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Original Article

The effect of combining trimetazidine and tongxinluo capsules on reducing the blood lipid levels and improving the heart function of CHD patients with DM

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Abstract: Objective: This study was designed to analyze the effects of trimetazidine combined with tongxinluo capsules on reducing the blood lipid levels and improving the heart function of CHD (coronary heart disease) patients with DM (diabetes mellitus). Methods: 97 CHD patients with DM in our hospital were retrospectively analyzed to gather their clinical data and divided into two groups according to the treatment method each received. The two groups were compared in terms of clinical efficacy, the number and duration of angina attacks, and changes in their blood lipid indexes, such as low-density lipoprotein (LDL-C), high density lipoprotein (HDL-C), total cholesterol (TC), and triacylglycerol (TG), as well as their heart function indexes, including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) before and after the treatment. Results: Compared with the CG, the OG yielded a higher total effective rate (95.92% versus 77.08%), higher HDL-C and LVEF, fewer and shorter angina attacks, and lower TDL-C, TG, TC, LVEDV, and LVESV ($P<0.05$). Conclusion: The application of trimetazidine combined with tongxinluo capsules in the treatment of CHD patients with DM demonstrated a significant clinical efficacy, reflected by the reduced number of and shorter angina attacks and the improved heart function and blood lipid status.

Keywords: CHD, DM, trimetazidine, tongxinluo capsule, blood lipid, heart function

Introduction

As one of the most common heart diseases seen in the clinic, CHD is generally associated with diet, smoking, obesity, hyperhomocysteinemia, hyperlipemia, hypertension, hyperglycemia, family history, gender, age, etc. [1]. Those factors are the initiators of inflammatory microorganisms and the contributors to the endothelial dysfunction of the coronary arteries, which damage blood vessel endothelia, promote atheromatous plaque and atherosclerosis, and finally result in CHD [2, 3].

DM is one of the major factors leading to CHD. In recent years, number of CHD patients DM rose significantly [4]. Regardless of a series of interventions, including exercise, drugs and special diets, which improve the prognosis of CHD patients with DM to a certain degree, because of poor vascular conditions, the elderly patients with CHD are extremely prone to acute adverse cardiovascular events, i.e., myocardial infarction, a severe threat to their health [5, 6]. Trimetazidine is a commonly prescribed drug developed for myocardial ischemia that improves the energy metabolism in the cardiac muscle group to reduce myocardial oxygen consumption and further effectively ameliorate patients' heart function [7]. Though some achievements have been made in the treatment of CHD patients DM in Western medicine, further improvements are still expected. With the continuously developing studies on traditional Chinese medicine, the unique advantages of TCM in CHD patients with DM are exposed [8]. Henceforth, to improve the prognosis of CHD patients with DM, trimetazidine was combined with tongxinluo capsules in this study.

In the past, Western medicine was more preferred for treating CHD patients with DM. However, from the perspective of traditional Chinese medicine, this study explored the effects of this combination with western medicine on improving blood lipids and heart function to demonstrate its significant feasibility and innovation.

Materials and methods

Materials

97 CHD patients with DM in our hospital were retrospectively analyzed to gather their clinical data and divided into two groups according to the treatment method each received. The CG included 48 patients (30 males and 18 females) treated with trimetazidine, and the OG consisted of 49 patients (32 males and 17 females) treated with trimetazidine combined with tongxinluo capsules. (1) Inclusion criteria: patients who met the DM diagnosis criteria formulated by the WHO Expert Committee on Diabetes in 1999 [9] with NYHD heart function between grades II and IV, and patients who had a history of myocardial infarction but no contraindication of medication. Informed consents were obtained from patients in order to participate in the study, which was approved by the medical ethics committee of our hospital. (2) Exclusion criteria: some patients were excluded as they had diseases endangering their lives or severe functional liver or kidney diseases, or they had acute coronary syndrome and heart failure in the last 3 months, or because they declined to participate in the study or failed to strictly comply with the doctor's suggestions on medication.

Methods

After their hospitalizations, all the patients were treated with a diuretic an angiotensin receptor antagonist, a β receptor blocker, an angiotensin converting enzyme inhibitor, Bayer aspirin, and nitrates as prescribed. On this basis, the patients in the CG were prescribed trimetazidine tablets (approval document no. GYZZ H20055465, manufacturer: Servier (Tianjin) Pharmaceuticals Co., Ltd., specification: 20 mg*30 tablets) three times a day at a dose of 20 mg each time. 1 course of treatment lasted 12 weeks. In addition to the trimetazidine administered in the same way, the patients in the OG were required to orally take tongxinluo capsules (approval document no. GYZZ Z19980015, manufacturer: Shijiazhuang Yiling Pharmaceuticals Co., Ltd., specification: 0.26 g*30 pieces) three times a day at a dose of 3 capsules each time. 1 course of treatment lasted 12 weeks.

Observation indicators

Efficacy evaluation criteria: the treatment is considered to be ineffective if the heart function grade has no change or goes down after the treatment. The treatment is considered to be effective if the heart function grade rises by 1 or markedly effective if it rises by 2 [10]. The total effective rate = effective rate + markedly effective rate.

The two groups were compared in terms of the number and duration of angina attacks before and after the treatment.

Indicators of blood lipid: before and after the treatment, 3 ml blood was drawn from the peripheral veins of the patients in both groups in the morning after fasting. The blood samples were centrifuged at a speed of 3000 r/min and measured for LDL-C, HDL-C, TC, and TG with an automatic biochemistry analyzer [11].

Indicators of heart function: before and after the treatment, an echocardiograph was used to measure the heart function indicators of all patients, including LVEDV, LVESV, and LVEF [12].

Adverse reactions: the adverse reactions in the two groups were compared.

Statistical analysis

The statistical analysis was performed with SPSS 22.0. The numerical data were expressed as the mean ± standard deviation, the comparisons were carried out using independent-samples *t* tests for data which were normally distributed and Mann-Whitney U tests for data which were not normally distributed. Paired tests were used for pre-and-pro comparisons within a group, and in cases of nominal data expressed as [n (%)]. Comparisons were carried out using X^2 tests for the intergroup compari-

Table 1. Comparison between the two groups in terms of the general data [n (%)]/($\bar{x}$ ± s)

Data		OG (n=49)	CG (n=48)	t/X^2	*P*
Gender (n)	Male	32 (65.31)	30 (62.50)	0.083	0.774
	Female	17 (34.69)	18 (26.47)		
Age (y)		62.15±3.28	62.12±3.22	0.045	0.964
Course of disease (y)		2.21±0.21	2.25±0.23	0.895	0.373
NYHA heart function grading (n)					
Grade II		12 (24.49)	10 (20.83)	0.025	0.988
Grade III		29 (59.18)	27 (56.25)		
Grade IV		8 (16.33)	11 (22.92)		
Degree of hypertension (n)					
Mild		19 (38.78)	18 (37.50)	0.158	0.962
Moderate		22 (44.50)	20 (41.67)		
Severe		8 (16.32)	10 (20.83)		
Degree of coronary artery (n)					
Mild		20 (40.82)	22 (45.83)	0.098	0.568
Moderate		18 (36.73)	16 (33.33)		
Severe		11 (22.45)	10 (20.83)		

Table 2. Comparison between the two groups in their efficacy [n (%)]

Group	n	Markedly effective	Effective	Ineffective	Total effective
CG	48	20 (41.67)	17 (35.42)	11 (22.92)	37 (77.08)
OG	49	32 (65.31)	15 (30.61)	2 (4.08)	47 (95.92)*
X^2					7.412
P					0.006

Note: *indicates P<0.05 as compared with the CG.

sons. For all the statistical comparisons, significance was defined as P<0.05.

Results

Comparison between the two groups in terms of the general data

The OG consisted of 32 (65.31%) males and 17 (34.69%) females ranging in age from 46 to 80, with mean value of (62.15±3.28) and who had adisease course ranging from 2 to 5 years with a mean value of (2.21±0.21). In the CG, there were 30 (62.50%) males and 18 (26.47%) females ranging in age from 47 to 79, with a mean age of (62.12±3.22) and a disease course ranging from 1 to 4 years, and a mean course of disease of (2.25±0.23). The number of patients with their heart function graded in NYHA classes II, III, and IV were 12 (24.49%), 29 (59.18%) and 8 (16.33%) in the OG and 10 (20.83%), 27 (56.25%), and 11 (22.92%) in the CG. Between the OG and the CG, no statistical differences were observed in terms of the general data, such as gender, age, course of disease, heart function grades, degree of hypertension, or coronary artery disease (P>0.05, **Table 1**).

Comparison between the two groups in terms of clinical efficacy

The OG yielded a total effective rate of 95.92% on the basis of 32 markedly effective, 15 effective, and 2 ineffective cases, which was higher than the rate in the CG, which was 77.08%, as calculated from 20 markedly effective, 17 effective, and 11 ineffective cases (P< 0.05, **Table 2**).

Comparison of the two groups in terms of the number and duration of angina attacks

In terms of the number and duration of angina attacks, no statistical difference was found between the two groups before the treatment (P>0.05), but a reduction was observed after the treatment (P<0.05). Compared with the CG, the number and duration of angina attacks were lower in the OG (P<0.05) (**Table 3**).

Comparison of the two groups in terms of blood lipid indicators

Before the treatment, the LDL-C, HDL-C, TG, and TC were (3.89±0.5) mmol/L, (0.92±0.22) mmol/L, (2.48±0.82) mmol/L and (6.07±0.35) mmol/L in the OG and (3.92±0.59) mmol/L, (0.95±0.19) mmol/L, (2.52±0.79) mmol/L, and (6.09±0.32) mmol/L in the CG, indicating no statistically significance differences (P>0.05) (**Figure 1**). After the treatment, the LDL-C, TG, and TC were (1.62±0.32) mmol/L, (1.02±0.09) mmol/L and (3.25±0.15) mmol/L in the OG, lower than (1.99±0.53) mmol/L, (1.93±0.19) mmol/L and (4.99±0.26) mmol/L, respectively in the CG (P<0.05). Besides, the HDL-C was (1.32±0.38) mmol/L in the OG, higher than the

Table 3. Comparison of the two groups in the number and duration of angina attacks ($\bar{x} \pm s$)

Group	Number of Attacks (number/week)		Duration (min/time)	
	Before treatment	After treatment	Before treatment	After treatment
CG (n=48)	24.56±5.15	16.89±3.52#	10.36±3.52	7.89±1.28#
OG (n=49)	24.59±5.13	7.52±1.29#,*	10.39±3.49	3.12±1.06#,*
t	0.029	17.476	0.042	20.007
P	0.977	0.000	0.967	0.000

Note: #indicates P<0.05 as compared with the conditions before the treatment; *indicates P<0.05 as compared with CG.

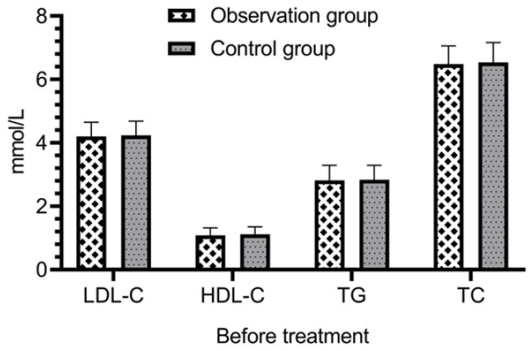

Figure 1. Comparison between the two groups for blood lipid indicators before the treatment. Before the treatment, LDL-C, HDL-C, TG, and TC were compared in the two groups, indicating no significant difference, P>0.05.

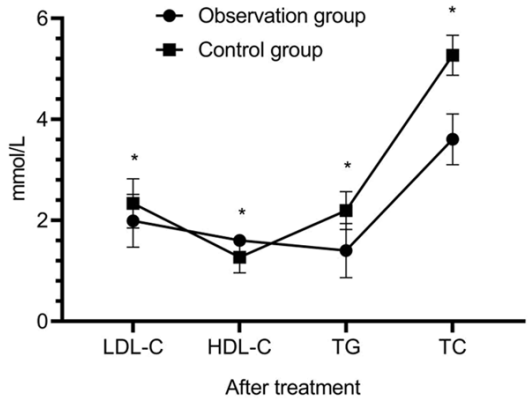

Figure 2. Comparison between the two groups for in their blood lipid indicators after the treatment. After the treatment, LDL-C, TG, and TC in the OG were lower than they were in the CG, and LDL-C was higher than it was in the CG, P<0.05. * indicates P<0.05 as compared with the CG.

(1.05±0.31) mmol/L in the CG (P<0.05) (**Figure 2**).

Comparison of the two groups in terms the of the heart function indicators

The LVEDV, LVESV and LVEF were almost the same in the two groups before the treatment (P>0.05); after the treatment, LVEDV and LVESV were reduced, and LVEF was elevated (P<0.05), but more sharply in the OG compared with the CG (P<0.05) (**Table 4**).

Comparison of the two groups in terms of adverse reactions

There were 2 cases of nausea and 3 cases of vomiting in the CG, making up 10.42% of the incidences of adverse reactions, but in the OG, there were 4 cases of nausea and 2 cases of vomiting, making up 12.24% of the incidences of adverse reactions. There was no significant difference in the incidences of adverse reactions in the two groups (P>0.05) (**Figure 3**).

Discussion

CHD is a diseases of the cardiovascular system that develops from atherosclerosis and has a high incidence and mortality. If no timely intervention is adopted, acute adverse cardiovascular events will occur and threaten patients' lives in severe cases [13, 14]. According to recent clinical studies, amongst the various factors leading to CHD, metabolism syndrome has the most serious impact. Other major factors related to CHD include abnormal glucose tolerance, hypertension, DM, obesity, and abnormal blood lipids [15, 16].

The pathomechanism of CHD complicated with DM is that in the various development stages of atherosclerosis, inflammation plays a key role. Patients with DM are more vulnerable to thrombosis, inflammatory changes [17], and coronary artery calcification compared to those without DM, and DM is closely correlated with the future development of cardiovascular and cerebrovascular events [18]. A high level of free fatty acids and hyperglycemia can induce lipid oxidation, increase myocardial steatosis, and lead to cardiac ischemia and then myocardial dysfunction [19]. Compared to patients without DM, patients with DM face

Table 4. Comparison of the two groups in heart function indicators ($\bar{x} \pm s$)

Group	LVEDV (ml)		LVESV (ml)		LVEF (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
CG (n=48)	195.12±12.52	172.56±8.52#,*	123.62±10.28	95.52±5.86#,*	33.12±1.52	36.12±2.18#,*
OG (n=49)	195.19±12.36	152.12±3.28#,*	123.69±10.19	82.12±2.28#,*	33.19±1.49	40.25±2.89#,*
t	0.028	15.652	0.034	14.898	0.229	7.933
P	0.978	0.000	0.972	0.000	0.819	0.000

Note: #indicates P<0.05 as compared with the conditions before treatment; *indicates P<0.05 as compared with CG.

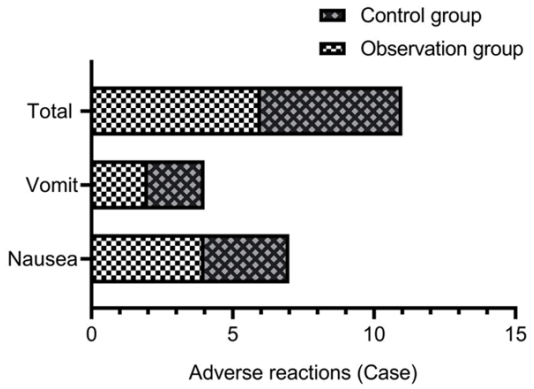

Figure 3. Comparison between the two groups for in terms of adverse reactions. There was no significant difference between the two groups (P>0.05).

two-times higher incidence of angiocardiopathy. Based on a majority of pathological and epidemic studies, DM is one an independent factors for CHD [20, 21]. Most DM patients also have microvascular complications to different degrees, not only worsening the microcirculatory disturbances, but also triggering stresses to glucose oxidase, resulting in reduced fibrinolytic activity, coagulation dysfunction, accelerated pathological changes of the coronary arteries, and elevated incidences of various adverse cardiovascular events [22].

Currently, there are various drugs for CHD, including diuretics, nitrates, angiotensin receptor antagonists, β receptor blockers, and angiotensin converting enzyme inhibitors, drugs that may affect hemodynamics and compromise patients' treatment tolerance to various degrees regardless of their certain efficacy [23]. Trimetazidine has been widely used in the treatment of myocardial ischemia. Its pharmacological effect is to promote the improvement of the energy metabolism of cardiac muscle groups, and to protect myocardial cells by inhibiting the fatty acid oxidation of long-chain 3-ketoacyl-coenzyme A thiolysis in the mitochondria [24]. Furthermore, trimetazidine works to alleviate calcium overload in cells to avoid any injury to cardiac muscle cells, ameliorate myocardial ischemia, and relieve the angina intensity [25]. For better clinical efficacy, in this study, the traditional Chinese medicine tongxinluo was added, and results showed that the OG had a higher total effective rate, a lower number of and shorter angina attacks, and more outstanding indicators for blood lipids and heart functions compared with the CG (P< 0.05), indicating that the combination of trimetazidine and tongxinluo capsules in the treatment of CHD complicated with DM can achieve a more significant clinical efficacy, including a reduced number and duration of angina attacks, improved heart function and blood lipid status. The underlying reasons are that tongxinluo capsule are composed of semen *Zizyphi spinosae*, borneol, lignum *Dalbergia odorifera*, *Boswellia carterii*, *Periostracum cicada*, sandalwood, centipede, Radix Paeoniae Rubra, scorpio, ground beetle, ginseng, and sanguisuge. Amongst those elements, some are sovereign drugs, such as ginseng which can replenish the vital energy, tonify the heart and Qi, sanguisuge which can enter the blood system to dredge collaterals, activate the circulation of blood remove blood stasis, and scorpio which can dredge collaterals to relieve convulsions [26]; ground beetle has the effect of removing blood stasis and clearing collaterals in cooperation with sanguisuge; centipede works to relieve convulsion and rheumatic pains, eliminate stagnation, dredge collaterals to relieve pain, and its effects of pain relieving and spasmolysis are enhanced in combination with the ground beetle; periostracum cicada can

relieve spasms by calming endogenous wind and removing ectogenous wind in combination with scorpio; *Radix Paeoniae Rubra* can dispel blood and promote blood circulation, relieve pain and remove blood stasis; sandalwood and lignum *Dalbergia odoriferae* can be combined to activate blood circulation and promote Qi; semen *Zizyphi spinosae* can nourish the liver and replenish Qi, and pacify the mind; the fragrance released by borneol can dredge the seven apertures by introducing other elements into the main and collateral channels. Those drugs in combination can activate the collaterals, relieve pain, promote the blood circulation to dissipate blood stasis, and notify Qi. According to modern pharmacological studies, tongxinluo capsules can promote coronary artery dilation, improve vascular endothelial functions, alleviate myocardial ischemic symptoms, and reduce blood lipid levels and myocardial oxygen consumption [27]. The combined use of trimetazidine and tongxinluo capsules is conducive to promoting the synergistic effects of the drugs, promoting each other and jointly improve the drugs' effects in the treatment of CHD patients with diabetes, so as to improve the heart function and blood lipid status of the patients.

In conclusion, the application of trimetazidine in combination with tongxinluo capsules in the treatment of CHD patients complicated with DM has demonstrated significant clinical efficacy, which are embodied as a reduced number of and shorter angina attacks and improved heart function and blood lipid status.

However, this study included fewer objects such that its results are less representative. In the future, studies based on larger sample sizes, longer durations, and covering more aspects are required.

Disclosure of conflict of interest

None.

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References

[1] Khamis RY, Ammari T and Mikhail GW. Gender differences in coronary heart disease. Heart 2016; 102: 1142-1149.

[2] Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N and Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016; 67: 1-12.

[3] Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R and Rader DJ. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med 2016; 375: 2349-2358.

[4] DiNicolantonio JJ, Lucan SC and O'Keefe JH. The evidence for saturated fat and for sugar related to coronary heart disease. Prog Cardiovasc Dis 2016; 58: 464-472.

[5] Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, Rexrode KM, Rimm EB and Hu FB. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in US adults. J Am Coll Cardiol 2017; 70: 411-422.

[6] Zhu KF, Wang YM, Zhu JZ, Zhou QY and Wang NF. National prevalence of coronary heart disease and its relationship with human development index: a systematic review. Eur J Prev Cardiol 2016; 23: 530-543.

[7] McCarthy CP, Mullins KV and Kerins DM. The role of trimetazidine in cardiovascular disease: beyond an anti-anginal agent. Eur Heart J Cardiovasc Pharmacother 2015; 2: 266-272.

[8] Song M, Chen FF, Li YH, Zhang L, Wang F, Qin RR, Wang ZH, Zhong M, Tang MX and Zhang W. Trimetazidine restores the positive adaptation to exercise training by mitigating statin-induced skeletal muscle injury. J Cachexia Sarcopenia Muscle 2018; 9: 106-118.

[9] Harrington RA. Targeting inflammation in coronary artery disease. N Engl J Med 2017; 377: 1197-1198.

[10] Varghese T, Schultz WM, McCue AA, Lambert CT, Sandesara PB, Eapen DJ, Gordon NF, Franklin BA and Sperling LS. Physical activity in the prevention of coronary heart disease: implications for the clinician. Heart 2016; 102: 904-909.

[11] Kearns CE, Schmidt LA and Glantz SA. Sugar industry and coronary heart disease research: a historical analysis of internal industry documents. JAMA Intern Med 2016; 176: 1680-1685.

[12] Nettleton JA, Brouwer IA, Geleijnse JM and Hornstra G. Saturated fat consumption and risk of coronary heart disease and ischemic stroke: a science update. Ann Nutr Metab 2017; 70: 26-33.

[13] Afarideh M, Noshad S, Ghajar A, Aryan Z, Khajeh E, Hosseini SS, Bonnet F and Esteghamati A. Family history of diabetes and the risk of coronary heart disease in people with or without type 2 diabetes. Diabetes Metab 2017; 43: 180-183.

[14] Leigh JA, Alvarez M and Rodriguez CJ. Ethnic minorities and coronary heart disease: an update and future directions. Curr Atheroscler Rep 2016; 18: 9.
[15] Chen W, Jin F, Cao G, Mei R, Wang Y, Long P, Wang X and Ge W. ApoE4 may be a promising target for treatment of coronary heart disease and Alzheimer's disease. Curr Drug Targets 2018; 19: 1038-1044.
[16] De Hert M, Detraux J and Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci 2018; 20: 31-40.
[17] Naito R and Miyauchi K. Coronary artery disease and type 2 diabetes mellitus. Int Heart J 2017; 58: 475-480.
[18] Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV and Virmani R. Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. Arterioscler Thromb Vasc Biol 2017; 37: 191-204.
[19] de Kreutzenberg SV, Solini A, Vitolo E, Boi A, Bacci S, Cocozza S, Nappo R, Rivellese A, Avogaro A and Baroni MG. Silent coronary heart disease in patients with type 2 diabetes: application of a screening approach in a follow-up study. J Diabetes Complications 2017; 31: 952-957.
[20] Bravo PE, Psaty BM, Di Carli MF and Branch KR. Identification of coronary heart disease in asymptomatic individuals with diabetes mellitus: to screen or not to screen. Colomb Med (Cali) 2015; 46: 41-46.
[21] Liang D, Li X, Wang L, Xu H, Tuo X and Jian Z. Current status and influence factors of ACEI/ARB application in elderly coronary heart disease outpatients complicated with diabetes mellitus in China. Zhonghua Yi Xue Za Zhi 2016; 96: 2917-2922.
[22] Sun X, He J, Ji XL, Zhao YM, Lou HY, Song XX, Shan LZ, Kang YX, Zeng WH and Pang XH. Association of chronic kidney disease with coronary heart disease and stroke risks in patients with type 2 diabetes mellitus: an observational cross-sectional study in Hangzhou, China. Chin Med J (Engl) 2017; 130: 57-63.
[23] Wei Y and Xu W. Effect of acarbose on cardiovascular events and new-onset diabetes in patients with coronary heart disease and impaired glucose tolerance. Future Cardiol 2019; 15: 127-133.
[24] Ibrahim TA, El-Mawardy RH, El-Serafy AS and El-Fekky EM. Trimetazidine in the prevention of contrast-induced nephropathy in chronic kidney disease. Cardiovasc Revasc Med 2017; 18: 315-319.
[25] Liu M and Zhang L. Impact of trimetazidine pre-treatment on 5-hydroxytryptamine and serotonin transporter in rats with experimental myocardial infarction and depression. Zhonghua Xin Xue Guan Bing Za Zhi 2017; 45: 137-141.
[26] Mao HM, Liu M, Qu H, Wang LQ and Shi DZ. Tongxinluo capsule for cardiac syndrome x: a systematic review and meta-analysis. Chin J Integr Med 2018; 24: 296-303.
[27] Liu S, Chang L and Wei C. The sonic hedgehog pathway mediates Tongxinluo capsule-induced protection against blood-brain barrier disruption after ischaemic stroke in mice. Basic Clin Pharmacol Toxicol 2019; 124: 660-669.