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Effect of fenofibrate on blood lipid, sICAM-1, ET-1 and prognosis in chronic heart failure patients complicated with diabetes

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ABSTRACT

This study was to observe the effects of fenofibrate on blood lipid, sICAM-1, ET-1 and prognosis in chronic heart failure patients complicated with diabetes. For this purpose, a total of 126 chronic heart failure patients complicated with diabetes admitted to our hospital from September 2020 to October 2021 were selected and divided into a control group and an observation group by random number table method, with 63 cases in each group. The control group received conventional drug treatment, and the observation group received fenofibrate treatment on the basis of the control group. After 12 months follow-up, the levels of blood lipid, sICAM-1, ET-1 were compared between the two groups at 3 months before and after treatment and 6, 12 months after treatment. Results showed that after 3 months of treatment, LDL-C, TG and TC were lower in the observation group than in the control group, showing a statistically significant difference (P<0.05). After 3 months of treatment, HDL-C was higher in the observation group than in the control group, showing a difference (P<0.05). After 3 months of treatment, sICAM-1 and ET-1 were lower in the observation group than in the control group, showing a difference (P<0.05). There was no significant difference in mortality after 6 months of treatment, re-hospitalization rate and mortality after 12 months of treatment between the two groups (P>0.05). The re-hospitalization rate of the observation group was 4.76% (3/63) after 6 months of treatment, which was lower than that of the control group in the same period, showing a significant difference (P<0.05). The conclusion was that fenofibrate can regulate blood lipids in chronic heart failure patients complicated with diabetes, inhibit sICAM-1 and ET-1, and reduce the re-hospitalization rate within 6 months after treatment. However, the effects on long-term re-hospitalization rate and mortality risk are consistent with those of conventional treatment.

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Introduction

As an end-stage disease of heart disease, heart failure has become a major public health problem worldwide due to its severe symptoms, high fatality rate and high re-hospitalization rate (1). Diabetes is a risk factor for heart failure. Compared with non-diabetic heart failure patients, heart failure patients complicated with diabetes have myofibrillar degeneration and myocardial fibrosis, and their pathological remodeling will aggravate ventricular centripetal hypertrophy and reconstruction and adversely affect the ventricular morphology and function. Diabetes is one important risk factor for heart failure. Compared with common heart failure patients, heart failure patients complicated with diabetes have more different pathophysiological changes, such as myofibrillar degeneration, myocardial fibrosis, etc. This pathological remodeling aggravates the ventricular centripetal reconstruction and hypertrophy, affecting ventricular morphology and function (2). An epidemiological survey found that the prevalence of diabetes in hospitalized patients with heart failure was above 40% (3). A large-sample baseline data survey among 88 domestic hospitals showed that the prevalence of heart failure complicated with diabetes was 21.7% (4). Dyslipidemia is considered an important risk factor for type 2 diabetes. Fenofibrate reduces fatty acid synthesis, inhibits hormone-sensitive lipase activity, and inhibits cardiovascular risk factors, which have been used in patients with diabetes and hyperlipidemia. Animal experiments confirmed that fenofibrate can improve myocardial energy metabolism, inhibit ventricular remodeling and protect the myocardium in rats with chronic heart failure. sICAM-1 and ET-1, serum factors associated with coronary heart disease and diabetes, are closely related to myocardial injury in patients. Abnormal myocardial capacity metabolism under heart failure is accompanied by increased oxidation of free fatty acids and inhibited glucose oxidative phosphorylation. Therefore, in this study, a randomized controlled study was carried out to observe the effects of fenofibrate on blood lipid, sICAM-1, ET-1 and prognosis in chronic heart failure patients complicated with diabetes, with the results summarized as follows.

Materials and Methods

General data A total of 126 chronic heart failure patients complicated with diabetes admitted to our hospital from September 2020 to October 2021 were selected and

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divided into a control group and observation group by random number table method, with 63 cases in each group. Inclusion criteria: ① Meet the diagnostic criteria of chronic heart failure in "2016 ESC Guidelines: Diagnosis and Treatment of Acute and Chronic Heart Failure"; ②Meet the diagnostic criteria of type 2 diabetes in the "Guidelines for Prevention and Treatment of Type 2 Diabetes"; ③ The age ranged from 40 to 75. Exclusion criteria: ①Allergy to the study drug; ② Participate in other clinical trials; ③ Patients who interrupted the treatment or left the group. The control group included 41 males and 22 females aged 47~68 years old, with an average age of (60.03 ± 4.26) years old. The New York NYHA cardiac function classification was grade III in 29 cases and grade IV in 34 cases. The NT-proBNP at admission ranged from 853.66 to 1954.42 pg/ml, with an average (1460.49 ± 237.05) pg/ml, LVEF < 40% in 15 cases, LVEF < 40%~49% in 23 cases, LVEF > 50% in 25 cases. HBA1c was 5.64%~10.30% before treatment, with an average value of (8.07 ± 1.21) %. The observation group included 43 males and 20 females aged 51~70 years old, with an average age of (59.00 ± 4.32) years old. The New York NYHA cardiac function classification was grade III in 30 cases and grade IV in 33 cases. The NT-proBNP at admission ranged from 973.78 to 2012.21pg/ml, with an average (1479.47 ± 220.36) pg/ml, LVEF < 40% in 16 cases, 40%~49%in 21 cases, LVEF > 50% in 26 cases. HBA1c was 4.64%~10.82% before treatment, with an average value of (7.90 ± 1.33) %. There was no statistical significance in gender, age, NYHA cardiac function grade, NT-proBNP, LVEF and HBA1c between the two groups (P>0.05), indicating strong comparability (Table 1).

Treatment methods

The control group was treated with conventional drugs. Lifestyle intervention, nutritional treatment and conventional drug treatment were adopted. Lifestyle intervention mainly included routine diet intervention and exercise intervention. Nutritional treatment was carried out with reference to the "Consensus Report on Self-management and Educational Support for Type 2 Diabetes (T2DM)" released by the American Diabetes Association (ADA) in 2020 (5). The control drug for heart failure was Shakubactril/valsartan sodium tablets (Novartis PharmaSchweiz AG, national drug approval number J20190002), 100mg, twice /d. The dosage was doubled once every 2 weeks until 200mg, twice /d as the maintenance dose. In case of patient intolerance, the drug should be labeled and replaced with valsartan tablets (Zhejiang Hisun Pharmaceutical Co., LTD., national drug approval number H20213635), 80mg, once per day with a maximum dose of 160 mg/d, and conventional diuretic should be added if necessary. Insulin aspartate 30 injection (Novo Nordisk A/S, registration number: S20140111) was injected subcutaneously before breakfast and dinner, with the initial dose set at 0.4U/kg·d. The attending physician adjusted the dosage of insulin aspartate 30 injections according to the patient's blood glucose monitoring, and the review was conducted after 3 months of continuous treatment. The treatment lasted 12 months.

The observation group was treated with fenofibrate on the basis of the control group. The patients took fenofibrate tablets 0.1g, 3 times /d after breakfast in the morning (manufacturer: Zhejiang Nexchem Pharmaceutical Co., LTD., national drug approval number: H20083062). After 2 months of continuous treatment, the dosage was changed to maintenance dosage (0.1g/d, once /d), and the review was conducted after 3 months of continuous treatment. The treatment lasted 12 months.

Observation indexes

Levels of blood lipid, sICAM-1 and ET-1

The research team extracted 5ml of fasting elbow venous blood from patients before treatment and after 3 months of treatment and centrifuged it at a rate of 3500r/min for 13min with a centrifugation radius of 8cm. The supernatant was taken and the blood lipid indexes (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC)) of the patients were determined by enzyme-linked immunosorbent assay (ELISA) using the automatic biochemical analyzer. Kit was provided by Shanghai Kang Lang Biological Technology Co., LTD., serum endothelin - 1 (endothelin 1, ET - 1) was tested by radioimmunoassay, sICAM-1 was tested by enzyme-linked immunosorbent assay (ELISA). All assays were performed in triplicate, with the average value taken. All indexes were tested by 2 professional medical examiners in strict accordance with the reagent instructions.

Patient prognosis

After 6 and 12 months of treatment, telephone follow-ups and re-visit at the hospital were conducted to investigate the re-hospitalization rate and mortality of the two groups. For re-hospitalization rate, patients re-hospitalized due to elevated blood glucose, ketoacidosis and cardiovascular adverse events were included in the statistics. For mortality, death cases due to diabetes or cardiovascular disease in the two groups were collected. The adverse reactions of the two groups were observed and recorded to determine the safety of fenofibrate.

Statistical methods

Medcalc 19.6-64-bit software was used as a statistical tool. Normal distribution measurement data were described by ($\bar{x}\pm s$). An independent sample t-test was used for comparison between groups. Statistical data were represented by (%). Intergroup comparison was conducted by $\chi 2$ test or Fisher exact probability method, with the correction level α=0.05. P< 0.05 indicates a statistically significant difference.

Results

Comparison of general data between the two groups

There was no statistically significant difference in the comparison of general data between the two groups (P>0.05) (Table 1).

Comparison of blood lipid levels between the two groups

At 3 months after treatment, LDL-C, TG and TC were decreased in both groups compared with that before treatment, showing a statistically significant difference (P<0.05). After 3 months of treatment, LDL-C, TG and TC were lower in the observation group than in the control group, showing a statistically significant difference

Table 1. Comparison of blood lipid levels between the two groups ($\bar{x}$±s, mmol/L).

Group (n)	gender		age (years)	NYHA grade		NT-proBNP (pg/ml)	LVEF (%)			HBA1c (%)
	male	female		III	IV		<40	40~49	>50	
(63) Control group	41	22	59.06±4.51	29	34	1460.49±237.05	15	23	25	8.07±1.21
(63) Observation group	43	20	59.97±4.07	30	33	1479.47±220.36	16	21	26	7.90±1.33
t	0.142		1.182	0.032		0.465	0.143			-0.724
P	0.707		0.240	0.859		0.643	0.931			0.470

Table 2. Comparison of blood lipid levels between the two groups ($\bar{x}$±s, mmol/L).

Group	LDL-C				HDL-C			
	Before treatment	3 months after treatment	*t*	*P*	Before treatment	3 months after treatment	*t*	*P*
Control group (63)	3.97±0.41	2.98±0.34	-18.423	< 0.001	0.94±0.08	1.24±0.28	9.577	< 0.001
Observation group (63)	3.87±0.36	2.10±0.26	-41.703	< 0.001	0.91±0.04	1.63±0.28	23.429	< 0.001
t	-1.455	-16.537			-1.897	7.845		
P	0.148	< 0.001			0.060	< 0.001		
Group	**TG**				**TC**			
	Before treatment	3 months after treatment	*t*	*P*	Before treatment	3 months after treatment	*t*	*P*
Control group(63)	2.38±0.29	1.58±0.26	-16.385	< 0.001	6.10±0.57	4.53±0.47	-18.816	< 0.001
Observation group(63)	2.36±0.29	1.24±0.18	-24.442	< 0.001	5.97±0.69	3.77±0.46	-29.670	< 0.001
t	-0.263	-8.452			-1.109	-9.148		
P	0.793	< 0.001			0.270	< 0.001		

Table 3. Comparison of sICAM-1 and ET-1 levels between the two groups ($\bar{x}$±s, mmol/L).

Group	sICAM-1(μg/ml)				ET-1(ng/ml)			
	Before treatment	3 months after treatment	*t*	*P*	Before treatment	3 months after treatment	*t*	*P*
Control group (63)	885.58±122.32	572.78±80.85	-23.106	< 0.001	80.44±11.30	55.92±6.06	-19.065	< 0.001
Observation group (63)	901.10±112.99	426.47±55.83	-37.415	< 0.001	78.35±11.19	45.13±4.33	-28.138	< 0.001
t	0.740	-11.819			-1.205	-11.503		
P	0.461	< 0.001			0.230	< 0.001		

Table 4. Comparison of re-hospitalization rate and mortality between the two groups [case (%)].

Group	Re-hospitalization rate		Mortality	
	6 months after treatment	12 months after treatment	6 months after treatment	12 months after treatment
Control group (63)	11(17.46)	14(22.22)	4	6(9.52)
Observation group (63)	3(4.76)	8(12.70)	0	1(1.59)
χ^2/Fisher exact probability	3.938	1.967	/	2.420
P	0.047	0.161	0.119	0.120

Note: "/" is the Fisher exact probability.

(*P*<0.05). HDL-C was higher in both groups at 3 months after treatment than that before treatment, showing a statistically significant difference (*P*<0.05). After 3 months of treatment, HDL-C was higher in the observation group than in the control group, showing a statistically significant difference (*P*<0.05). (Table 2).

Comparison of sICAM-1 and ET-1 between the two groups

sICAM-1 and ET-1 were decreased in both groups at 3 months after treatment compared with that before treatment, showing a statistically significant difference (*P*<0.05). Three months after treatment, sICAM-1 and ET-1 were lower in the observation group than in the control group, showing a statistically significant difference (*P*<0.05). (Table 3).

Comparison of patient prognosis between the two groups

After 6 months of treatment, there was no statistically significant difference in mortality between the two groups (*P*>0.05). After 12 months of treatment, there was no statistically significant difference in re-hospitalization rate and mortality between the two groups (*P*>0.05). The re-hospitalization rate of the observation group was 4.76% (3/63) after 6 months of treatment, which was lower than that of the control group, showing a statistically significant difference (*P*<0.05). (Table 4).

Comparison of adverse drug reactions After 12 months of follow-up, no obvious adverse reactions was observed in the two groups, demonstrating the good safety of fenofibrate.

Discussion

Chronic heart failure is a symptom and sign that gradually evolved based on the patient's existing chronic heart disease, which is usually accompanied by the compensatory cardiac enlargement or hypertrophy. Heart failure patients complicated with diabetes are affected by long-term and persistent hyperglycemia in the body. Heart failure patients not only need to face myocardial remodeling and activation of the renin-angiotensin-aldosterone system but also have hyperglycemic toxicity, formation and deposition of advanced glycation end products, hyperlipidemia and lipotoxicity, cardiac autonomic nerve remodeling and microvascular lesions, etc. (6). There is controversy over whether heart failure patients should use lipid-lowering drugs. For example, a large randomized trial of statin therapy in heart failure patients found that statins moderately reduced the risk of hospitalization due to non-fatal heart failure, but did not reduce the hospitalization risk of non-fatal heart failure and risk of death from heart failure (7). At the same time, fenofibrate can reduce the triglyceride level in diabetic patients. Combined with behavioral improvement and blood sugar control, it can reduce the risk of coronary heart disease death in diabetic patients (8). Therefore, treatment regimens for heart failure patients with diabetes should increase lipid metabolism regulation strategies to reduce patients' risk of poor prognosis.

Chronic heart failure patients complicated with diabetes have similarities in various pathological mechanisms, and controlling the synergistic effect of the two diseases can ensure patient stability in blood sugar and improve the prognosis of heart failure (9). Fenofibrate is a PPAR-α agonist mainly present in the liver, kidney, heart and muscle. After PPAR-αactivation, fatty acid metabolism, cholesterol homeostasis, endothelial progenitor cell differentiation and various inflammatory cytokine systems of patients are activated (10,11). Fenofibrate can reduce the concentrations of C-reactive protein and interleukin 6 in patients with rheumatoid arthritis. Meanwhile, for patients with diabetes, 8-week fenofibrate treatment can effectively reduce the endothelial dysfunction level, and reduce vascular inflammation, which plays an important role in improving adiponectin levels and insulin sensitivity (12,13). As an important member of adhesion molecules, sICAM-1 can mediate adhesion reactions and produce feedback effects on the inflammatory response of the body. Studies have reported that sICAM-1 can produce specific binding to vascular endothelial cell-related receptors in chronic heart failure patients, and increase the adhesion of monocytes, neutrophils and other inflammatory factors and endothelial cells (14). ET-1 is a cardiovascular active polypeptide in the process of endogenous injury, which can produce a vasoconstriction effect. The increase of ET-1 will cause vascular endothelial injury, so ET-1 can be used to observe the extent of vascular endothelial injury (15). Accordingly, blood lipid, sICAM-1 and ET-1 should be further improved for chronic heart failure patients complicated with diabetes, in order to achieve the purpose of improving prognosis.

The results of this study showed that adding fenofibrate to chronic heart failure patients complicated with diabetes on the basis of conventional treatment could reduce LDL-C, TG and TC and promote the increase of HDL-C. It is considered that, by using a peroxisome-activated proliferator receptor, fenofibrate can increase the gene expression of apolipoprotein AI and lipoprotein lipase, rapidly degrade LDL-C and chylomicron in blood, thus reducing the TC and TG levels in blood and reducing the blood lipid levels in heart failure patients (16-18). At the same time, this study further observed the sICAM-1 and ET-1 levels after 3 months of treatment. The results showed that the sICAM-1 and ET-1 levels decreased faster in the fenofibrate treatment group. Inhibition of PPARα and sirtuin-1 (Sirt1) signaling pathways may help reduce autophagy flux and mitochondrial dysfunction seen in various forms of cardiomyopathy (19,20). Therefore, fenofibrate generates autophagy flux promoting myocardial cells by activating the PPAR-α pathway, thereby maintaining mitochondrial homeostasis, reducing oxidative stress, alleviating heart injury, and reducing sICAM-1 level. Fenofibrate can affect the PPARα/Sirt1 signaling pathway under the influence of fibroblast growth factor 21, a key factor in cardiac metabolism and a key cause of fatty acid oxidation, ketogenesis and insulin resistance. By activating the PPARα/Sirt1 signaling pathway to increase fibroblast growth factor 21, it is possible to further reduce the level of oxidative stress and improve the heart energy. An animal experiment suggested that fenofibrate could inhibit the expression and transcription level of ET-1 induced by thrombin (21). Jen et al. observed the effect of fenofibrate on large ventricular remodeling in chronic heart failure, finding that fenofibrate down-regulated the expression of the myocardial ET-1 gene in chronic heart failure rats and improved ventricular remodeling (22). Meanwhile, this study compared the prognostic re-hospitalization rate and case fatality rate between the two groups. It was found that the main difference was the re-hospitalization rate at 6 months after treatment (observation group: 4.76% vs. control group: 17.46%), which was related tofenofibrate's ability to reduce the risk of cardiovascular adverse events (23). In this study, adverse reactions during medication were further compared, finding that the addition of fenofibrate did not affect patients' medication safety.

In conclusion, fenofibrate can regulate blood lipids in chronic heart failure patients combined with diabetes, inhibit sICAM-1 and ET-1, and reduce the re-hospitalization rate within 6 months after treatment. However, the effects on long-term re-hospitalization rate and mortality risk are consistent with those of conventional treatment.

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