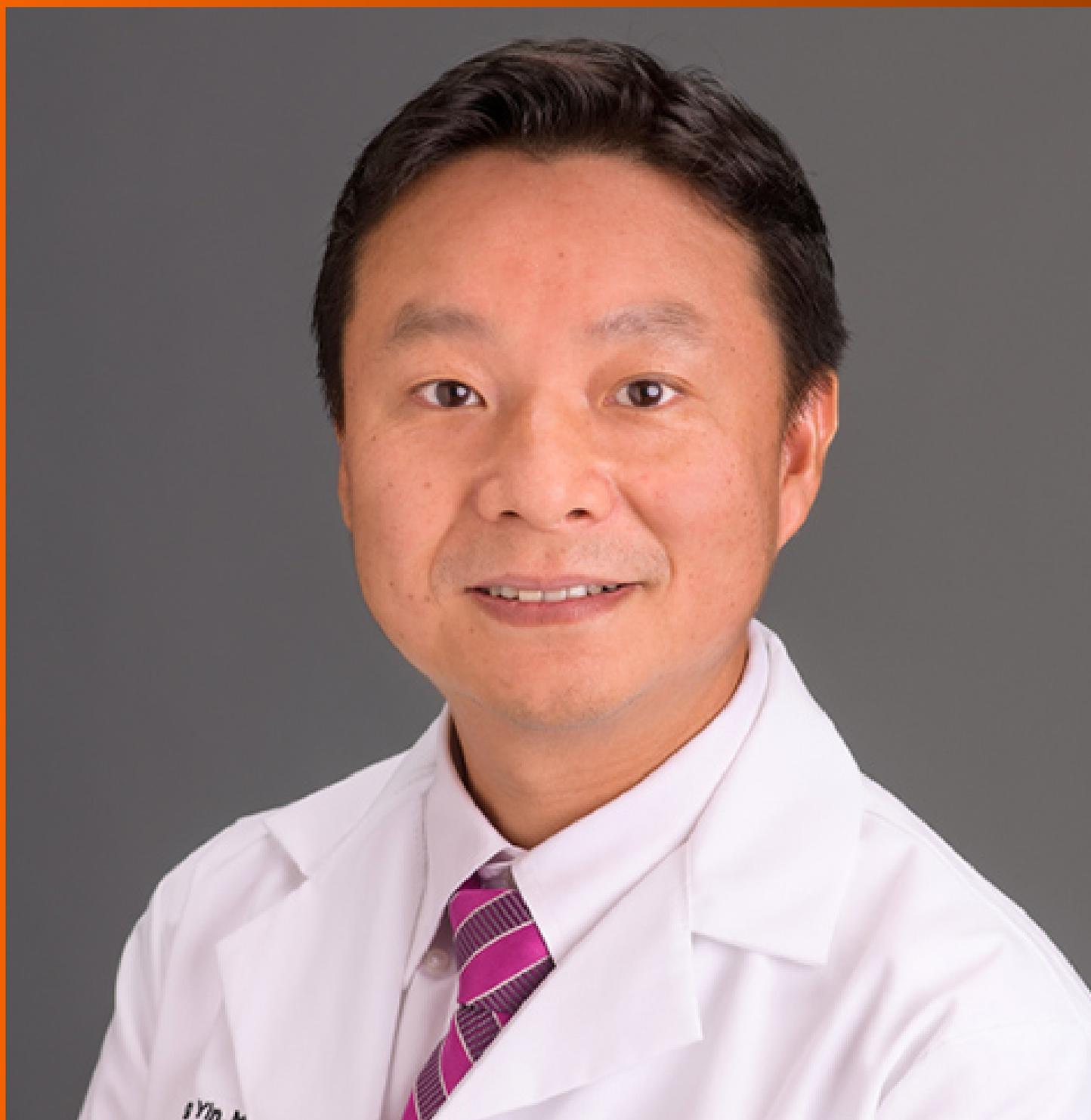


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Case Control Study

Correlation between betatrophin/angiogenin-likeprotein3/lipoprotein lipase pathway and severity of coronary artery disease in Kazakh patients with coronary heart disease

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Abstract

BACKGROUND

The results of previous animal experiments and clinical studies have shown that there is a correlation between expression of betatrophin and blood lipid levels. However, there are still differences studies on the correlation and interaction mechanism between betatrophin, angiogenin-likeprotein3 (ANGPTL3) and lipoprotein lipase (LPL). In our previous studies, we found an increase in serum ANGPTL3 Levels in Chinese patients with coronary heart disease (CHD). Therefore, we retrospectively studied Kazakh CHD patients.

AIM

To explore the correlation between the betatrophin/ANGPTL3/LPL pathway and severity of coronary artery disease (CAD) in patients with CHD.

METHODS

Nondiabetic patients diagnosed with CHD were selected as the case group; 79 were of Kazakh descent and 72 were of Han descent. The control groups comprised of 61 Kazakh and 65 Han individuals. The serum levels of betatrophin and LPL were detected by enzyme-linked immunosorbent assay (ELISA), and the double antibody sandwich ELISA was used to detect serum level of ANGPTL3. The levels of triglycerides, total cholesterol, and fasting blood glucose in each group were determined by an automatic biochemical analyzer. At the same time, the clinical baseline data of patients in each group were included.

RESULTS

Betatrophin, ANGPTL3 and LPL levels of Kazakh patients were significantly higher than those of Han patients ($P = 0.031, 0.038, 0.021$ respectively). There was a positive correlation between the Gensini score and total cholesterol (TC), trigly-

cerides (TG), low-density lipoprotein cholesterol (LDL-C), betatrophin, and LPL in Kazakh patients ($r = 0.204, 0.453, 0.352, 0.471, \text{ and } 0.382$ respectively), ($P = 0.043, 0.009, 0.048, 0.001, \text{ and } P < 0.001$ respectively). A positive correlation was found between the Gensini score and body mass index (BMI), TC, TG, LDL-C, LPL, betatrophin in Han patients ($r = 0.438, 0.195, 0.296, 0.357, 0.328, \text{ and } 0.446$ respectively), ($P = 0.044, 0.026, 0.003, 0.20, 0.004, \text{ and } P < 0.001$). TG and betatrophin were the risk factors of coronary artery disease in Kazakh patients, while BMI and betatrophin were the risk factors in Han patients.

CONCLUSION

There was a correlation between the betatrophin/ANGPTL3/LPL pathway and severity of CAD in patients with CHD.

Key Words: Betatrophin/angiogenin-likeprotein3/Lipoprotein lipase pathway; Coronary heart disease; Gensini integral; Coronary artery disease

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Core Tip: The correlation analysis of this study suggested that the Gensini score of Kazakh patients in the coronary heart disease (CHD) group was positively correlated with the levels of total cholesterol, triglyceride (TG), low-density lipoprotein cholesterol, betatrophin and lipoprotein lipase. Logistic regression analysis showed that TG and betatrophin are risk factors for CHD in Kazakh individuals, while betatrophin and body mass index are risk factors for Han individuals. Unlike previous studies, the lipoprotein lipase levels in the two CHD groups did not decrease but increased.

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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death worldwide, with high morbidity and mortality [1]. Coronary atherosclerosis is one of the important risk factors for CHD[2], and many studies have shown that dyslipidemia is an important risk factor for coronary atherosclerosis[3]. Betatrophin was discovered as a tumor-associated antigen in 2004, and it is expressed in liver and adipose tissue. Because the protein structure of betatrophin is similar to that of angiopoietin-like proteins (ANGPTLs), it was also named ANGPTL8[4]. Chen *et al*[5] found that it can inhibit the activity of lipoprotein lipase (LPL) and lead to increase of plasma triglyceride (TG) levels.

One of the other ANGPTL family members, ANGPTL3, has a dose-dependent inhibitory effect on the metabolism and transport function of LPL[6]. Because LPL can decompose TG, promote the transfer of cholesterol, phospholipids, and apolipoproteins between lipoproteins, and increase the binding and uptake of chylomicron (CM) residues to LPL receptors, the inhibition of LPL activity will lead to the increase of TG and CM levels, which can promote the development of arteriosclerosis[7]. However, there is still a dispute about the interaction mechanism between betatrophin, ANGPTL3 and LPL. Based on the differences in previous studies, it is necessary to conduct clinical research on CHD patients to explore their association. This study investigated Chinese Kazakh CHD patients. Exploration of the relationship between the betatrophin/ANGPT L3/LPL pathway and the severity of coronary artery disease (CAD) may provide new clinical research evidence for the regulation of lipids in CHD patients.

MATERIALS AND METHODS

Study subjects

This case-control study involved 277 individuals in the First Affiliated Hospital of Shihezi University School of Medicine. From September 2017 to October 2020, 79 Kazakh and 72 Han patients with CHD confirmed by coronary angiography (CAG) were randomly included as the case groups. Sixty-one Kazakh and 65 Han individuals with normal CAG results were selected as the control group (Figure 1). The study was completed in the Immunology Laboratory of Shihezi University. The sample size met the

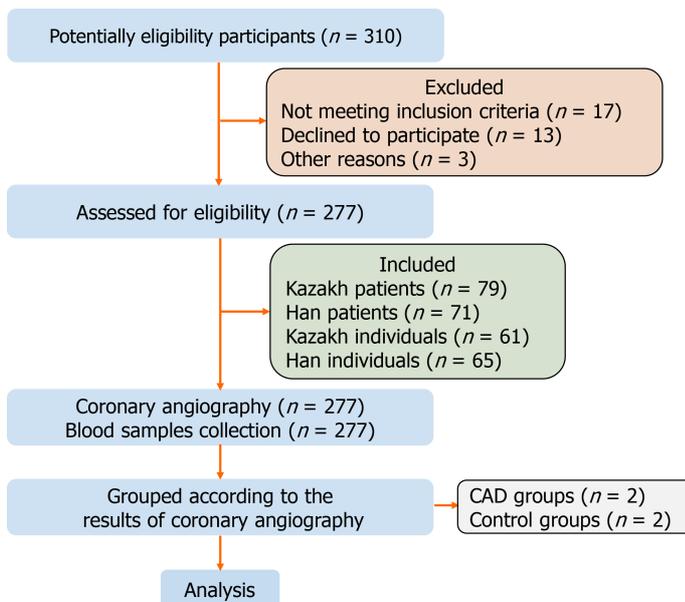


Figure 1 Flow diagram for research. 310 Potentially eligibility participants were included in the initial stage, after evaluation according to the inclusion and exclusion criteria, a total of 277 patients completed coronary angiography and were eventually included in this study. The included cases were divided into groups according to the results of coronary angiography.

design requirements of the case-control study, and the experiment and data analysis of the study adopted the double-blind principle.

Inclusion and exclusion criteria

Inclusion criteria: The diagnostic criteria for CHD followed the ACC/AHA 2014 guidelines. Moreover, the age range was 35–75 years. Participants completed CAG in the same hospital, and echocardiography (EPIQ 7C; Philips, Netherlands) was used to evaluate the cardiac function of patients. According to the evaluation standards of the New York Heart Association, patients with cardiac function grade I or II were included in the study.

Exclusion criteria: (1) According to the Medical Diagnosis and Treatment Standard of Diabetes formulated by the American Diabetes Association in 2019, patients diagnosed with type 1 or type 2 diabetes; (2) Patients with cardiomyopathy, congenital heart disease, severe valvular disease, pulmonary heart disease with pulmonary hypertension, and heart failure with cardiogenic shock were also excluded; (3) Patients with malignant tumors who were receiving radiotherapy and chemotherapy, patients with new cerebral hemorrhage, and patients who received surgery or thrombolytic therapy for cerebral infarction within 1 year; (4) Liver is the main synthetic organ of betatrophin and ANGPTL3, and liver failure may lead to abnormal synthetic function, so it was necessary to exclude patients diagnosed with liver failure. The diagnostic criteria for liver failure are based on the Guidelines for Diagnosis and Treatment of Liver Diseases in China. In order to prevent the occurrence of contrast medium nephropathy, the renal function of all selected cases was evaluated before CAG, and patients with renal failure were excluded (diagnostic criteria for renal failure: Blood urea nitrogen ≥ 21.42 mmol/L, serum creatinine > 442 mmol/L, and glomerular filtration rate < 5 mL/min); and (5) Patients who had quit smoking < 6 mo before the time of diagnosis, as well as those treated with statins, antiplatelet drugs, and nitrates with a withdrawal time < 2 wk.

Evaluation criteria of CAG

CAG was performed by doctors with > 5 years of experience. Based on the double-blind design, the results of CAG were judged by three experienced cardiologists. The Gensini stenosis scoring system was used to evaluate the severity of coronary lesions[8], and the average value of the Gensini score calculated by the three cardiologists was taken as the final score. Mild lesions were defined as Gensini score ≤ 24 . Those with a score ≥ 25 but < 53 were defined as moderate lesions, while those with a score ≥ 53 were defined as severe lesions. According to the Gensini scores, patients in the case groups were divided into three subgroups: mild, moderate and severe.

Detection of betatrophin, ANGPTL3 and LPL levels in each group

Detection of betatrophin: ELISA was selected to detect the level of betatrophin in serum (hz-EL-H2206c; Huzhen Biotechnology, China). The sensitivity of detection was 4 pg/mL, while the coefficient of variation was $< 9\%$, and the coefficient of variation between batches was $< 15\%$.

Detection of ANGPTL3: Serum ANGPTL3 was determined by the double antibody sandwich ELISA method (ab254510; Abcam, Cambridge, United Kingdom). The optical density (OD) was read by spectrophotometer (UV7; Mettler Toledo, Switzerland), and the results were calculated by the standard curve method.

Detection of LPL: The serum LPL level was also detected by ELISA (SP10920; Saibo Biotechnology, China). After the OD values were read by the spectrophotometer (UV7), the diluted concentration of each standard tube was used as the abscissa, and the measured OD value is used as the ordinate to construct the standard curve.

Detection of blood biochemical indexes in each group

Blood samples collected from individuals in all groups were centrifuged for 5 min at 3500 rpm and the supernatant (serum) was used for the detection of biochemical indexes. The levels of total cholesterol (TC), TG, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), glucose (GLU), fasting plasma glucose (FPG) and fasting insulin (FINS) in serum samples of each group were determined by automatic biochemical analyzer (AU-2700; Olympus, Japan).

Insulin resistance and islet β -cell function assessment

Homeostasis model assessment insulin resistance (HOMA-IR) was used to evaluate insulin resistance level. The function of an individual's islet β cells was evaluated by HOMA- β . $HOMA-IR = (FINS \times FPG) / 22.5$, $HOMA-\beta = 20 \times FINS / (FP-3.5)$.

Statistical analysis

Data were analyzed by SPSS version 25.0. The data are expressed as mean \pm SD, and the statistical differences between the data were compared by independent sample *t*-test. Differences between groups were analyzed by two-way analysis of variance, multigroup analysis of variance, correlation analysis by Spearman correlation, and risk factor assessment by ordered logistic regression analysis. $P < 0.05$ indicated that there were significant differences between the groups.

RESULTS

Comparison of baseline data between Kazakh and Han patients

There was no significant difference in age, systolic blood pressure and diastolic blood pressure between Kazakh and Han CHD groups and their respective control groups ($P = 0.14, 0.24,$ and 0.15 respectively). Similarly, there was no significant difference in the levels of GLU, fructosamine, HOMA-IR and HOMA- β between Kazakh and Han CHD groups and their respective control groups ($P = 0.24, P = 0.13, P = 0.09,$ and $P = 0.11$ respectively). In the comparison of blood lipid levels, there was no significant difference in HDL-C level between Kazakh and Han CHD groups and their respective control groups ($P = 0.26$). BMI, TC, TG and LDL-C in the two groups were significantly higher than in the control groups ($P = 0.03, P = 0.004, P = 0.006,$ and $P = 0.02$ respectively) (Table 1).

Comparison of serum betatrophin, ANGPTL3 and LPL levels between the two groups

The levels of betatrophin, ANGPTL3 and LPL in Kazakh and Han CHD groups were higher than those in their respective control groups ($P < 0.01, P = 0.022,$ and $P = 0.043$ respectively). The level of serum betatrophin and ANGPTL3 in the Kazakh CHD group was higher than that in the Han CHD group ($P = 0.031, P = 0.038, P = 0.021$ respectively) (Table 2).

Comparison of betatrophin, ANGPTL3 and LPL levels after stratification according to Gensini score

In the Kazakh and Han CHD groups, the levels of serum betatrophin, ANGPTL3 and LPL in patients with severe CAD were significantly higher than those in patients with moderate and mild CAD ($P < 0.001$). The levels of serum betatrophin and ANGPTL3 in the Kazakh CHD group with severe CAD were significantly higher than those in the Han CHD group with severe CAD ($P < 0.001$). However, there was no significant difference in serum LPL levels in patients with mild CAD ($P = 0.16$) (Table 3).

Correlation between included variables and severity of CHD

There was a positive correlation between the Gensini score and TC, TG, LDL-C, betatrophin and LPL levels in Kazakh patients in the CHD group ($r = 0.204, r = 0.453, r = 0.352, r = 0.471,$ and $r = 0.382$ respectively). There was a positive correlation between the Gensini score, BMI, TC, TG, LDL-C, betatrophin and LPL levels in Han patients in the CHD group ($r = 0.438, r = 0.195, r = 0.296, r = 0.357, r = 0.446$ and $r = 0.328$). Logistic regression analysis revealed that TG and serum betatrophin were risk factors for coronary atherosclerosis in Kazakh patients, and BMI and serum betatrophin were risk factors for coronary atherosclerosis in Han patients. In the Kazakh CHD group, the Gensini score was

Table 1 Comparison of general baseline data between Kazakh and Han patients with coronary heart disease

Variables	Kazakh			Han		
	CHD (n = 79)	Non-CHD (n = 72)	P value	CHD (n = 61)	Non-CHD (n = 65)	P value
Age (yr)	52.27 ± 12.10	53.77 ± 12.24	0.16	53.78 ± 13.56	52.63 ± 11.73	0.14
SBP (mmHg)	135.13 ± 15.46	129.24 ± 13.42	0.27	129.44 ± 15.69	125.58 ± 16.81	0.24
DBP (mmHg)	84.85 ± 13.21	81.34 ± 12.52	0.18	81.41 ± 16.39	79.26 ± 12.14	0.15
BMI	27.43 ± 2.97 ^{1,3}	24.76 ± 3.22	0.007	26.74 ± 2.43 ²	24.22 ± 3.37	0.03
GLU (mmol/L)	5.53 ± 0.62	54.06 ± 14.16	0.26	5.16 ± 0.37	4.73 ± 0.52	0.24
Fructosamine (μmol/L)	241.82 ± 23.42	235.89 ± 18.54	0.33	246.02 ± 21.42	239.71 ± 18.25	0.13
HOMA-IR	0.95 ± 0.11	0.93 ± 0.09	0.13	0.89 ± 0.06	0.87 ± 0.07	0.09
HOMA-β	0.81 ± 0.06	0.80 ± 0.09	0.15	0.78 ± 0.14	0.79 ± 0.07	0.11
TC (mmol/L)	5.37 ± 0.73 ^{1,3}	4.28 ± 0.34	0.005	5.01 ± 1.09 ²	4.12 ± 0.76	0.004
TG (mmol/L)	1.36 ± 0.60 ^{1,3}	1.14 ± 0.56	0.007	1.15 ± 0.65 ²	1.08 ± 0.37	0.006
LDL-C (mmol/L)	3.15 ± 0.62 ^{1,3}	2.56 ± 0.44	0.004	2.98 ± 1.02 ²	2.87 ± 0.56	0.02
HDL-C (mmol/L)	1.85 ± 0.39	1.93 ± 0.23	0.21	1.87 ± 0.38	2.01 ± 0.36	0.26

¹Comparison between Kazakh CHD patients and control group patients ($P < 0.01$).

²Comparison between Han CHD patients and control group patients ($P < 0.05$).

³Comparison between Kazakh and Han patients ($P < 0.01$).

CHD: Coronary heart disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; GLU: Glucose; HOMA-IR: Homeostasis model assessment-insulin resistance; HOMA-β: Homeostasis model assessment-β cells; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

Table 2 Comparison of serum betatrophin, angiotensin-like protein 3 and lipoprotein lipase levels in coronary heart disease group and control group

Variables	Kazakh			Han		
	CHD (n = 79)	Non-CHD (n = 72)	P value	CHD (n = 61)	Non-CHD (n = 65)	P value
Betatrophin (pg/mL)	435.32 ± 60.36 ^{1,2}	243.21 ± 62.73 ¹	< 0.001	408.26 ± 57.45 ²	219.73 ± 59.37	0.031
ANGPTL3 (ng/mL)	3.42 ± 1.63 ^{1,2}	2.69 ± 1.33 ¹	0.022	3.27 ± 1.45 ²	2.52 ± 1.53	0.038
LPL (ng/mL)	56.37 ± 13.27 ^{1,2}	42.37 ± 13.16 ¹	0.043	54.52 ± 14.52 ²	41.42 ± 12.26	0.021

¹Compared with control group ($P < 0.05$).

² P : Compared with Han CHD group ($P < 0.05$).

CHD: Coronary heart disease; SBP: Systolic blood pressure; ANGPTL3: Angiotensin-like protein 3; LPL: Lipoprotein lipase.

taken as the dependent variable, and TC, TG, LDL-C, betatrophin, and LPL as the independent variables in logistic regression analysis. Similarly, the Gensini score was taken as the dependent variable, and BMI, TC, TG, LDL-C, serum betatrophin and LPL as the independent variables in the logistic regression analysis of the Han CHD group (Tables 4 and 5).

DISCUSSION

The results of this study suggest that the betatrophin/ANGPTL3/LPL pathway is related to the severity of CHD. In addition, the results showed that the levels of LPL and ANGPTL3 in CHD patients increased, and their increasing trends were consistent. According to previous research, the functional difference of ANGPTL family members lies in the difference between C-terminal and N-terminal domains (Figure 2). Betatrophin was recognized as an atypical new member of the ANGPTL family because of its lack of a fibrinogen-like domain in the C terminus[5]. However, betatrophin is closely related to ANGPTL3, which can promote the cleavage of ANGPTL3 and indirectly reduce the inhibitory effect of ANGPTL3 on LPL[9-11]. Jiao *et al*[12] used ApoE^{-/-} mice to prove that betatrophin is highly expressed during the development of arteriosclerosis. Luo *et al*[13] believe that betatrophin plays an

Table 3 The levels of betatrophin, angiopoietin-like protein 3, and lipoprotein lipase were compared between the two coronary heart disease groups after stratification according to Gensini integral

	Groups	n	Betatrophin (pg/mL)	ANGPTL3 (ng/mL)	LPL (ng/mL)
Kazakh	Gensini ≤ 24	32	356.86 ± 58.61	2.34 ± 0.57	50.22 ± 12.27
	25 ≤ Gensini < 53	22	380.03 ± 61.56	3.56 ± 1.03	57.59 ± 10.41
	Gensini ≥ 53	18	452.74 ± 62.24 ^{1,2}	5.94 ± 1.46 ^{1,2}	59.35 ± 13.19 ^{1,2}
Han	Gensini ≤ 24	35	326.07 ± 50.56	2.00 ± 1.32	50.16 ± 13.48 ³
	25 ≤ Gensini < 53	21	369.64 ± 53.44	3.33 ± 0.83	54.39 ± 12.33 ³
	Gensini ≥ 53	9	422.39 ± 59.14 ¹	5.19 ± 1.21 ¹	57.60 ± 12.35 ¹

¹Comparison between mild and moderate within the group ($P < 0.05$).

²Compared with Han CHD group ($P < 0.05$).

³Compared with Han CHD group ($P > 0.05$).

Angiopoietin-like protein 3; LPL: Lipoprotein lipase.

Table 4 Correlation between Gensini score and risk factors of atherosclerosis in two groups of patients with coronary heart disease

Group		TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	Betatrophin (pg/mL)	LPL (ng/mL)	BMI (ng/mL)
Kazakh	<i>r</i>	0.204	0.453	0.352	0.471	0.382	0.097
	<i>P</i> value	0.043	0.009	0.048	0.001	0.001	0.261
Han	<i>r</i>	0.195	0.296	0.357	0.446	0.328	0.438
	<i>P</i> value	0.026	0.003	0.20	0.001	0.004	0.044

TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; BMI: Body mass index; LPL: Lipoprotein lipase.

Table 5 Ordinal logistic regression analysis of two coronary heart disease groups

	Variables	B value	<i>P</i> value	Exp (B)
Kazakh	TG	3.292	0.03	3.632
	Betatrophin	1.258	0.043	1.802
Han	BMI	5.635	0.01	2.457
	Betatrophin	1.170	0.036	1.615

TG: Triglycerides; BMI: Body mass index.

important role as a regulator in metabolic disorders. Chi *et al*[14] verified that betatrophin promotes the combination of ANGPTL3 and LPL. The above studies have shown the synergistic function between betatrophin and ANGPTL3 and play a role together in the process of lipid regulation (Figure 3). In previous clinical studies, Leiherer *et al*[15] included 201 CAD patients for an 8-year follow-up study, and the results showed that elevated levels of betatrophin have predictive value for the occurrence of cardiovascular events. Moreover, the study by Fadaei *et al*[16] revealed that the higher circulating levels of betatrophin in patients with CHD are related to BMI, TG and endothelial dysfunction. In a previous study based on Chinese CHD patients, Jiao *et al*[17] also showed that the circulating full-length betatrophin levels in nondiabetic CHD patients were increased, and they could be used as an independent risk factor for CHD. Our findings also showed similar patterns and the levels of betatrophin in the CHD group were higher than in the control group, and we also found that the level of betatrophin was positively correlated with the severity of coronary artery stenosis. However, the difference from previous studies was that the serum levels of LPL and ANGPTL3 showed a consistent increase.

ANGPTL3 has become a new target for the treatment of patients with dyslipidemia. Recent studies have confirmed the safety and effectiveness of using monoclonal antibodies or antisense oligonucleotides to inhibit ANGPTL3, and the goal of lipid regulation has been achieved[18-20]. The current

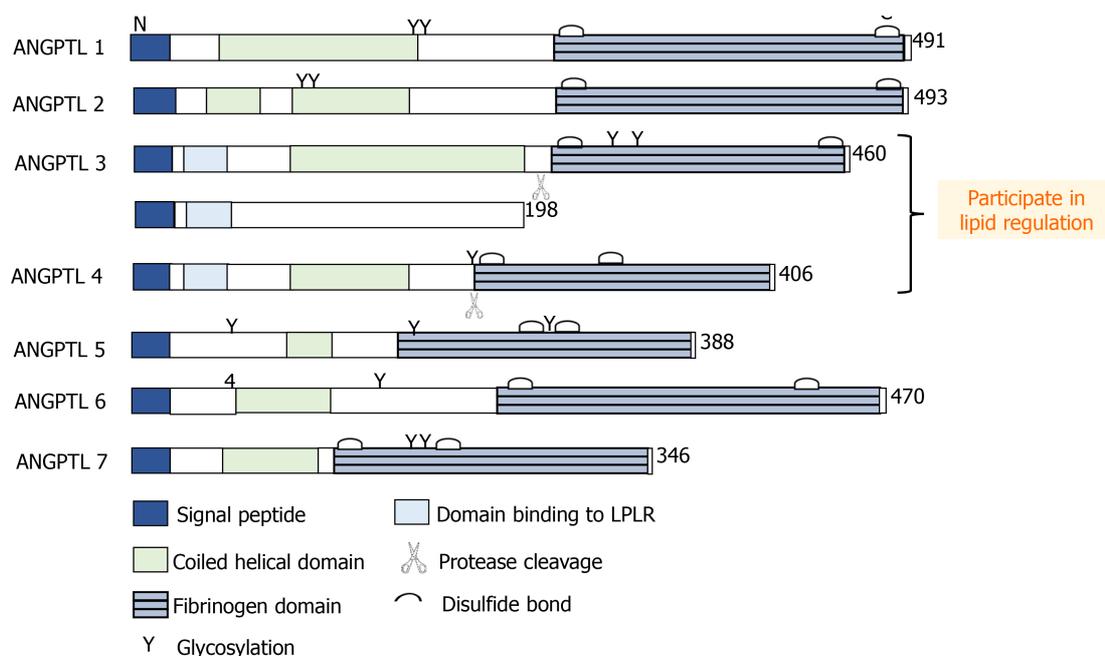


Figure 2 Schematic diagram of structural characteristics of angiopoietin-like proteins members. The members of the angiopoietin-like proteins (ANGPTLs) have their own different structural characteristics, betatrophin is considered an atypical new member of the ANGPTLs because of the lack of the C-terminal fibrinogen-like domain. However, betatrophin, angiogenin-likeprotein3, and angiogenin-likeprotein4 all possess protein domains that bind to low density lipoprotein receptor. These characteristics provide evidence for their joint participation in lipid regulation.

evidence supports that ANGPTL3 inhibits the activity of LPL in a manner dependent on betatrophin activation, and there is consistency between them. The results of our study also showed that the level of ANGPTL3 in Kazakh and Han CHD patients was significantly higher than that in their respective control groups. Moreover, the level of serum in the Kazakh CHD group was higher than that in the Han CHD group. After the severity of CAD was stratified according to the Gensini score, there was no significant difference in serum LPL levels between patients with moderate CAD and the control group, and the same result was found in patients with mild CAD. Based on the above results, we consider that severe coronary lesions may be one of the factors that induce the compensatory increase of betatrophin levels in the circulation. The combination of increased betatrophin and ANGPTL3 indirectly reduces the inhibition of LPL by ANGPTL3, allowing activated LPL to participate in lipid regulation.

Kazakh individuals are mainly descendants of Turks and medieval Mongolians, living in the mountains and pastures of Northern Xinjiang. They have their specific dietary characteristics, such as high-salt and high-fat diet, and less intake of vegetables and fruits. Risk factors related to cardiovascular disease in the Kazakh population include obesity, hypertension and metabolic syndrome[21-23], leading to the high incidence of CHD in this population[24]. The correlation analysis showed that there was a positive correlation between the Gensini score and TC, TG, LDL-C, betatrophin and LPL levels of Kazakh patients with CHD. Logistic regression analysis confirmed that TG and betatrophin were risk factors for CHD in Kazakh patients, and BMI and betatrophin were risk factors in Han patients. As a key enzyme in TG metabolism[25,26], LPL can hydrolyze TG carried by CM and very low density lipoprotein into glycerol and fatty acids. When the activity of LPL is inhibited by ANGPTL3, it may lead to accumulation of TG. However, the results of this study showed that the levels of LPL in Kazakh and Han CHD patients were significantly higher than those in their respective control groups, and there was no significant decrease. According to our analysis, the reasons for the above results may be as follows. At a certain point in time, the level of LPL does not represent the characteristics of change over time, and the level of LPL may show a downward trend with disease progression. The increase in lipid level stimulates the liver to synthesize betatrophin, and the increase of betatrophin promotes cleavage of ANGPTL3, which leads to a decrease in the inhibitory effect of ANGPTL3 on LPL. After the activation of LPL, the increase in its activity and level promote lipid metabolism. Based on the above process, the increase of betatrophin, ANGPTL3 and LPL levels in this pathway may be consistent, but the increased ANGPTL3 may be the product of cleavage. Patients with acute coronary syndrome may induce expression of betatrophin, ANGPTL3 and LPL in the short term due to the combined effects of atherosclerotic plaque rupture, activation of inflammatory pathways, and stress. However, for relatively stable CHD patients, there may be differences with the above results.

Detection of the betatrophin/ANGPTL3/LPL pathway may be used in clinical practice as one of the assessment tools of CAD severity in CHD patients. The detection of this pathway in CHD patients with acute coronary occlusion may have more diagnostic value. Betatrophin can also be used as a target for new lipid regulation treatments to provide clues for the development of new drugs[27]. Regarding the

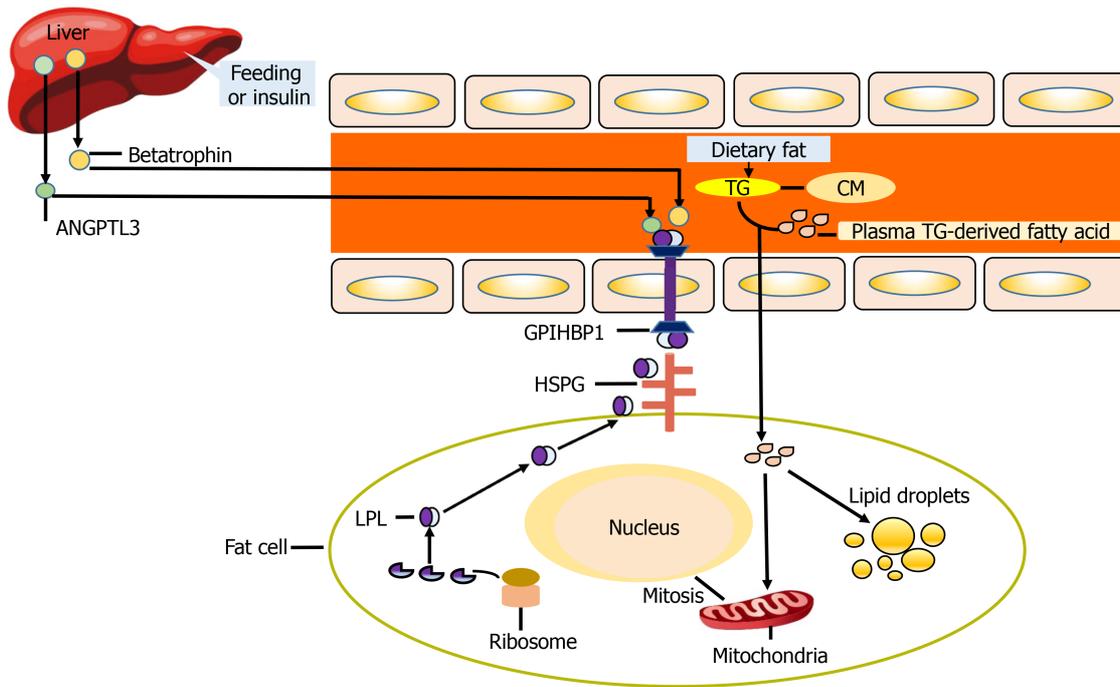


Figure 3 Schematic diagram of betatrophin and angiogenin-like protein 3 participating in lipid regulation. Betatrophin synthesized by the liver under the stimulation of feeding or insulin can promote the cleavage of angiogenin-like protein 3 (ANGPTL3) to release the active N-terminal catalytic core domain (CCD) domain, which leads to a decrease in the inhibitory effect of ANGPTL3 on Lipoprotein lipase (LPL) activity and indirectly promotes LPL to participate in lipid metabolism. When triglyceride-derived fatty acids enter the adipocytes, some of them form lipid droplets, while the other part induces the increase of LPL synthesis in adipocytes, and enters the blood circulation to participate in lipid metabolism mediated by glycosylphosphatidylinositol high density lipoprotein binding protein 1. GPIIIBP1: Glycosylphosphatidylinositol high density lipoprotein binding protein 1; HSPG: Heparan sulfate proteoglycan; CM: Chylomicrons; TG: Triglycerides.

other functions of betatrophin, progress has been made not only in the field of lipid metabolism, but also in the exploration of betatrophin gene polymorphism[28] and inflammation-related pathways[29]. The results of Catalano *et al*[30] revealed that betatrophin specifically regulates TG-rich lipoproteins through the LPL pathway. Therefore, the expression of betatrophin and its participation in lipid regulation pathways still need more exploration.

CONCLUSION

There is a positive correlation between the betatrophin/ANGPTL3/LPL pathway and the severity of CAD in Kazakh patients with CHD. This pathway is involved in the lipid regulation of CHD, and betatrophin has the possibility of being used as a diagnostic marker of CHD.

ARTICLE HIGHLIGHTS

Research background

Lipid metabolism plays an essential role in the pathogenesis of atherosclerosis, a major cause for coronary heart disease (CHD). Lipid regulation therapy can reduce major adverse cardiovascular events. Although previous studies have shown that betatrophin, angiogenin-like protein 3 and lipoprotein lipase are jointly involved in lipid regulation, the interaction and mechanism of action between them are still controversial.

Research motivation

The purpose of this study was to explore the correlation between the betatrophin/angiogenin-like protein 3 (ANGPTL3)/lipoprotein lipase (LPL) pathway and severity of coronary artery disease in patients with CHD. The detection of this pathway in CHD patients with acute coronary occlusion may have more diagnostic value. Betatrophin can also be used as a target for new lipid regulation treatments to provide clues for the development of new drugs.

Research objectives

The betatrophin/ANGPTL3/LPL pathway is related to the severity of CHD. In addition, the results showed that the levels of LPL and ANGPTL3 in CHD patients increased, and their increasing trends were consistent. The detection of this pathway can be used as one of the non-invasive tools to evaluate the severity of coronary artery disease (CAD) lesions in patients with CHD. Not only that, betatrophin may also serve as a new target for lipid regulation therapy.

Research methods

This case-control study involved 277 individuals. Nondiabetic patients diagnosed with CHD were selected as the case group; 79 were of Kazakh descent and 72 were of Han descent. The control groups comprised of 61 Kazakh and 65 Han individuals. The serum levels of betatrophin and LPL were detected by enzyme-linked immunosorbent assay (ELISA), and the double antibody sandwich ELISA was used to detect serum level of ANGPTL3. The data are expressed as average \pm standard deviation, and the statistical differences between the data were compared by independent sample *t*-test. Differences between groups were analyzed by two-way analysis of variance, multigroup analysis of variance, correlation analysis by Spearman correlation, and risk factor assessment by ordered logistic regression analysis.

Research results

The betatrophin/ANGPTL3/LPL pathway is positively correlated with the severity of CAD. The levels of serum betatrophin and ANGPTL3 in the Kazakh CHD group with severe CAD were significantly higher than those in the Han CHD group with severe CAD. However, there was no significant difference in serum LPL levels in patients with mild CAD. Logistic regression analysis revealed that TG and serum betatrophin were risk factors for coronary atherosclerosis in Kazakh patients, and BMI and serum betatrophin were risk factors for coronary atherosclerosis in Han patients. Other expression mechanisms of betatrophin in lipid regulation still need to be explored. The inflammatory response and autophagy mediated by betatrophin in atherosclerosis may become a new research direction.

Research conclusions

There was a correlation between the betatrophin/ANGPTL3/LPL pathway and severity of CAD in patients with CHD.

Research perspectives

The expression of betatrophin in other tissues and its new mechanism of lipid regulation, as well as the inflammatory response and autophagy of atherosclerosis mediated by betatrophin may become new research directions. Not only that, betatrophin can also be used as a target for new lipid regulation treatments to provide clues for the development of new drugs.

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FOOTNOTES

Author contributions: Qin L interpreted the data and drafted the manuscript; Ma X designed the study and corrected the manuscript; Ainiwaer A participated to the collection of the human material; Rehemuding R served as scientific advisor and participate to the collection of human material; Qin L and Ainiwaer A completed the experiment of this study; Ma X had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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