【 ORIGINAL ARTICLE 】

Influence of Serum Cholinesterase Levels on Patients Suspected of Having Stable Coronary Artery Disease

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Abstract:

Objective The serum cholinesterase (ChE) level has been used for the evaluation of the nutritional status in daily practice. It has been reported that the serum ChE level is significantly more elevated in patients with three-vessel coronary disease than in normal subjects. Thus, the aim of this study was to assess the influence of serum ChE levels in patients suspected of having stable coronary artery disease (CAD).

Methods The relationship between myocardial ischemia and the serum ChE levels was evaluated in 559 consecutive patients suspected of having stable CAD without a history of cardiovascular disease admitted to our hospitals to undergo coronary angiography.

Results This study revealed that, in patients suspected of having stable CAD, 1) the frequency of myocardial ischemia was significantly increased in accordance with the serum ChE levels (p<0.001); 2) higher ChE levels were associated with a higher body mass index (p<0.001) and the co-existence of dyslipidemia (p< 0.001), including higher values of low-density lipoprotein-cholesterol (p<0.001) and triglycerides (p<0.001) and serum albumin (p<0.001), as well as a younger age (p<0.001); 3) the specificity and sensitivity of myocardial ischemia were 0.599 and 0.658 at the ChE level of 286 IU/L, respectively; and 4) an increased serum ChE (OR=1.66, p<0.001) was an independent risk factor for myocardial ischemia, in patients suspected of having stable CAD.

Conclusion The serum ChE level may be an important diagnostic biomarker in patients suspected of having stable CAD.

Key words: cholinesterase, coronary artery disease, myocardial ischemia

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Introduction

Cholinesterase (ChE) is an enzyme found in hepatocytes and is well-known to be a marker of liver dysfunction (1). The serum ChE level has been used to evaluate nutritional status in daily practice (2), and it is elevated under conditions of a fatty liver, obesity (3-5), and diabetes mellitus (6). A reduced serum ChE level has recently been reported to be a useful prognostic marker for predicting adverse outcomes in patients with heart failure (7, 8). Furthermore, it has been reported that the serum ChE level is significantly more elevated in patients with severe myocardial ischemia with three-vessel coronary disease than in normal subjects (9). However, the relationship between the ChE levels and suspicion of stable coronary artery disease (CAD) remains unclear. The present study therefore assessed the influence of the serum ChE level on patients suspected of having stable CAD.

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Materials and Methods

Study population and laboratory analyses

This study was approved by the institutional review committee and ethics review board of our hospitals. From 2009 to 2014, 559 consecutive patients (340 men and 219 women with a mean age of 71.6±10.9 years old) suspected of having stable CAD in our hospitals without a history of cardiovascular disease, including acute coronary syndrome (ACS), old myocardial infarctions (OMI), vasospastic angina (VSA), aortic dissections and aneurysms, aortic stenosis (AS), arteriosclerosis obliterans (ASO), and congestive heart failure, who were admitted to our hospitals to undergo coronary angiography (CAG) were evaluated. Patients with liver dysfunction, including a fatty liver, alcoholic liver damage, liver cirrhosis, hepatocellular carcinoma, other cancers, malnutrition [body mass index (BMI) less than 18] that affected the blood ChE level, nephrotic syndrome, hyperthyroidism, rheumatoid arthritis (RA), and renal dysfunction [serum creatinine (s-Cr) ≥1.5 mg/dL] who who had undergone hemodialysis were excluded. The ChE levels were measured by the p-hydroxi-benzoil choline method (10). All patients had their history recorded and underwent a physical examination and laboratory analysis. All patients had symptoms, including chest pain/discomfort, dyspnea, etc.

The evaluation of coronary artery lesions by CAG and the detection of myocardial ischemia

The coronary lesions were evaluated in all patients who underwent CAG. Patients with severe coronary stenosis (>75%) were evaluated for myocardial ischemia before or after CAG. To evaluate the myocardial ischemia, they underwent examinations combined with exercise stress testing, ^{201}Tl-schintigraphy, and/or fractionated flow reserve (FFR) measurements, as previously described (11). Myocardial ischemia was defined as positive exercise stress testing, ^{201}Tl-schintigraphy, and/or FFR measurements.

Statistical analyses

The numerical results are expressed in the text as the mean ± standard deviation. If the data showed a normal distribution, we analyzed the values by Student's *t*-test and Pearson's correlation coefficient, and if data showed a non-normal distribution, we analyzed the values with Wilcoxon's rank-sum test and Spearman's rank correlation coefficient. Comparisons among four groups were performed using the chi-square test for categorical variables and a one-way analysis of variance for continuous variables. A logistic regression analysis was performed with continuous variables according to the quartiles of the serum ChE levels. The sensitivity and specificity of myocardial ischemia associated with ChE were evaluated by the receiver-operating characteristic (ROC) curve analysis. A multivariate logistic regression analysis was carried out to examine the independent

factors of CAD. A p value of <0.05 was considered to indicate statistical significance. All analyses were performed with the SPSS v22.0 software program for Windows (IBM Japan, Tokyo, Japan).

Results

Patients' characteristics, laboratory analysis findings, and the relationship between the serum ChE levels and prevalence of myocardial ischemia

Myocardial ischemia was detected in 275 patients by examinations combined with CAG, exercise stress testing, ^{201}Tl-schintigraphy, and/or FFR measurements. The serum ChE level (315.8±87.6 vs. 267.4±83.3 IU/L; p<0.001) was significantly higher in the ischemic (IS) group than in the non-ischemic (N-IS) group (Supplementary material). Therefore, the patients were divided into 4 groups [low (<234 IU/L; n=138), low-normal (234 to <292 IU/L; n=141), high-normal (292 to <345 IU/L; n=138), and high (≥345 IU/L; n =142) groups] according to the quartiles of the serum ChE levels, and the clinical background was compared (Table 1). There were no significant differences in the prevalence of men (p=0.598), co-existence of hypertension (p=0.835) or diabetes mellitus (p=0.169), the prevalence of the internal use of renin-angiotensin system inhibitors (p=0.964) or beta-blockers (p=0.053), or the aspartate transaminase (AST) (p= 0.069), alanine transaminase (ALT) (p=0.200), γ-glutamyl transpeptidase (γ-GTP) (p=0.168), total bilirubin (p=0.071), high-density lipoprotein (HDL)-cholesterol (p=0.488), highly sensitive C-reactive protein (hs-CRP) (p=0.302), and HbA1c (p=0.378) values among the 4 groups (Table 1).

However, the prevalence of a younger age (p<0.001), higher BMI (p<0.001), co-existence of dyslipidemia (p< 0.001) and current smoking (p=0.038), prevalence of the internal use of statins (p<0.001), number of diseased vessels (single- or multi- vessel disease) (p<0.001), and albumin (p< 0.001), low-density lipoprotein (LDL)-cholesterol (p<0.001), and triglyceride (p<0.001) values were significantly increased in accordance with the serum ChE levels (Table 1). Furthermore, the serum creatinine (S-Cr) (p<0.020) value was significantly decreased in accordance with the serum ChE levels (Table 1). Myocardial ischemia was also significantly increased in accordance with the serum ChE levels (p<0.001) (Fig. 1).

The ROC curve analysis of cholinesterase level is shown in Fig. 2. The specificity and sensitivity of myocardial ischemia were 0.599 and 0.658, respectively, at the ChE level of 286 IU/L. The area under the curve (AUC) and 95% confidence interval of the AUC were 0.659 and 0.614-0.704, respectively. Thus, a ChE ≥286 IU/L may be an important predictor of myocardial ischemia in patients suspected of having stable CAD.

Table 1. Patient Characteristics.

	Low (n=138)	Low-normal (n=141)	High-normal (n=138)	High (n=142)	p value
Male	90 (66%)	82 (58%)	84 (61%)	82 (58%)	0.598
Age (years)	77.0±11.3	76.0±9.1	70.0±10.0	68.0±11.1	<0.001
Body mass index (kg/m^2)	23.0±3.1	23.0±3.1	24.0±2.8	24.0±3.1	<0.001
Co-existence					
Hypertension	82 (60%)	87 (62%)	86 (63%)	89 (63%)	0.835
Dyslipidemia	26 (19%)	52 (37%)	52 (38%)	63 (45%)	<0.001
Diabetes mellitus	22 (16%)	11 (8%)	16 (12%)	20 (14%)	0.169
Current smoker	27 (20%)	30 (21%)	30 (22%)	34 (24%)	0.038
Medication					
ACE-I / ARBs	47 (34%)	46 (33%)	44 (32%)	47 (33%)	0.964
Statins	20 (15%)	40 (28%)	48 (35%)	55 (39%)	<0.001
β-blockers	17 (12%)	17 (12%)	6 (4%)	11 (8%)	0.053
Laboratory analysis					
Albumin (g/dL)	3.77±0.51	3.89±0.42	4.10±0.33	4.24±0.41	<0.001
Serum creatinine (mg/dL)	0.99±0.74	0.91±0.28	0.82±0.22	0.86±0.67	0.020
AST (IU/L)	27±18	28±17	23±8	24±12	0.069
ALT (IU/L)	22±20	21±13	20±8	23±13	0.200
γ-GTP (IU/L)	40±42	41±47	32±25	37±31	0.168
Total bilirubin (mg/dL)	0.74±0.44	0.64±0.32	0.60±0.34	0.56±0.26	0.071
LDL-cholesterol (md/dL)	104.0±34.2	109.0±27.2	123.5±29.9	127.0±34.1	<0.001
Triglyceride (mg/dL)	96.0±48.6	100.0±72.5	101.0±70.6	151.0±103.3	<0.001
HDL-cholesterol (mg/dL)	52.0±14.0	56.0±15.0	54.5±14.1	53.0±12.2	0.488
Highly sensitive C-reactive protein (mg/dL)	0.29±0.62	0.30±0.53	0.30±0.48	0.31±0.58	0.302
HbA1c (NGSP; %)	6.0±1.3	5.8±0.6	5.7±0.7	6.1±1.0	0.378
Number of diseased vessels					
Single-vessel disease	21 (15%)	35 (25%)	44 (32%)	49 (35%)	<0.001
Multi-vessel disease	14 (10%)	31 (22%)	35 (26%)	43 (56%)	

Low : ChE<234 IU/L, Low-Normal : 234 ≤ ChE<292 IU/L, High-Normal : 292 ≤ ChE<345 IU/L, High : 345 ≤ ChE IU/L. ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, AST: aspartate transaminase, ALT: alanine transaminase, γ-GTP: γ-glutamyl transpeptidase, LDL: low density lipoprotein, HDL: high density lipoprotein, NGSP: national glycohemoglobin standardization program
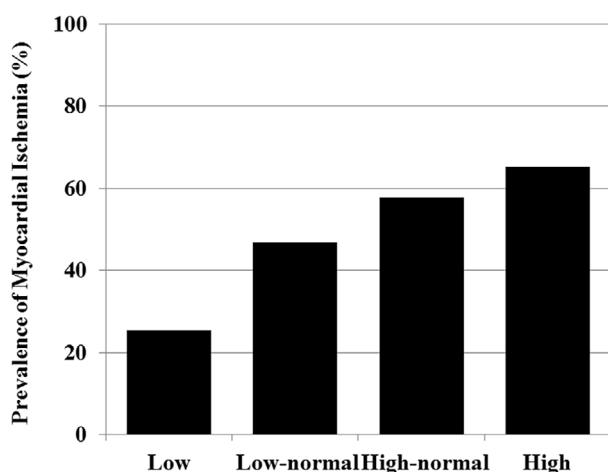

Figure 1. The prevalence of myocardial ischemia according to the quartiles of the serum cholinesterase (ChE) levels. The Low, Low-normal, High-normal, and High groups had serum ChE levels of <234 IU/L (n=137), 234 to <292 IU/L (n=141), 292 to <345 IU/L (n=137), and ≥ 345 IU/L (n=141), respectively. The prevalence of myocardial ischemia significantly increased with the serum ChE level (p<0.001).
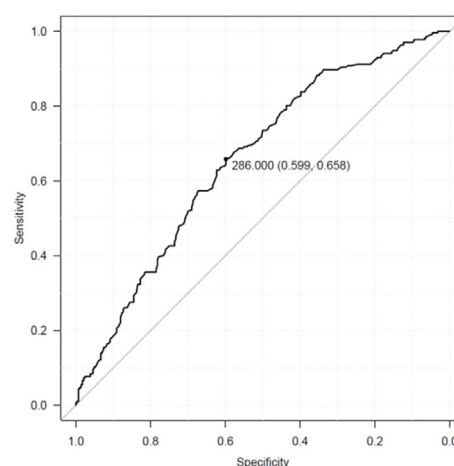

Figure 2. The receiver-operating characteristic curve analysis of the cholinesterase (ChE) level. The specificity and sensitivity of myocardial ischemia were 0.599 and 0.658, respectively, at a ChE level of 286 IU/L.

Table 2. Univariate and Multivariate Analysis.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Male	2.49 (1.75-3.54)	<0.001	2.49 (1.75-3.54)	<0.001
Age (years)	0.97 (0.96-0.99)	0.001	0.99 (0.98-1.02)	0.943
Body mass index (kg/m^2)	1.14 (1.07-1.20)	<0.001	1.01 (0.71-1.73)	0.745
Co-existence				
Hypertension	1.15 (0.81-1.62)	0.432	1.11 (0.71-1.73)	0.642
Dyslipidemia	1.83 (1.29-2.61)	0.001	1.46 (0.92-2.32)	0.107
Diabetes mellitus	1.76 (1.06-2.95)	0.030	1.76 (0.92-3.36)	0.085
Current smoker	2.55 (1.67-3.89)	<0.001	2.09 (1.22-3.59)	0.008
Laboratory analysis				
Cholinesterase (IU/L)	1.72 (1.47-2.02)	<0.001	1.66 (1.35-2.05)	<0.001
Albumin (g/dL)	1.72 (1.15-2.57)	0.009	1.05 (0.57-1.93)	0.874
Serum creatinine (mg/dL)	0.87 (0.62-1.22)	0.420	0.71 (0.35-1.43)	0.334
AST (IU/L)	0.99 (0.98-1.00)	0.188	1.01 (0.98-1.03)	0.589
ALT (IU/L)	1.00 (0.99-1.01)	0.668	0.99 (0.96-1.02)	0.385
γ-GTP (IU/L)	1.00 (0.99-1.00)	0.849	0.99 (0.96-1.01)	0.358
Total bilirubin (mg/dL)	0.44 (0.26-0.77)	0.004	0.41 (0.20-0.83)	0.013
LDL-cholesterol (md/dL)	1.00 (0.99-1.01)	0.132	1.00 (0.99-1.01)	0.608
Triglyceride (mg/dL)	1.01 (1.00-1.01)	<0.001	1.00 (0.99-1.01)	0.278
HDL-cholesterol (mg/dL)	0.97 (0.96-0.99)	<0.001	0.98 (0.96-0.99)	0.036
Highly sensitive C-reactive protein (mg/dL)	0.93 (0.66-1.32)	0.691	0.98 (0.68-1.42)	0.361
HbA1c (NGSP; %)	1.18 (0.84-1.65)	0.347	1.20 (0.87-1.68)	0.079

OR: odds ratio, CI: confidence interval, AST: aspartate transaminase, ALT: alanine transaminase, γ-GTP: γ-glutamyl transpeptidase, LDL: low density lipoprotein, HDL: high density lipoprotein, NGSP: national glycohemoglobin standardization program

Independent risk factors of myocardial ischemia in patients with stable CAD

The independent predictors of myocardial ischemia were determined using a logistic regression analysis. A multivariate analysis with all of the significant single variable factors of myocardial ischemia based on the results of the univariable analysis and after adjusting for the age and sex was performed (Table 2). As a result, a high prevalence of men (OR=2.49, p<0.001), increased serum ChE (OR=1.66, p<0.001), decreased T-bil (OR=0.41, p=0.013), and decreased HDL-cholesterol (OR=0.98, p=0.036) were found to be independent risk factors of myocardial ischemia.

Discussion

This study revealed that, in patients suspected of having stable CAD, 1) the serum ChE level (315.8±87.6 vs. 267.4±83.3 IU/L; p<0.001) was significantly higher in the IS group than in the N-IS group (Supplementary material); 2) the frequency of myocardial ischemia and the number of diseased vessels significantly increased in accordance with the serum ChE levels (p<0.001) (Fig. 1, Table 1); 3) higher ChE levels were associated with a higher BMI (p<0.001) and the co-existence of dyslipidemia (p<0.001), including higher values of LDL-cholesterol (p<0.001) triglycerides (p<0.001), and serum albumin (p<0.001), as well as a younger age (p<0.001); 4) the specificity and sensitivity of myocardial ischemia were 0.599 and 0.658 at the ChE level of 286 IU/L, re-

spectively (Fig. 2); and 5) a high prevalence of men (OR=2.49, p<0.001), current smokers (OR=2.09, p=0.008), increased serum ChE (OR=1.66, p<0.001), decreased T-bil (OR=0.41, p=0.013), and decrease HDL-cholesterol (OR=0.98, p=0.36) were independent risk factors of myocardial ischemia in patients suspected of having stable CAD. Male gender and cigarette smoking are well-known major coronary risk factors (12). Furthermore, a decreased T-bil and HDL-cholesterol level are also well-known coronary risk factor in patients with diabetes mellitus (13).

ChE and common conditions/diseases

ChE is a well-known diagnostic biomarker of liver dysfunction and the nutritional state (2, 14). Its activity in men is commonly higher than that in women and gradually decreases with age (14). These findings were compatible with the finding that the ChE levels in younger patients were significantly higher than those in older patients (Table 1) in this study. Furthermore, the ChE level is reportedly closely related to common conditions/diseases, including obesity (4), diabetes mellitus (6), and dyslipidemia (3, 15). Its activity is increased in cases of obesity, hypernutrition, and hypercholesteroremia (3, 4, 6). These findings were also compatible with the finding that the ChE level had a positive correlation with obesity (BMI), dyslipidemia (including LDL-cholesterol), and the triglyceride levels and had a negative correlation with the HDL-cholesterol level (Table 1). Obesity, diabetes mellitus, and dyslipidemia are well-known major coronary risk factors. In this study, the rate of myo-

cardial ischemia was significantly increased in accordance with the serum ChE levels (p<0.001) (Fig. 1). Thus, the serum ChE levels may reflect and be connected to the major coronary risk factors of obesity (BMI), diabetes mellitus, LDL-cholesterol levels, and triglyceride levels and act as a major coronary risk factor itself causing myocardial ischemia.

A recent report showed that intensive lipid-lowering therapies could decrease the serum ChE levels by way of the LDL-cholesterol levels (16). However, in this study, there were no significant differences in the LDL-cholesterol levels between the IS and the N-IS groups (Supplementary material), even though the ChE level was higher in the IS group than in the N-IS group. Because the prevalence of internal use of statins was significantly higher in the IS group than in the N-IS group (38% vs. 22%; p<0.001) (Supplementary material), the LDL-cholesterol levels may have been suppressed by statins in the IS group. In addition, the ChE level in the IS group may also have been suppressed by statins, possibly explaining why the ChE level in the IS group was higher. Furthermore, it has been reported that the serum ChE levels have a negative correlation with the concentration of adiponectin (17), which is recognized as an important factor for preventing the progression of atherosclerosis and cardiovascular events in patients with diabetes mellitus (18).

Diagnostic biomarkers of ChE for myocardial ischemia in patients suspected of having stable CAD

Recently, reduced serum ChE levels have been reported as a useful prognostic marker for the prediction of an adverse outcome in patients with heart failure (7, 8). However, the present study revealed that a higher serum ChE level was an independent risk factor of myocardial ischemia. Thus, the serum ChE level may be a unique prognostic and diagnostic biomarker of cardiovascular disease. Regarding the assessment of the serum ChE levels in daily practice, 1) this is a very common inspection worldwide, 2) the measurement system is already well established, 3) such evaluations are covered by medical health insurance and come with a low cost, and 4) its circadian variation is very low (19). As such, the serum ChE level may be an important, feasible, useful, and convenient diagnostic biomarker for patients suspected of having stable CAD. Thus, physicians should be aware of the condition when examining patients suspected of having stable CAD, especially in the presence of a high ChE level exceeding 286 IU/L, which may be an extremely important risk factor for the progression of cardiovascular events in patients suspected of having stable CAD.

Limitations of the study

Our study was limited by its retrospective design and single-center setting. Although high levels of LDL-cholesterol and serum creatinine and co-existence of diabetes mellitus are known to be important predictors of CAD, they were not found to be independent predictors in this study. This study enrolled symptomatic patients only, and so the sample size was very small, and the prevalence of internal use of statins was significantly higher in the IS group than in the N-IS group (38% vs. 22%; p<0.001) (Supplementary material). Thus, there may have been some bias in the patient population that affected the results. In addition, myocardial ischemia was defined based on positive results of exercise stress testing, ^{201}Tl-schintigraphy, and/or FFR measurements in this study. However, the sensitivity of exercise stress testing was not high. Furthermore, we were unable to clarify whether or not ChE inhibition prevented the onset and progression of cardiovascular events, including myocardial ischemia, and whether or not ChE inhibitors, which are widely used for managing dementia, increased cardiovascular events, including myocardial ischemia. Thus, whether or not our results can be reproduced in prospective, multi-center trials including a larger number of patients should be determined in further studies.

Conclusion

The serum ChE level may be an important, feasible, useful, and convenient diagnostic biomarker in patients suspected of having stable CAD.

The authors state that they have no Conflict of Interest (COI).

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