Int J Clin Exp Med 2019;12(10):12552-12558
www.ijcem.com /ISSN:1940-5901/IJCEM0099574

Original Article

Correlation between serum total bile acid levels and coronary heart disease

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Received July 12, 2019; Accepted September 3, 2019; Epub October 15, 2019; Published October 30, 2019

Abstract: Objective: The aim of the current study was to investigate correlation levels between serum total bile acid and occurrence of coronary heart disease. Methods: Patients that underwent coronary angiographies in Linyi people's Hospital, between December 2015 to December 2016, were selected. Patients with coronary artery disease (diagnosed by coronary angiographies) were included in the observation group (102 cases). Patients with no significant abnormalities were included in the control group (80 cases). Basic information of the patients was collected and levels of total cholesterol (TC), triacylglycerol (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), glucose (Glu), and total bile acid (TBA) were measured. Results were analyzed statistically. Results: Levels of TC, TG, LDL-C, TBA, and Glu in the observation group were significantly higher than those in the control group. HDL-C was significantly lower than that in the control group (all $P < 0.05$). The abnormal rate of TBA (72.55%) was significantly higher than that of TC, HDL-C, and LDL-C in the observation group (all $P < 0.05$). Pearson's linear correlation analysis showed that TC, TG, and LDL-C levels were positively correlated with TBA expression levels and negatively correlated with HDL-C expression levels (all $P < 0.05$). Logistics multivariate analysis showed that smoking, hypertension, diabetes, hyperlipidemia, and TBA are independent risk factors for coronary heart disease. Conclusion: Serum total bile acid was closely related to occurrence of coronary heart disease and could be a good response to the metabolic statuses of coronary heart disease patients. Thus, it is worthy of promotion as an auxiliary indicator of coronary heart disease detection.

Keywords: Serum total bile acid, coronary heart disease, total cholesterol, atherosclerosis

Introduction

Coronary heart disease (CHD) is a type of cardiovascular disease. With an aging population, irregular diets, and other relative factors, soaring incidence rates have been observed [1-3]. Occurrence of coronary heart disease depends largely on metabolic abnormalities of patients. Metabolic abnormalities in the body can lead to increased endotoxins, damaging the lipid molecular layer on the cell membrane surface. It can also damage myocardial cells and the vascular wall structure, inducing inflammatory reactions [4]. Local inflammation could also result in an increase in exotoxin secretion from bacteria. This will stimulate the blood vessel walls, causing accumulation of platelets and lipid macromolecules. The cumulative effects may destroy the permeability of blood vessel walls and cause atherosclerosis. This will increase the resistance to blood transport and cause vascular injuries, eventually leading to myocardial insufficiency [5, 6].

In addition, many studies have shown that elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels are major risk factors for development of CHD. Bile acid is the main metabolite of endogenous TC in the body, helping to absorb cholesterol in food. Related molecular mechanisms that affect glucose and lipid metabolism have been scientifically explained in a previous report [7]. Animal studies have shown that hyperlipidemia is prone to atherosclerosis and that bile acid levels in the blood of hyperlipidemic animals are

significantly lower than those in healthy animals [8, 9]. In addition, studies have shown that exogenous increases in chelating ions could significantly reduce reabsorption of bile acids in the intestine, increase expression of cytochrome P450 7A1 (CYP7A1), accelerate cholesterol degradation, and reduce TC and LDL-C levels. Therefore, correlation levels between serum total bile acid and occurrence of coronary heart disease should receive more clinical attention.

The current study aimed to explore the roles of serum total bile acid levels in the diagnosis and pathogenesis of coronary heart disease, providing a theoretical basis for future clinical treatment.

Materials and methods

Patient information

The present study was approved by the Ethics Committee of the Linyi people's Hospital. Patients undergoing coronary angiography (CAG) procedures were recruited from Linyi people's Hospital, between December 2015 to December 2016. Based on results of clinical diagnoses of coronary angiograms, patients with clinically dominant coronary artery disease were included in the observation group (102 patients) [10]. Patients with no angiographic changes were included in the control group (80 patients). Inclusion criteria: (A) In the observation group, CAG examinations showed arterial vascular stenosis of more than 50%; (B) In the control group, CAG examinations showed atherosclerotic lesions < 50% with no history of strokes; and (C) Aged 50-70 years old [10]. Exclusion criteria: (A) Patients with incomplete clinical data and testing items; (B) Patients with heart failure, myocarditis, and other types of heart diseases; and (C) Patients with other diseases. All included patients provided informed consent.

Methods

Data collection

According to admission diagnoses and medical history investigations, relevant case information was collected, including gender, age, height, weight, disease history (hypertension, hyperglycemia, hyperlipidemia, and heart disease), and smoking status.

Biochemical indicators measurement

Biochemical indicators related to this study at the time of first visit were recorded, including levels of TC, triacylglycerol (TG), high density lipoprotein-cholesterol (HDL-C), LDL-C, glucose (Glu), and total bile acid (TBA).

Coronary angiography determination

Coronary angiography procedures were performed using the Digital Subtraction Angiography system (DSA, INNOVA3100). Results of the lesions in patients with coronary heart disease were diagnosed by professional physicians after joint determination [10].

Outcome measures

Main outcome measures: Before blood biochemical testing, patients were required to have fasting preparations for more than 8 hours. Anticoagulant tubes were used for venous blood collection the next day. Each tube contained 2-3 mL of a total of 2 tubes. TC, TG, HDL-C, LDL-C, Glu, and TBA levels were determined by enzyme colorimetry using an Olympus biochemical analyzer (OLYMPUS Optical Co., Ltd., Au400). The number of abnormalities in TC, TG, HDL-C, LDL-C, and TBA, along with their proportion in the total number, were analyzed statistically.

Secondary outcome measures: Hypertension determination: Systolic blood pressure was measured 3 days in a row (once a day); Mean systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or the patient had a history of hypertension [11]. Diabetes determination: Clinical manifestations of patients showed diabetes symptoms (more eating, drinking, and polyuria) and blood glucose values ≥ 11.1 mmol/L for three random samplings, along with ≥ 7.0 mmol/L for fasting blood glucose [12]. Hyperlipidemia determination: High cholesterol (blood TC ≥ 6.22 mmol/L); High triglycerides (blood TG ≥ 2.26 mmol/L). High-density lipoprotein determination: Blood HDL-C < 0.91 mmol/L. Low-density lipoprotein determination: LDL-C ≥ 4.14 mmol/L. Abnormalities in one or more of the above lipid parameters were classified as hyperlipidemia [13, 14]. Abnormal TBA: Blood TBA ≥ 10 μmol/L [15]. Smoking determination: A person that smokes more than 5 cigarettes

Table 1. Comparison of clinical baseline data between the two groups

Item	Control group	Observation group	t/χ^2	P
Case (n)	80	102		
Gender (n)			4.167	0.035
Male	38 (47.5)	65 (62.7)		
Female	42 (52.5)	37 (37.3)		
Age (year)	59.97±8.68	62.56±7.85	1.222	0.114
BMI (kg/m^2)	25.56±9.27	34.82±10.48	3.143	0.002
Hypertension (n, %)	8 (10.00)	29 (28.43)	8.300	0.003
Hyperlipidemia (n, %)	16 (20.00)	43 (42.16)	9.060	0.002
Diabetes (n, %)	10 (12.50)	33 (32.35)	8.724	0.003

per day, with a smoking history of more than 5 years.

Statistical analysis

SPSS 21.0 software was used for statistical analysis. Measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Measurement data with normal distribution was examined with t-tests. Measurement data without normal distribution was examined with rank-sum tests. Count data are expressed by percentages and were compared with χ^2 and Fisher's exact tests. Pearson's correlation was used to analyze correlation levels between indicators of the two groups. Multivariate logistic regression was used to analyze correlation levels between multiple factors and occurrence of coronary heart disease. $P < 0.05$ indicates statistically significant differences.

Results

Comparison of baseline data between two groups

There were no significant differences between the two groups in age ($P > 0.05$). For the proportion of males, BMI, hypertension, hyperglycemia, and hyperlipidemia, results in the observation group were significantly higher than those in the control group (all $P < 0.05$, **Table 1**).

Comparison of biochemical indicators between two groups

Levels of TC, TG, LDL-C, TBA, and Glu in blood in the observation group were significantly higher than those in the control group, while blood HDL-C levels in the observation group were significantly lower than those in the control group (all $P < 0.05$, **Figure 1**).

Rate of TBA and dyslipidemia in patients with coronary heart disease

The abnormal rate of TBA in patients with coronary heart disease reached 72.55%, significantly higher than that of TC, HDL-C, and LDL-C (all $P < 0.05$). There were no significant differences between the abnormal rate of TBA and TG in patients with coronary heart disease ($P > 0.05$, **Table 2**).

Correlation analysis of TBA and influencing factors of coronary heart disease

Pearson's linear correlation analysis showed that TC, TG, and LDL-C levels were positively correlated with TBA expression levels, but negatively correlated with HDL-C expression levels (all $P < 0.05$, **Figure 2**).

Logistic multivariate regression analysis of coronary heart disease

With or without coronary heart disease was defined as a dependent variable. Smoking, hypertension, diabetes, hyperlipidemia, and TBA were used as independent variables. Multivariate logistic regression analysis was performed in the previous situation (α level = 0.05). Results showed that all factors mentioned above were included as independent variables of the regression equation as risk factors for occurrence of coronary heart disease (**Table 3**).

Discussion

In recent years, with an increase in the intake of lipids and bad living habits, the number of patients with coronary heart disease has increased significantly. It seriously affects the quality of life of patients, increasing the medical burden. Coronary heart disease-related studies have confirmed that the disease is related to genetics, living environment, poor living habits, and other factors, especially after the intake of a large amounts of lipids [16, 17]. These factors will increase the gastrointestinal glycolysis burden, resulting in excess nutrients. This leads to bile acid and other metabolic disorders, elevating blood lipids. Malondialdehyde, produced by abnormal oxidative metabo-

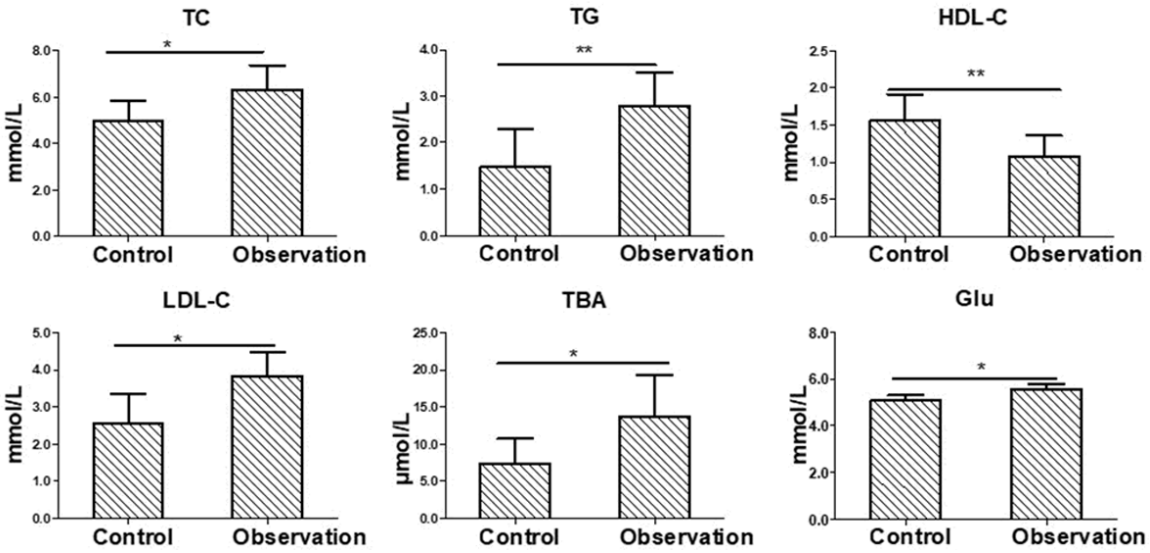

Figure 1. Comparison of biochemical indicators between the two groups (*P < 0.05, **P < 0.01) TC, total cholesterol; TG, triacylglycerol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; Glu, glucose; TBA, total bile acid.

Table 2. The rate of TBA and dyslipidemia in patients with coronary heart disease

Item	TG	TC	HDL-C	LDL-C	TBA
Abnormal number of cases (n)	75	61	42	48	74
Abnormal rate (%)	73.53	59.80	41.18	47.06	72.55
χ^2	0.025	4.861	20.464	12.745	
P	0.875	0.028	< 0.001	< 0.001	

Note: *P* value indicates the comparison between abnormal number of abnormal indicators and abnormal number of TBA. TC, total cholesterol; TG, triacylglycerol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TBA, total bile acid.

lism of fat, can easily destroy the lipid bilayer of vascular wall epithelial cells, causing local vascular disease [18, 19].

The decomposition of lipid molecules can produce metabolites that adhere to the blood vessel walls to form foreign antigens, thereby stimulating the body's immune organs to cause local autoimmune reactions. This damages the integrity of the vessel wall [20]. Therefore, abnormal lipid metabolism and vascular structural damage are the main causes of local atherosclerotic artery atherosclerosis. Atherosclerosis of the arteries will aggravate the agglutination of platelets, leading to local vascular insufficiencies. Lesions occurring in the aorta and coronary arteries may induce coronary heart disease in patients [21, 22].

TC and LDL-C levels have received a lot of attention. However, despite factors, such as high cholesterol diets and increased endogenous synthesis, an abnormal metabolism of cholesterol can cause increases in TC and LDL-C levels, compensating for the rising levels of cholesterol in the human body [23]. For the determination of cholesterol metabolism, analysis is mainly based on bile acid content of the intermediate metabolite. Bile acid is an effective regulating substance in maintaining bile solubility. The structure of cholesterol is stabilized by the dissolution of bile acids. Secretion of bile acids in healthy bodies can effectively maintain the dissolution of cholesterol and other lipids in the blood and bile. When metabolic abnormalities interfere with bile acid secretion, this will indirectly lead to hyperlipidemia in the blood, caused by high cholesterol. Clinical studies have confirmed that approximately one-third of human TCs are metabolized in the form of bile acids [24]. Therefore, there is a close correlation between the metabolism of blood lipids and bile acids. Once metabolic disorders of fat occur, the anabolism of TBA will also be abnormal.

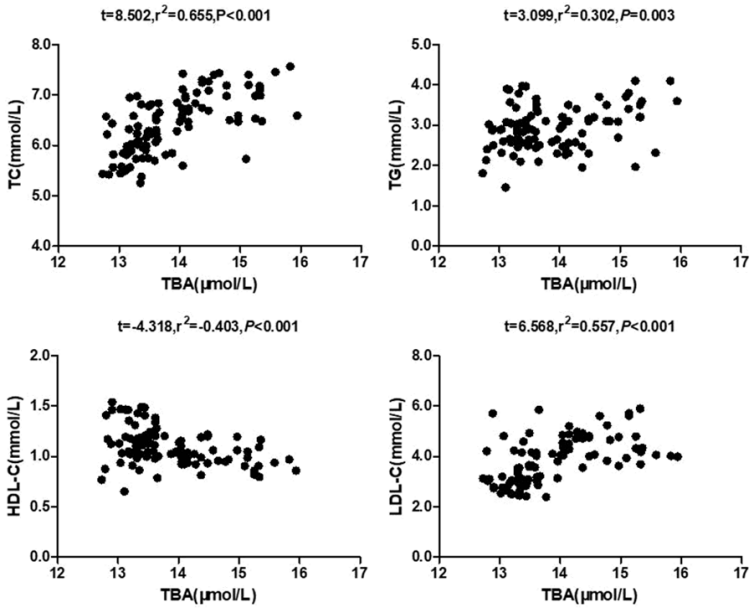

Figure 2. Correlation analysis of TBA and influencing factors of coronary heart disease TC, total cholesterol; TG, triacylglycerol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TBA, total bile acid.

Table 3. Logistic multivariate regression analysis of coronary heart disease

Index	B	SE	Wald	OR	95% CI	P
Smoking	2.069	0.893	5.374	7.918	1.377, 45.530	0.020
Hypertension	2.676	0.870	9.454	14.524	2.638, 79.954	0.002
Diabetes	1.882	0.872	4.653	6.564	1.188, 36.275	0.031
Hyperlipidemia	2.369	0.867	7.475	10.690	1.965, 58.422	0.006
TBA	1.677	0.825	4.133	5.347	1.062, 26.919	0.042

Note: SE: standard error; Wald: Wald test; OR: odd ratio; CI: confidence interval; TBA, total bile acid.

Results of the current study showed that the observation group, with severe coronary heart disease, had significantly higher blood TC, TG, LDL-C, TBA, and Glu levels than the control group. HDL-C levels were significantly lower than those in the control group (all $P < 0.05$). The major cause of differences in the above indicators between the two groups is that polyunsaturated fatty acids and steroid compounds can activate farnesoid X receptor (FXR). This can further activate expression of nuclear receptor small heterodimer partner (SHP). The SHP receptor can then react with liver receptor homolog-1 (LRH-1, as CYP7A1 trans-activator), which inactivates cytochrome P450 7A1 and increases bile acid levels [25]. Current studies have shown that bile acids can also affect the synthesis of fatty acids, triglycerides, and low-density lipoproteins via FXR, SHP, and Liver X Receptor (LXR) [25, 26]. Results showed that the abnormal rate of TBA in patients with coronary heart disease was 72.55%, close to the abnormal rate of TG. Moreover, the abnormal rate of TBA was significantly higher than that of TC, HDL-C, and LDL-C (all $P < 0.05$).

Therefore, TBA abnormalities may be the cause of lipid metabolism disorders in coronary heart disease. Decreasing levels of TBA in serum may be beneficial to other indicators, helping them to return to the normal range. In addition, Pearson's linear correlation analysis results showed that TC, TG, and LDL-C levels were positively correlated with TBA expression levels, but negatively correlated with HDL-C expression levels (all $P < 0.05$). TBA can also be used as an endogenous inhibitor of 11β-hydroxysteroid dehydrogenase-2 (11β-OHSD), which is more common in the study of the pathogenesis of hypertension [27]. Moreover, 11β-OHSD can rapidly catalyze the conversion of cortisol to bioactive corticosteroids, ensuring aldosterone specific binding with the mineralocorticoid receptors. If 11β-OHSD is deficient, cortisol will compete with mineralocorticoid receptors. This may lead to aldosterone-like reactions and hypertension [28]. Present results also confirmed that smoking, hypertension, diabetes, hyperlipidemia, and TBA are risk factors for occurrence of coronary heart disease. Present results are consistent with previous reports [29].

However, the number of patients involved in the current study was relatively small. Most patients had received prior drug treatment. These factors may have affected the accuracy of results. The patients were not regularly followed-up. Thus, this study could not obtain rel-

evant biochemical indicators after conditions improved. Therefore, present research results require further confirmation. Future studies will follow-up patients for at least 2 years, exploring signal pathways and molecular mechanisms involved in the occurrence of coronary heart disease, aiming to provide a new way for prevention and treatment of coronary heart disease.

In conclusion, patients with coronary heart disease usually have glucose and lipid metabolism disorders. Bile acids could respond well to lipid metabolism in patients and show correlation with TC, TG, HDL-C, and LDL-C levels.

Disclosure of conflict of interest

None.

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