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Research Article
Inhibitory Effect of *Astragalus membranaceus* Extract on Myocardial Damage in Diabetes Complicated by Cardiomyopathy

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Abstract

Background and Objective: Diabetic cardiomyopathy is a specific complication of diabetic heart disease and its etiology and mechanisms are not yet fully understood. *Astragalus membranaceus* is a commonly used traditional Chinese medicinal herb. This work demonstrated the impact of *Astragalus membranaceus* extract on glycemic and lipid metabolism disturbances as well as myocardial injury in patients with diabetic cardiomyopathy. **Materials and Methods:** In this research, qualitative analysis of *Astragalus membranaceus* extract injection was conducted using liquid chromatography. The 96 patients with type 2 diabetic cardiomyopathy were recruited and rolled into the control group (CG) treated with rosiglitazone tablets and the observation group (OG) treated with rosiglitazone tablets in combination with *Astragalus membranaceus* extract injection. After treatment, changes in patients' serum glucose metabolism, lipid metabolism, myocardial injury markers and adhesion molecule levels were assessed and echocardiography was employed to evaluate differences in left ventricular (LV) structure and function among the patients. **Results:** The characteristic chromatographic profile of *Astragalus membranaceus* extract injection exhibited marked changes in polar compounds within the 0- 10 min range. Serum analysis indicated that relative to CG, patients in OG exhibited decreased fasting blood glucose, glycated hemoglobin, triglycerides, total cholesterol, low-density lipoprotein cholesterol, creatine kinase-MB, creatine kinase, soluble vascular cell adhesion molecule-1 and soluble intercellular adhesion molecule-1, along with increased high-density lipoprotein cholesterol ($p<0.05$). Ultrasound structural analysis demonstrated that, in comparison to CG, patients in OG had reduced dimensions of the left ventricle and left atrium at end-systole, while LV ejection fraction, short-axis fractional shortening and the ratio of early to late diastolic peak flow velocities increased ($p<0.05$). **Conclusion:** In summary, *Astragalus membranaceus* extract injection was found to restore normal glycemic and lipid profiles, improve myocardial injury markers, promote LV remodeling, enhance LV diastolic and systolic function and exert cardioprotective effects by reducing cardiac adhesion molecule levels in patients with type 2 diabetic cardiomyopathy.

Key words: *Astragalus membranaceus* extract, type 2 diabetes mellitus, cardiomyopathy, glycolipid metabolism, myocardial damage

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The incidence of diabetes is steadily increasing and the complications of diabetes-related cardiovascular diseases lead to mortality in patients with Type 2 Diabetes Mellitus (T2DM)[1]. It was confirmed that prolonged exposure of the body to high blood glucose levels leads to disruptions in glucose and lipid metabolism, resulting in oxidative stress damage. This, in turn, induces apoptosis in myocardial cells, ultimately causing widespread structural abnormalities in the myocardium. This is manifested as reduced cardiac function and heart failure in patients[2-4]. Diabetic cardiomyopathy is a cardiovascular complication of diabetes and it tends to exacerbate the progression of diseases such as coronary heart disease and hypertension, creating a vicious cycle[5].

Astragalus membranaceus, also known as Huangqi, typically grows in dry grasslands and mountainous regions and is considered one of the representative plants of the "*Astragalus membranaceus* grasslands". *Astragalus membranaceus* contains a variety of bioactive components, with the most prominent ones being flavonoids, polysaccharides, amino acids and trace elements. These constituents confer diverse pharmacological effects on *Astragalus membranaceus*, including antioxidant, immunomodulatory, anti-inflammatory and anti-tumor activities. Due to these pharmacological properties, *Astragalus membranaceus* has been traditionally used in traditional medicine to enhance the immune system, promote healing, alleviate fatigue and treat various diseases[6]. *Astragalus membranaceus* extract is derived from the roots of the *Astragalus membranaceus* plant and is typically obtained using water, alcohol solvents, or other suitable extraction methodologies to extract its bioactive constituents. *Astragalus membranaceus* extract mainly consists of glycosides and *Astragalus membranaceus* total glycosides exhibit a wide range of pharmacological effects: (i) Antiviral activity: *Astragalus membranaceus* total glycosides have been shown to exert *in vitro* antiviral effects against herpes simplex virus type II and hepatitis B virus, preventing infection of myocardial cells[7]; (ii) Hepatoprotective effects: These glycosides can inhibit the proliferation of activated hepatic stellate cells and collagen synthesis, suppress the proliferation of liver cancer cells and induce apoptosis[8]; (iii) Anticancer properties: *Astragalus membranaceus* total glycosides can inhibit the proliferation, migration and invasion of tumor cells while promoting tumor cell apoptosis[9,10] and (iv) Cardioprotective effects: They can improve heart function, protect myocardial cells and enhance myocardial contractility[11]. In terms of myocardial injury, *Astragalus membranaceus* extract can exert its effects through various pathways, including promoting myocardial cell regeneration, reducing oxidative stress and inflammatory responses in myocardial cells and improving heart function. Tao *et al.*[12] analyzed those compounds from *Astragalus membranaceus* primarily function in the treatment of heart failure in diabetes by mediating the RAGE pathway, IL-17 pathway and HIF-1 pathway. Importantly, these compounds exhibit a multi-target, multi-pathway characteristic. Yuetao *et al.*[13] conducted a study using *Astragalus membranaceus* in therapy of adriamycin-induced heart failure in rats and found that it effectively controlled cardiac dysfunction and metabolic disturbances in heart failure rats. These actions may hold promise in reducing the severity of myocardial injury, decreasing the risk of heart failure and improving patient outcomes.

The mechanism of action of *Astragalus membranaceus* extract injection in therapy of T2DM mellitus complicated with myocardial disease was analyzed in this work, focusing on glucose and lipid metabolism as well as myocardial damage in patients. The research aimed to provide insights into the mechanism of action of *Astragalus membranaceus* extract injection in therapy of diabetic cardiomyopathy, to enhance treatment outcomes and prognosis for patients.

MATERIALS AND METHODS

Qualitative analysis of *Astragalus membranaceus* injection: The main chemical components of *Astragalus membranaceus* extract injection (Shanghai Xinya Pharmaceutical Co., Ltd., Gaoyou Branch, China) include six flavonoid compounds, namely mangostensin, calycosin, 6″-O-acetyl anthocyanin, ononin, pratensein 7-O-glucopyranoside and calycosin-7-O-β-D-glucoside. It also contains one rhododendron compound with the structure of 9,10-dimethoxy-pterocarpane-3-O-β-D-glucoside and one isoflavan compound with the structure of 2′-dihydroxy-3′,4′-dimethoxyisoflavan-7-O-β-D-glucopyranoside and six *Astragalus* saponin compounds (acetylastragaloside I, astragaloside I, isoastragaloside I, isoastragaloside II, astragaloside II and astragaloside III).

Qualitative analysis of the drug solution was conducted using liquid chromatography with an Agilent ZORBAX SB-C18 column (250×4.6 mm, 5 μm) (Beijing GEA Technology Development Co. Ltd., China). The column was eluted with acetonitrile-water solutions in different ratios: 2:98, 5:95, 15:85, 40:60 and 100:0, at various time intervals of 0, 15, 20, 40 and 55 min. The column temperature was maintained at 25°C, with a flow rate of 1 mL/min and a sample injection volume of 10 μL.

Research objects: This work included 96 patients with type 2 diabetic cardiomyopathy who were hospitalized in Beijing Tongren Hospital for treatment from March, 2021 to March, 2023. These patients were rolled into the control group (CG) and observation group (OG), each consisting of 48 patients. In CG, there were 21 females and 27 males, aged 40 to 77 (65.1±7.8) years. Diabetes duration ranged from 5 to 10 years, averaging (5.5±0.8) years. Regarding New York Heart Association (NYHA) functional classification, 28 patients were classified as NYHA class I and 20 were class II. In OG, there were 25 females and 23 males, aged 40 to 75 (66.2±8.3) years. Diabetes duration was 5 to 11 years, averaging (5.7±0.6) years. According to NYHA functional classification, 25 patients were classified as NYHA class I and 23 were class II. The general characteristics between the two groups demonstrated inconsiderable differences ($p>0.05$).

Ethical consideration: This work was approved by the ethics committee of the hospital and all enrolled patients provided informed consent.

Inclusion criteria: (1) Patients who met diagnostic criteria for diabetic cardiomyopathy; (2) Doppler ultrasound showed changes in left atrial diameter and cardiac ejection parameters, indicating cardiac pump dysfunction and (3) Voluntary participation in the study.

Exclusion criteria: (1) Use of antidiabetic or lipid-lowering medications in the three months before admission; (2) Severe hematologic or coagulation disorders; (3) Concomitant liver or kidney dysfunction; (4) Contraindications to the treatment drugs and (5) Poor treatment compliance.

Treatment methods: The patients in the CG group received oral administration of rosiglitazone tablets (Chengdu Hengrui Pharmaceutical Co. Ltd., China) of based on a controlled diet. The dosage was 4 mg per administration, once daily, for a treatment duration of 6 months. In contrast, OG underwent a combined treatment regimen consisting of oral rosiglitazone (4 mg per dose, once daily) and intravenous infusion of *Astragalus membranaceus* extract injection (10-20 mL per dose, once daily) for a duration of 6 months.

Outcome measures: To detect glucose metabolism, 5 mL of venous blood were collected from patients on an empty stomach and 2 hrs postprandial and serum was centrifuged at 3,000 rpm for 10 min at 25°C. The ELISA was employed to measure fasting plasma glucose (FPG) and Glycated Hemoglobin (HbA1c) levels in the serum. The FPG test kits and HbA1c test kits were purchased from Shanghai Kanglong Biotechnology Co. Ltd., China.

To detect lipid metabolism, serum obtained from fasting venous blood was analyzed employing a fully automated biochemical analyzer (Hitachi High-Tech Corporation, Japan) to determine triglycerides (TG), total cholesterol (TC), High Density Lipoprotein-Cholesterol (HDL-C) and Low Density Lipoprotein-Cholesterol (LDL-C).

To detect cardiac injury markers, serum samples from fasting venous blood were tested using ELISA to measure the levels of cardiac isoform of creatinine kinase-myocardial band (CK-MB) and CK. The CK and CK-MB test kits were purchased from Baoan Kang Biological Technology Co. Ltd., China.

Echocardiographic evaluation was performed using a cardiovascular color Doppler ultrasound imaging system (General Electric Company, USA) with a probe frequency ranging from 1.5 to 4.0 MHz. Patients were examined in a supine position. Routine echocardiographic measurements included left atrial end-systolic diameter (LAESD), LV end-systolic diameter (LVESD), LV Posterior Wall (LVPW) thickness and interventricular septum thickness (IVS). Ejection fraction (EF), fractional shortening (FS), early diastolic peak filling velocity (PVE) and late diastolic peak filling velocity (PVA) were also assessed and the PVE/PVA ratio was calculated.

To detect serum adhesion molecule markers, serum samples from fasting venous blood were analyzed using ELISA to measure serum Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) and Soluble Intercellular Adhesion Molecule-1 (sICAM-1). The sVCAM-1 and sICAM-1 test kits were purchased from R&D Systems, Ltd., UK.

Statistical analysis: Employing SPSS 22.0, continuous variables with normal distribution were denoted as Mean±Standard Deviation and compared by t-test. Categorical data were presented as percentages and compared using the χ^2 test. The $p<0.05$ was statistically significant.

RESULTS

Detection of *Astragalus membranaceus* extract injection: The characteristic chromatogram of *Astragalus membranaceus* extract injection was analyzed using liquid chromatography, as depicted in Fig. 1. It was observed that there were notable alterations in the peaks of chemically polar components in the characteristic chromatogram of the purchased *Astragalus membranaceus* injection within the first 10 min.

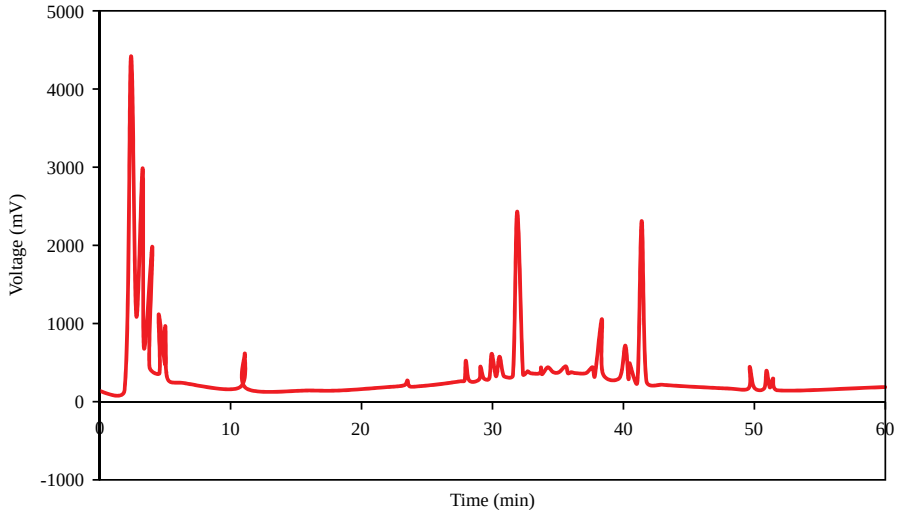

Fig. 1: Characteristic spectrum of *Astragalus membranaceus* injection

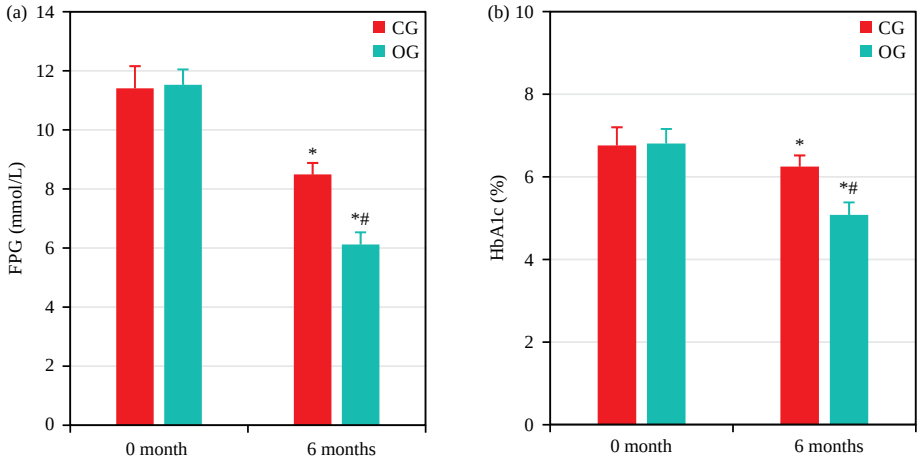

Fig. 2(a-b): Comparison of glucose metabolism indicators among patients, (a) FPG levels and (b) Hemoglobin levels

*#Means p<0.05 vs the same group before treatment (0 month) and vs CG, respectively

Differences in glucose metabolism before and after treatment: The differences in serum glucose metabolism markers were assessed before and after treatment in patients with T2DM complicated by cardiomyopathy in both CG and OG. Before treatment, the serum FPG (Fig. 2a) and HbA1c (Fig. 2b) levels differed inconsiderably between CG and OG (p>0.05). After treatment, both CG and OG exhibited drastically inferior serum FPG and HbA1c levels to their respective pre-treatment levels (p<0.05). Furthermore, after treatment, OG demonstrated markedly inferior serum FPG and HbA1c levels to CG (p<0.05).

Differences in lipid metabolism before and after treatment: The differences in serum lipid metabolism markers were assessed before and after treatment in patients with T2DM complicated by cardiomyopathy in both CG and OG. Before treatment, serum TG (Fig. 3a), TC (Fig. 3b), HDL-C (Fig. 3c) and LDL-C (Fig. 3d) demonstrated neglectable differences between CG and OG (p>0.05). After treatment, both CG and OG exhibited substantially inferior serum TG, TC and LDL-C, while HDL-C levels were considerably superior to their respective pre-treatment levels (p<0.05). Furthermore, after treatment, OG showed dramatically inferior serum TG, TC and LDL-C to CG, with HDL-C being drastically superior to CG (p<0.05).

Differences in myocardial injury before and after treatment: This study assessed the differences in serum cardiac injury markers in patients with T2DM complicated by cardiomyopathy in both CG and OG. Before treatment, serum

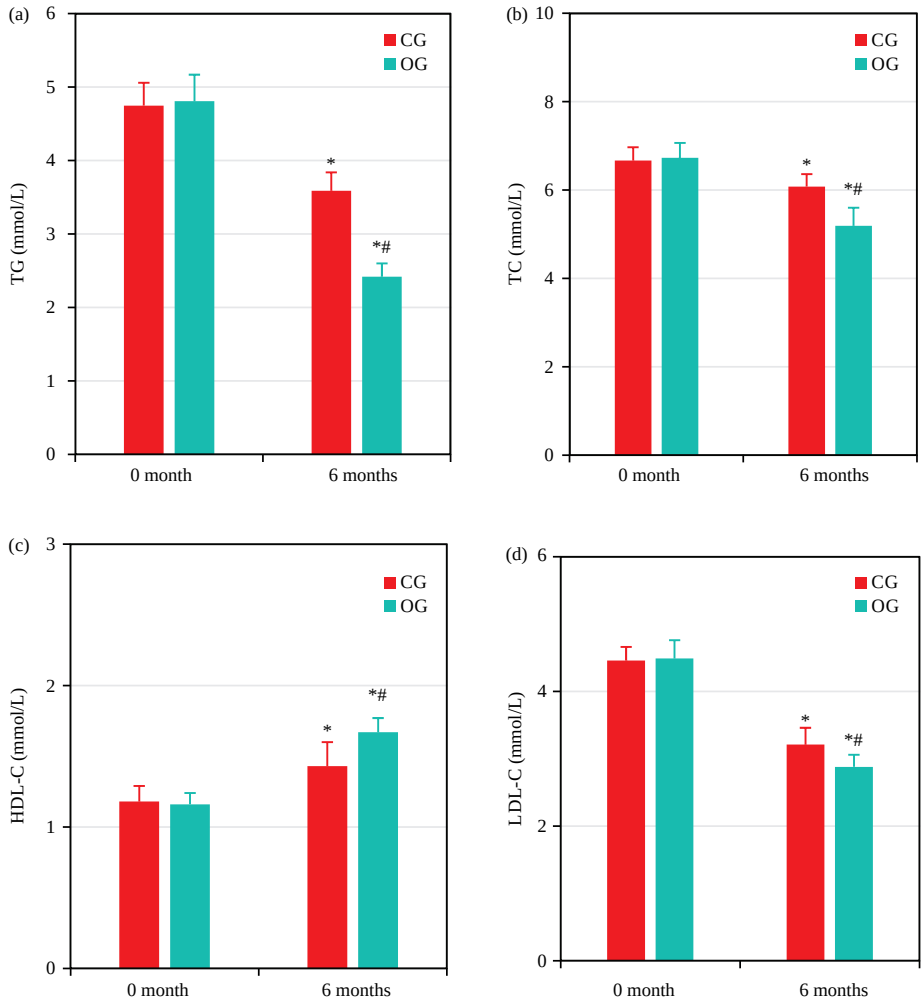

Fig. 3(a-d): Comparison of lipid metabolism indicators among patients, (a) TG levels, (b) TC level, (c) HDL-C and (d) LDL-C
*#Means p<0.05 vs the same group before treatment (0 month) and vs CG, respectively

CK (Fig. 4a) and CK-MB (Fig. 4b) levels differed slightly between CG and OG (p>0.05). After treatment, both CG and OG showed markedly inferior serum CK and CK-MB levels to their respective pre-treatment levels (p<0.05). Furthermore, after treatment, OG exhibited dramatically inferior serum CK and CK-MB levels to CG (p<0.05).

Differences in cardiac function before and after treatment: In this context, patients experience reduced LV compliance, LV hypertrophy and impaired contractile function. After treatment, the LV internal diameter in patients decreased (Fig. 5). In Fig. 5a, before treatment, there was no significant difference in LAESD between the CG and OG (p>0.05). After six months of treatment, the OG exhibited a significantly lower LAESD compared to the CG (p<0.05). In Fig. 5b, before treatment, there was no significant difference in LVESD between the CG and OG (p>0.05). After six months of treatment, the OG showed a significantly lower LVESD compared to the CG (p<0.05). In Fig. 5c, both before treatment and after six months of treatment, there was no significant difference in LVPW between the CG and OG (p>0.05). In Fig. 5d, both before treatment and after six months of treatment, there was no significant difference in IVS between the CG and OG (p>0.05). In Fig. 5e, as shown in the echocardiogram, the lesion shadow was significantly reduced after six months of treatment compared to before treatment.

The differences in LV function parameters before and after treatment in both CG and OG were evaluated (Fig. 6). In Fig. 6a, before treatment, there was no significant difference in EF ratio between the CG and OG (p>0.05). After six months of treatment, the OG showed a significantly higher EF ratio compared to the CG (p<0.05). In Fig. 6b, before treatment, there was no significant difference in FS between the CG and OG (p>0.05). After six months of treatment, the OG exhibited

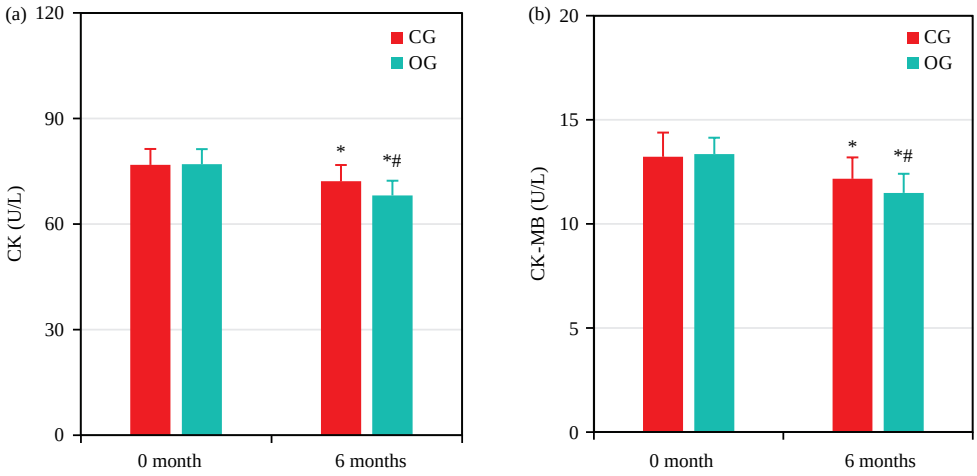

Fig. 4(a-b): Comparison of myocardial injury indicators among patients, (a) Phosphate creatine kinase level and (b) Myocardial isoenzyme levels

*#Means p<0.05 vs the same group before treatment (0 month) and vs CG, respectively

a significantly higher FS compared to the CG (p<0.05). In Fig. 6c, before treatment, there was no significant difference in PVE between the CG and OG (p>0.05). After six months of treatment, both groups showed a significant increase compared to pre-treatment levels (p<0.05), with the OG demonstrating a significantly greater increase compared to the CG (p<0.05). In Fig. 6d, before treatment, there was no significant difference in PVA between the CG and OG (p>0.05). After six months of treatment, the OG exhibited a significantly lower PVA compared to the CG (p<0.05) and there was also a significant difference between the OG and CG (p<0.05). In Fig. 6e, before treatment, there was no significant difference in PVE/PVA between the CG and OG (p>0.05). After six months of treatment, both groups showed a significant increase compared to pre-treatment PVE/PVA (p<0.05), with the OG demonstrating a significantly greater increase compared to the CG (p<0.05).

Differences in serum adhesion molecule levels before and after treatment: This study evaluated the differences in serum sVCAM-1 (Fig. 7a) and sICAM-1 (Fig. 7b) levels before and after treatment in both CG and OG. Before treatment, no considerable difference existed in serum sVCAM-1 and sICAM-1 between CG and OG (p>0.05). After treatment, serum sVCAM-1 and sICAM-1 in both CG and OG were markedly inferior to their respective pre-treatment levels (p<0.05). Furthermore, after treatment, OG exhibited notably lower serum sVCAM-1 and sICAM-1 versus CG (p<0.05).

DISCUSSION

Diabetic patients with long-term disruption of glucose metabolism may experience extensive myocardial necrosis, resulting in cardiac dysfunction and ultimately progressing to heart failure, arrhythmias, or cardiogenic shock[14-16]. Among the diabetic population, type 2 diabetic cardiomyopathy has a relatively high incidence rate, with patients predominantly presenting clinical symptoms such as palpitations, shortness of breath and chest tightness. Factors like insulin resistance and glycemic instability are closely associated with the development of diabetic cardiomyopathy[17,18]. To assess the effect of *Astragalus membranaceus* extract on myocardial damage in patients with diabetes mellitus complicated by cardiomyopathy, this study enrolled patients with type 2 diabetic cardiomyopathy as the research subjects and analyzed the differences in the therapeutic effects of rosiglitazone tablets alone and in combination with *Astragalus membranaceus* injection. Initially, the chemical composition of the *Astragalus membranaceus* injection was determined, revealing significant changes in the HPLC chromatogram peaks of the *Astragalus membranaceus* injection. This could be attributed to factors such as acetyl hydrolysis of astragaloside and isoastragaloside compounds, possibly induced by NaOH treatment, increasing astragaloside content. Subsequently, it was observed that the levels of FPG and HbA1c in patients with type 2 diabetic cardiomyopathy treated with a combination of rosiglitazone tablets and *Astragalus membranaceus* injection were significantly lower

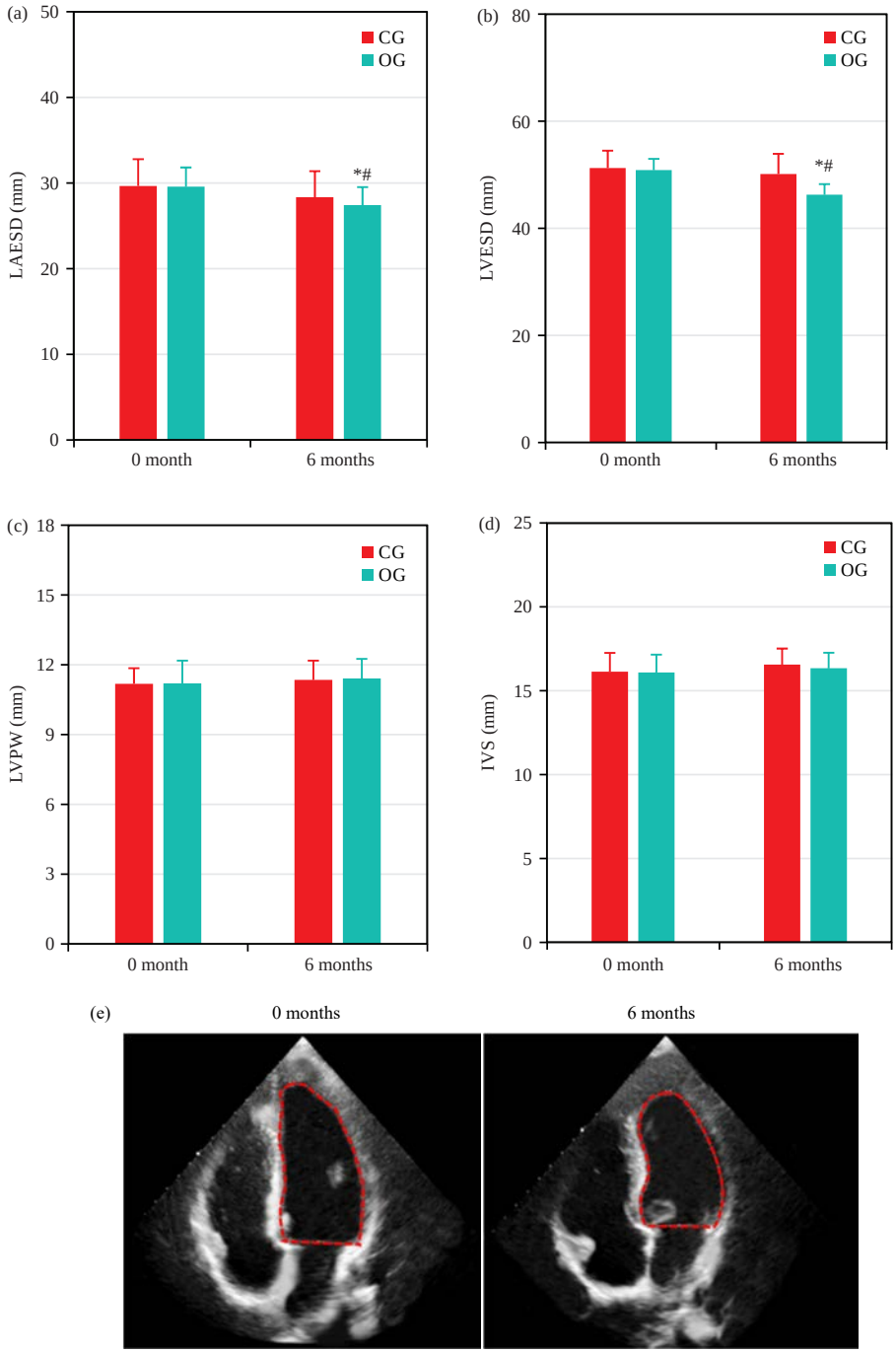

Fig. 5(a-e): Comparison of LV structural indicators among patients, (a) LAESD, (b) LVESD, (c) LVPW, (d) IVS and (e) Example of echocardiography

*#Means p<0.05 vs the same group before treatment (0 month) and vs CG, respectively

than those treated solely with rosiglitazone tablets. Elevated extracellular glucose levels in myocardial cells can directly lead to changes in intracellular calcium ion concentrations, resulting in defects in calcium transport within cardiac myocytes[19]. Additionally, glycosylation of collagen deposits in cardiac myocytes can lead to fibrosis of the cardiac interstitium. *Astragalus membranaceus* contains active components such as *Astragalus* polysaccharides, which remarkably improve insulin resistance, promote insulin secretion and facilitate the metabolism of glucose in the body,

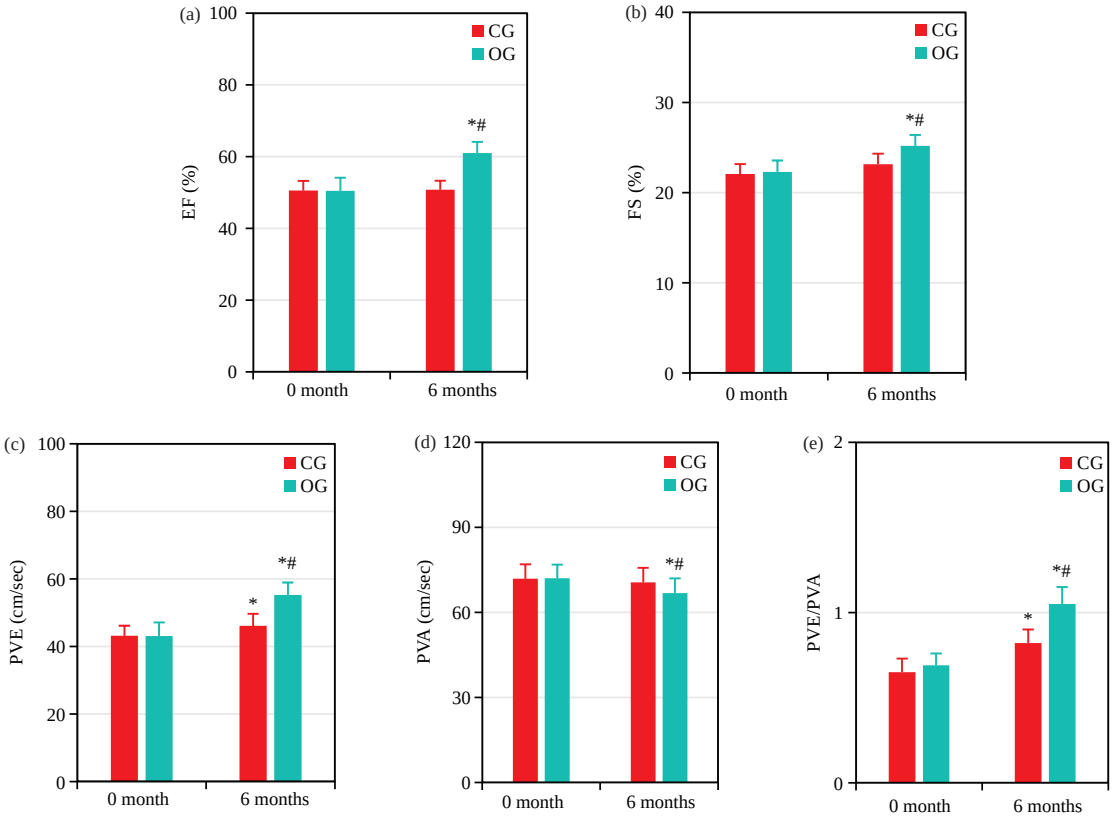

Fig. 6(a-e): Comparison of LV function indicators among patients, (a) EF, (b) FS, (c) PVE, (d) PVA and (e) PVE/PVA

*#Means p<0.05 vs the same group before treatment (0 months) and vs CG, respectively

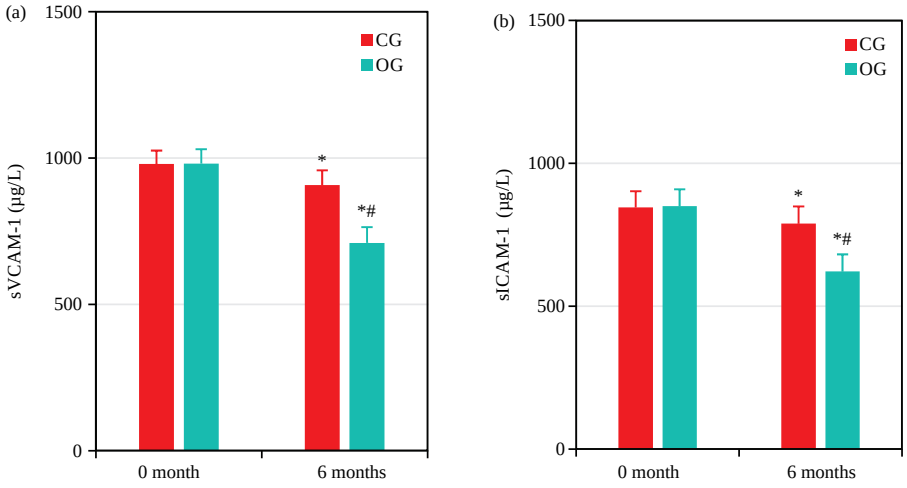

Fig. 7(a-b): Comparison of serum adhesion molecule indicators among patients, (a) sVCAM-1 and (b) sICAM-1

*#Means p<0.05 vs the same group before treatment (0 months) and vs CG, respectively

thus exerting a hypoglycemic effect[20]. This indicated that the *Astragalus membranaceus* extract injection can regulate glucose metabolism disorders in patients with type 2 diabetic cardiomyopathy, which holds significant importance for improving the cardiac function of these patients.

The onset of T2DM is closely related to insulin resistance, which triggers a series of biochemical reactions, including disturbances in lipid metabolism, resulting in metabolic dysregulation in patients[21]. Elevated lipid levels increase the risk of coronary artery atherosclerosis and stenosis and may

lead to issues such as myocardial hypertrophy and reduced cardiac function[22]. Diabetic patients have a greatly superior likelihood of developing hyperlipidemia to the general population. Currently, there is no research confirming the lipid-lowering effect of *Astragalus membranaceus*. However, it was observed in this study that the levels of TG, TC and LDL-C in patients with type 2 diabetic cardiomyopathy treated with a combination of rosiglitazone tablets and *Astragalus membranaceus* injection were significantly lower than those treated solely with rosiglitazone tablets, while the level of HDL-C was significantly higher. *Astragalus membranaceus* can improve microcirculation, enhance the body's immune response and exhibit antioxidant effects[23,24]. This suggested that *Astragalus membranaceus* extract injection can partially regulate lipid metabolism disorders in patients with type 2 diabetic cardiomyopathy. However, further exploration is needed to elucidate its regulatory mechanisms.

Free fatty acids serve as a critical energy source for the heart. Nevertheless, during states of high glucose, the accumulation of free fatty acids can lead to damage to elements such as myocardial calcium, thereby affecting myocardial cell function and causing cell apoptosis[25]. Myocardial cell apoptosis is one of the primary etiological factors in diabetic cardiomyopathy. The CK is an enzyme that is widely present in various muscle tissues throughout the body. Elevated CK levels indicate damage to muscle tissues, including skeletal muscles, smooth muscles and cardiac muscles[26]. The CK-MB is a serum marker of myocardial necrosis and its levels drastically rise in cases of myocardial injury[27]. This study found that the levels of CK and CK-MB in patients with type 2 diabetic cardiomyopathy treated with a combination of rosiglitazone tablets and *Astragalus membranaceus* injection were significantly lower than those treated solely with rosiglitazone tablets. The research posits that diabetic cardiomyopathy arises from disruptions in glucose metabolism, leading to endocrine system activation, autonomic nervous system dysfunction and ultimately resulting in impaired cardiac function and cellular changes[28-30]. Furthermore, this study revealed that the LAESD and LVESD in patients with type 2 diabetic cardiomyopathy treated with a combination of rosiglitazone tablets and *Astragalus membranaceus* injection were significantly smaller than those treated solely with rosiglitazone tablets, while the EF and FS were significantly greater than those with rosiglitazone monotherapy. In recent years, research has revealed a significant elevation in vascular and serum cell adhesion molecule levels in patients with diabetic cardiomyopathy[31]. Adhesion molecules are membrane-bound glycoproteins produced by cells that mediate interactions between cells. They play a crucial role in cell signaling, activation, mobility, growth, differentiation and inflammatory responses[32,33]. This study found that the levels of peripheral blood sVCAM-1 and sICAM-1 in patients with type 2 diabetic cardiomyopathy treated with a combination of rosiglitazone tablets and *Astragalus membranaceus* injection were significantly lower than those treated solely with rosiglitazone tablets. This indicates that the treatment with rosiglitazone tablets combined with *Astragalus membranaceus* injection can improve left ventricular systolic and diastolic function in patients with type 2 diabetic cardiomyopathy by reducing the levels of peripheral blood sVCAM-1 and sICAM-1, thereby exerting a protective effect against myocardial damage. This may be attributed to the effective components such as astragaloside IV in *Astragalus membranaceus*, which can promote myocardial cell metabolism, improve myocardial contractility and to some extent, exert a cardiac protective effect.

CONCLUSION

The injection of *Astragalus membranaceus* extract is capable of promoting the normalization of glycemic and lipid metabolism and cardiac damage markers in type 2 diabetic cardiomyopathy patients. It facilitates LV remodeling and enhances LV diastolic and systolic function in these patients. Furthermore, it exerts a protective effect against myocardial injury by reducing the levels of cardiac adhesion molecules, ultimately promoting cardiac function improvement. These findings highlight the practical applicability of *Astragalus membranaceus* extract in clinical contexts.

SIGNIFICANCE STATEMENT

This study aimed to evaluate the therapeutic effects of *Astragalus membranaceus* extract injection on patients with type 2 diabetic cardiomyopathy, particularly its influence on glucose and lipid metabolism disorders and myocardial injury. Key findings include that *Astragalus membranaceus* extract injection promotes the restoration of serum glucose and lipid metabolism indicators in patients, improves myocardial injury, facilitates left ventricular remodeling and protects myocardium by reducing levels of cardiac adhesion molecules, thereby enhancing patient cardiac function. Further exploration of the effects of *Astragalus membranaceus* extract injection in patients with different types of diabetic cardiomyopathy and evaluation of its long-term efficacy over different treatment periods are warranted.

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