and the level of AGEs in the treatment group was lower than that in the control group (P<0.05).

Conclusion: Modified Danggui Sini Decoction can improve clinical symptoms in patients with diabetic foot ulcers of Wagner grade 0 and it shows therapeutic effects on diabetes complicated with vascular diseases.

Keywords: diabetic foot; Wagner grade 0; Danggui Sini Decoction; glycosylation end products; randomized controlled trial
加味当归四逆汤治疗0级糖尿病足的疗效及对血糖晚期糖基化终产物水平的影响：随机对照试验

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背景：许多研究证实晚期糖基化终产物（advanced glycation end product，AGE）与糖尿病血管病变密切相关，中医药在该类疾病治疗中存在一定优势。

目的：加味当归四逆汤治疗 Wagner 0级糖尿病足患者的临床疗效、安全性及其对血糖 AGE 水平的影响。设计、场所、受试者和干预措施：采用随机、阳性药物对照研究方案。以 72 例血瘀证、肾阳虚证 Wagner 0 级糖尿病足患者随机分为治疗组和对照组，每组 36例，均为广州中医药大学茂名市中医院门诊和住院患者。患者签署知情同意书之前已经被口头或者书面告知研究过程。该研究由广州中医药大学茂名市中医院伦理委员会批准。

治疗组口服加味当归四逆汤，对照组予西药西洛他唑治疗。两组均以 14 d 为 1 个疗程，连续治疗 3 个疗程。

主要结局指标：观察两组治疗前后临床症状、踝肱指数（ankle-brachial index, ABI）、肌电图、下肢动脉超声多普勒血流动力学指标、空腹血糖、糖基化血红蛋白、纤维蛋白原和 AGE 水平变化。记录实验室检查结果和不良事件作为安全性评估的依据。

结果：治疗组好转后临床症状、ABI、下肢动脉超声多普勒血流动力学和神经传导速度等指标较对照组改善，差异有统计学意义（P < 0.05，P < 0.01）。治疗后两组血糖 AGE 均明显下降，且治疗组与对照组比较，差异亦有统计学意义（P < 0.01）。

结论：加味当归四逆汤可显改善 Wagner 0 级糖尿病足患者的临床症状，并对糖尿病血管病变有一定的治疗作用。

关键词：糖尿病足；Wagner 0级；当归四逆汤；糖基化终产物；随机对照试验

It is estimated that approximately 15% of more than 150 million people with diabetes mellitus (DM) worldwide will at some stage develop diabetic foot ulceration[1]. Foot problems are indeed a global problem and there is no area in the world that does not report the development of foot lesions as a consequence mainly of neuropathy and peripheral vascular disease[2]. Diabetic foot (DF) is a severe common complication in DM patients. The risk of amputation is 5–15 times in DM patients as compared with non-diabetic patients. Every year more than 50% patients for non-traumatic amputation are DM patients. The reasons for 85% in DM patients for non-traumatic amputation are infections caused by foot ulcer or gangrene[3]. The main risk factors of amputation are vascular factors[2]. The key elements for preventing disability caused by DM are precaution and treatment in time. Recent study has shown that advanced glycation end products (AGEs) are associated with diabetic angiopathy[4]. The aim of the present study was to test the therapeutic effects of modified Danggui Sini Decoction, a compound traditional Chinese herbal medicine for nourishing blood to warm meridians, on plasma level of AGEs in diabetic foot patients as compared with cilostazol.

1 Clinical data and methods

1.1 Clinical data

1.1.1 Research subject Seventy-two DM outpatients and inpatients in Maoming Hospital of Traditional Chinese Medicine, Guangzhou University of Chinese Medicine from March 2005 to August 2008 were collected.

1.1.2 Diagnostic criteria 1) Diagnostic criteria for syndromes was from Diagnostic and Therapeutic Effect Evaluation Criteria of Diseases and Syndromes in Traditional Chinese Medicine[5]. 2) Diagnostic criteria for DF issued by World Health
Organization\(^{[x]}\). 3) Wagner grade 0 DF with risk factors of foot ulcer\(^{[x]}\).

1.1.3 Inclucling criteria Consistent with diagnostic criteria of the above diagnostic criteria 1), 2) and 3).

1.1.4 Excluding criteria 1) Arteriosclerosis obliterans in lower extremity and other lower extremity arterial diseases of non-diabetic patients. 2) Complicated with serious diseases such as angina pectoris, diabetic ketoacidosis, and diabetic nephropathy, etc. 3) Diabetic gangrene, infections of lower extremity or lower limb ulcer. 4) Patients with incomplete data or treatment interruption including dropout and adverse events.

1.2 Study method

1.2.1 Study design A random and positive control design was employed. Seventy-two cases of Wagner classification of grade 0 diabetic foot ulcers with blood stasis or and kidney-yang deficiency syndrome were randomly divided into treatment group and control group, and there were thirty-six cases in each group.

1.2.2 Drug and treatment method Strengthening propaganda and education on DM patients were done. Patient’s blood sugar was controlled effectively [fasting blood glucose (FBG) 4.4 – 6.6 mmol/L, non-FBG 4.4 – 7.8 mmol/L] by sulfonylurea hypoglycemic agents or and insulin. Patients complicated with hypertension or and hyperlipemia were treated by drugs. Patients in the treatment group were treated with modified Danggui Sini Decoction (15 g of Radix Angelicae Sinensis, 10 g of Radix Paoniae, 15 g of Ramulus Cinnamomi, 6 g of Herba Asari, 10 g of Phertima Aspergillum, 20 g of Radix Salviae Yunnanensis, 30 g of Spatolobus suberectus Dunn, 20 g of Pseudostellaria heterophylla, 10 g of Atractylodes macrocephala Koidz, 15 g of Poria cocos, 20 g of Cornus officinalis Sieb, and the above drugs were decocted in water for oral use) twice daily. Patients in the control group were treated with cilostazol tablets (Xi’an Daheng Pharmaceutical Co., Ltd) state approval number H20040579, 50 mg/tablet) 50 mg twice per day with boiled water. Two weeks were taken as one treatment course, and patients in the two groups were treated for 3 courses.

1.2.3 Observed indexes

1.2.3.1 Clinical symptom score Clinical symptom scores were compared before and after treatment between the two groups. The symptom scores were assessed with self-made scoring standard: point 0 as no symptom, point 2 as mildest symptom, point 4 as moderate symptom, point 6 as severe symptom. The main evaluation items were as the following. 1) intermittent claudication (walking speed is at 50 – 60 m/min); point 0 as covering 500 m without pain; point 2 as covering 300 – 499 m with pain; point 4 as covering 100 – 299 m with pain; point 6 as covering less than 100 m or unable to walk. 2) Sense of pain; point 0 as no pain; point 2 as pain but few using anodyne; point 4 as pain using anodyne frequently; point 6 as sleep and appetite affected by sustainable pain or unable to be alleviated by anodyne. 3) Sense of numbness; point 0 as no symptom; point 2 as numbness; point 4 as numbness with other abnormal senses; point 6 as sustainable numbness unable to endure. 4) Sense of cold and heaviness; point 0 as no symptom; point 2 as mild symptom; point 4 as moderate symptom; point 6 as severe symptom.

1.2.3.2 Therapeutic index Therapeutic index = (symptom scores before treatment – symptom scores after treatment)/symptom scores before treatment \(\times 100\%\). The symptom scores in the two groups before and after treatment were calculated and assessed by nimoidine method. All determinations were done in duplication, and mean was calculated by two co-chief physicians (consistency test kappa value = 0.80).

1.2.3.3 Blood biochemical index, lower extremity arterial hemodynamics and nerve conduction velocity

Blood samples were drawn into glass tubes containing ethylenediamine tetracetic acid (EDTA), which were immediately spun at 3 500 \(\times\) g for 15 min at 4 \(\degree\)C. Plasma was isolated and stored at \(-20\) \(\degree\)C until analysis. Plasma concentration of AGEs was measured by enzyme-linked immunosorbent assay (ELISA) (Tianjin Ruaijin Biological Technology Co., Ltd.). All samples were analyzed in duplication and mean concentrations were calculated. The plasma levels of FBG, hemoglobin Alc (HbAlc), fibrinogen (FIB), and blood, urine and stool routine, liver and renal function were measured by using routine laboratory methods. The changes in lower extremity arterial hemodynamics were detected by using ACUSON 128XP/10 type color Doppler ultrasonic diagnostic apparatus. Keypoint type electromyogram instrument was used to observe the changes of motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV).

1.2.3.4 Efficacy evaluation criteria The criteria for clinical curative effects of the two interventions on DF were divided into three levels according to the reference\(^{[x]}\). Obviously effective: the symptom score decreased by 70% – 100% after treatment or ankle-brachial index (ABI) more than 0.1 higher than the original value; effec-
tive; the symptom score decreased by 30%–69% after treatment or ABI more than 0.05–0.1 higher than the original value; ineffective; the symptom score decreased by 0%–30% after treatment or increased.

1.2.3.5 Safety evaluation The safety of drug was assessed with blood, urine and stool routine, liver and renal function before and after the treatment. The adverse reactions were recorded at the same time.

1.3 Statistical analysis All analyses were performed by using SPSS 15.0. Categorical variables were presented as frequency or percentage. Continuous variables with normal distribution were generally presented as $\bar{x} \pm s$. For comparisons between the two groups, the student’s $t$ test was used for continuous variables and the $\chi^2$ test for categorical variables. Significance was accepted at $\alpha = 0.05$.

2 Results

2.1 Baseline data There were no significant differences in baseline data including sex ratio, age and diabetic duration, etc., between the two groups ($P > 0.05$). There were 36 cases with age ranging from 50 to 76 years in the treatment group; the diabetic duration was from 1.2 to 12.2 years, and the diabetic foot duration was from 4 months to 6 years. There were 36 cases with age ranging from 49 to 73 years in the control group; the diabetic duration was from 1.4 to 10.8 years, and the diabetic foot duration was from 3 months to 5.5 years. The detailed information was shown in Table 1. All the patients were involved in the analysis of results without deletion. The flow diagram of this randomized trial was shown in Figure 1.

2.2 Clinical effects In the treatment group, the obviously effective rate was 41.67% (15/36), the effective rate was 44.44% (16/36), the ineffective rate was 13.89% (5/36), and the total effective rate was 86.11% (31/36). In the control group, the obviously effective rate was 22.22% (8/36), the effective rate was 36.11% (13/36), the ineffective rate was 41.67% (15/36), and the total effective rate was 58.33% (21/36). There was significant difference in the total effective rate between the two groups ($P < 0.05$).

2.3 Lower extremity arterial hemodynamics There was no statistical difference in lower extremity arterial hemodynamics between the two groups before the treatment, and the lower extremity arterial hemodynamics after the treatment were all improved in the two groups as compared with those before the treatment ($P < 0.05$, $P < 0.01$). The effect of Danggui Sini Decoction on lower extremity arterial hemodynamics was better than that of cilostazol ($P < 0.05$, $P < 0.01$). The information was shown in Table 2 and Table 3.

<table>
<thead>
<tr>
<th>Item</th>
<th>$n$</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female (Cases)</td>
<td>36</td>
<td>17/19</td>
<td>20/16</td>
</tr>
<tr>
<td>Age ($\bar{x} \pm s$, years)</td>
<td>36</td>
<td>63.35 ± 7.04</td>
<td>64.09 ± 7.30</td>
</tr>
<tr>
<td>Diabetic duration ($\bar{x} \pm s$, years)</td>
<td>36</td>
<td>5.14 ± 2.88</td>
<td>4.77 ± 1.52</td>
</tr>
<tr>
<td>Diabetic foot duration ($\bar{x} \pm s$, months)</td>
<td>36</td>
<td>24.0 ± 18.2</td>
<td>21.6 ± 17.2</td>
</tr>
</tbody>
</table>

2.4 ABI, MNCV and SNCV There were no statistical differences in MNCV and SNCV of peroneal nerve and ABI between the two groups before treatment ($P > 0.05$). MNCV and SNCV in the treatment group were improved as compared with those before treatment ($P < 0.01$), and there were also significant differences in MNCV, SNCV and ABI between the two groups after treatment ($P < 0.05$). The information was shown in Table 4.

2.5 FBG, HbA1c, AGEs and FIB There were no statistical differences in FBG, HbA1c, FIB and AGEs between the two groups before treatment ($P > 0.05$). The values of indexes in the two groups were all decreased after treatment ($P < 0.05$, $P < 0.01$). The values of FIB and AGEs in the treatment group were lower than those in the control group ($P < 0.05$, $P < 0.01$). The information was shown in Table 5.

2.6 Safety assessment There were no adverse reactions in the two groups. Blood, urine and stool routine, and liver and renal function were not obviously changed.
Table 2  Lower extremity arterial hemodynamics of the pedis artery

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Diameter (cm)</th>
<th>Blood flow (mL/min)</th>
<th>Peak flow (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>0.18±0.03</td>
<td>22.04±5.35</td>
<td>32.86±4.43</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>0.20±0.04*</td>
<td>24.54±5.19*</td>
<td>36.26±3.93**</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>0.18±0.04</td>
<td>21.70±5.12</td>
<td>34.05±5.36</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>0.26±0.05**</td>
<td>34.46±8.11**</td>
<td>41.14±5.50**△△</td>
</tr>
</tbody>
</table>

* P <0.05, ** P <0.01, vs before treatment; △ P <0.05, △△ P <0.01, vs control group.

Table 3  Lower extremity arterial hemodynamics of the popliteal artery

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Diameter (cm)</th>
<th>Blood flow (mL/min)</th>
<th>Peak flow (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>0.42±0.05</td>
<td>197.41±17.46</td>
<td>50.55±5.22</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>0.45±0.05*</td>
<td>209.85±22.67*</td>
<td>53.45±5.36*</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>0.40±0.06</td>
<td>196.73±26.85</td>
<td>52.25±9.42</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>0.52±0.07* △△</td>
<td>269.18±22.14**△△</td>
<td>60.53±8.79**△△</td>
</tr>
</tbody>
</table>

* P <0.05, ** P <0.01, vs before treatment; △ P <0.05, △△ P <0.01, vs control group.

Table 4  MNCV and SNCV of peroneal nerve and ABI in the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MNCV (m/s)</th>
<th>SNCV (m/s)</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>38.57±4.35</td>
<td>32.25±3.57</td>
<td>1.09±0.31</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>39.75±4.58</td>
<td>33.96±3.66</td>
<td>1.18±0.29</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>37.75±5.21</td>
<td>32.46±3.92</td>
<td>1.08±0.32</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>43.46±4.32*</td>
<td>38.22±4.06**△</td>
<td>1.24±0.30△</td>
</tr>
</tbody>
</table>

* * P <0.05, △△ P <0.01, vs before treatment; △ P <0.05, △△ P <0.01, vs control group.

Table 5  FBG, HbA1c, AGEs and FIB in the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>FBG (mmol/L)</th>
<th>HbA1c (%)</th>
<th>FIB (g/L)</th>
<th>AGEs (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>10.7±0.9</td>
<td>8.9±1.7</td>
<td>7.89±0.82</td>
<td>38.4±11.8</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>7.2±0.6**</td>
<td>6.8±1.9**</td>
<td>5.21±0.74*</td>
<td>31.3±10.8*</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36</td>
<td>10.1±1.4</td>
<td>8.7±2.1</td>
<td>7.87±1.05</td>
<td>37.2±9.8</td>
</tr>
<tr>
<td>After</td>
<td>36</td>
<td>6.9±0.8*</td>
<td>6.7±0.7*</td>
<td>4.02±0.81*△</td>
<td>26.6±8.6**△</td>
</tr>
</tbody>
</table>

* P <0.05, ** P <0.01, vs before treatment; △ P <0.05, △△ P <0.01, vs control group.

3 Discussion

Diabetic foot is indeed a global problem and there is no area in the world that does not report the development of it as a consequence mainly of neuropathy and peripheral vascular disease. It is not surprising that diabetic foot problems are common in Chinese diabetic patients. The peripheral vascular disease plays an important and significant role in the pathogenesis of diabetic foot. Some studies show that the damage to the small blood vessels could exist in the early stage of diabetes. Wagner grade 0 diabetic foot patients exhibit varying degrees of atherosclerosis. And lower extremity arteriosclerosis obliterans is an independent risk factor for patients with diabetic foot. Wagner grade 0 diabetic foot is the critical stage of development of lower extremity disorders such as ulceration and gangrene. Treatment of Wagner grade 0 diabetic foot is important and practical to prevent the occurrence of foot ulcers from amputation, and to prevent the occurrence of ischemic lesions. Early symptoms of diabetic foot ulcer include intermittent claudication, redness of the skin, blistering, numbness and other signs of irritation. Most of diabetic patients are
frail with old age and long duration.

AGEs are the result of a chain of chemical reactions after an initial glycation reaction. The link between high plasma glucose levels and tissue damage is at least in part due to the formation and accumulation of AGEs in tissues. In the pathogenesis of diabetes-related AGE formation, hyperglycemia results in higher cellular glucose levels in those cells which are unable to reduce glucose intake. Animal experiments confirmed that AGEs may accelerate the formation of atherosclerosis in diabetic rats. The mechanism for AGE-induced vascular lesions in diabetic foot patients is extremely complex and not yet fully understood. Among the many potential pathogenic mechanisms responsible for the progression in diabetic foot, the involvement of three factors has been suggested: 1) Cell signaling pathway: this in turn results in increased levels of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH), increasing the proton gradient beyond a particular threshold at which the complex II prevents further increase by stopping the electron transport chain. This results in mitochondrial production of reactive oxygen species, activating poly (ADP-ribose) polymerase I (PARP) by damaging DNA. 2) Vascular endothelial cell injury: the composite products of AGEs and receptor for AGE (RAGE) can lead to vascular endothelial cell injury. 3) Neuronal nitric oxide affected by AGEs: activity of nitric oxide (NO) can be intervened by composition of AGEs and blood vessel matrix. And producing and releasing of NO can affect the function of relaxation of smooth muscle cells.

Chinese medicine practitioners believe that Xiaoike is caused by consumption due to chronic disease and overstrain or weakness and kidney qi deficiency syndrome. All of them eventually lead to deficiency of both qi and blood. The symptoms of redness of the skin or local cold pain will be caused by qi deficiency and inability to propel blood in chronic disease and gradual formation of blood stasis due to blood flow inhibition. Limb paralysis and cold skin are due to yang qi deficiency that fails to warm. Intermittent claudication is due to blood deficiency that fails to nourish the body. The major pathological feature of Wagner grade 0 diabetic foot is blood stasis caused by deficiency. The treatment is warming meridians to disperse cold, nourishing blood and promoting blood circulation. Danggui Sini Decoction is a main prescription for constitutional deficiency of blood and yang qi. Modified Danggui Sini Decoction in treatment of Wagner grade 0 diabetic foot was based on the theory above mentioned. At the same time, a cilostazol control group was set up. Cilostazol is a selective phosphodiesterase inhibitor with therapeutic focus on increasing cyclic adenosine monophosphate (cAMP). An increase in cAMP results in an increase in protein kinase A (PKA), which is directly related with an inhibition in platelet aggregation. At the same time cilostazol is a main medication for the treatment of intermittent claudication. Patients with intermittent claudication develop pain if walking, because the blood oxygen is not enough to reach active leg muscles. Cilostazol reduces the pain of intermittent claudication by dilating the arteries, thereby improving the blood flow and oxygen to the legs by decreasing the action of phosphodiesterase 3. It also reduces the ability of blood clotting. Cilostazol enables patients with intermittent claudication to walk longer and faster before developing pain.

In conclusion, the present study demonstrated that serum AGEs were significantly increased in diabetic foot patients. The levels of AGEs decreased in the two groups after treatment. AGEs in the treatment group decreased more significantly as compared with the control group. Modern pharmacological studies show that Cornus officinalis Sieb, Salvia miltiorrhiza Bunge, Ligusticum chuanxiong Hort, and Pseudostellaria heterophylla can reduce the generation of AGEs by varying degrees in vitro. And these Chinese herbs can improve diabetic microangiopathy due to increase of AGEs. The treatment of diabetic foot by modified Danggui Sini Decoction includes complex mechanism. Past studies had shown that Danggui Sini Decoction could improve the clinical symptoms and prognosis in diabetic patients by inhibition of platelet aggregation, improvement of hemorhology, regulation of blood lipids, and improvement of nerve conduction velocity, etc. The present results showed that modified Danggui Sini Decoction could reduce the generation of AGEs, alleviate lower limb atherosclerosis, expand blood vessels, and improve microcirculation.

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