Serum Non–High-Density Lipoprotein Cholesterol Is Negatively Correlated With the Severity of Depressive Disorder

Xin Guo, MM, Jing Wang, MB,† Jingjuan Pang, MM,‡ Yueying Lu, MM,* Shaobo Lv, MD,§ Ning Wang, MM,* and Jie Yuan, MD||*

Abstract:

Background: The aim of this study was to investigate the serum non–high-density lipoprotein cholesterol (non-HDLC) levels of first-episode, drug-naive depressive patients and the correlative factors.

Methods: The study group comprised 308 subjects including 150 drug-naive patients with first-episode depressive disorder and 158 control subjects diagnosed in the Affiliated Kailuan Mental Health Center, North China University of Science and Technology, Tangshan, Hebei, China, from June 2014 to November 2015. The total cholesterol, triglyceride, HDLC, and low-density lipoprotein cholesterol were measured, whereas the depressive symptoms were tested by using the Self-rating Depression Scale (SDS). The statistical analysis was performed by independent-samples *t* test and 1-way analysis of variance, as well as partial correlation analysis and stepwise multiregression analysis.

Results: The significant difference was observed in serum non-HDLC of depressive patients compared with control group. Furthermore, there were remarkable differences of non-HDLC levels in sex, age, educational background, and depression severity. Partial correlation analysis indicated SDS standard scores were negatively correlated with total cholesterol, triglyceride, low-density lipoprotein cholesterol, and non-HDLC, suggesting SDS standard scores negatively forecast serum non-HDLC levels according to stepwise multiregression analysis.

Conclusions: Depression was associated with non-HDLC level, suggesting that the risk of cardiovascular disease in depressive patients should be focused on.

Key Words: cardiovascular disease, depressive disorder, non–high-density lipoprotein cholesterol

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Depression is a common, affective disorder that is mainly featured with prominent and persistent low emotional state, affecting approximately 0.35 billion of the global population.[1,2] The outstanding clinical manifestation is emotional disorder accompanied by cognitive deficit that is characterized by executive dysfunction.[3] The World Health Organization has predicted that depression will become the second burden of disease globally by 2020, ranking behind ischemic heart disease.[4] In some developed regions such as the United States, depression might be the primary leading cause of the economic burden of disease.[5] In addition, in China, depression morbidity has been estimated to be at least 20.1%.[6]

Depressive disorder is considered to be the consequence of interactions of various biological, social, and psychological factors. A recent study has reported that depression is associated with the incidence of atherosclerosis that is the pathological basis of coronary heart disease, ischemic stroke, and atherosclerotic cardiovascular disease (ASCVD).[7] Furthermore, dyslipidemia featured with elevated low-density lipoprotein cholesterol (LDLC) or total cholesterol (TC) levels is a major risk factor for the progression of ASCVD; consequently, blood lipid management, which normally consists predominantly of cholesterol levels adjustment, is one of the key methods to decrease the risk of ASCVD.[8] It is absolutely true that LDLC treat-to-goal approaches appear to be a great way to optimize lipid-modifying therapy to prevent ASCVD.

However, increasing evidence has displayed that serum non–high-density lipoprotein cholesterol (non-HDLC) levels comprehensively reflect the concentration of total atherogenic cholesterol, which in turn play important roles in the occurrence and development of atherosclerosis.[9] Zhu et al[10] have found that, in comparison with LDLC, serum non-HDLC levels are much more strongly related with atherogenic lipoprotein subfractions in patients with coronary artery disease, implying that non-HDLC levels might be better in evaluating the risk of cardiovascular disease (CVD). Thus, non-HDLC levels are also regarded as the primary target for the diagnosis and prevention of ASCVD, which might be more appropriate for lipid management setting. In addition, accumulating evidence has confirmed that serum non-HDLC levels are linked with subclinical atherosclerosis, suggesting that it has a great research value in the diagnosis of subclinical atherosclerosis.[11] Previous reports have demonstrated that non-HDLC levels function as a potential predictor for the early diagnosis, risk assessment, and prognosis of CVD and diabetes.[12,13] Nevertheless, there is rarely report about the relationship between depressive disorder and serum non-HDLC levels.

The present study aimed to examine and compare the serum non-HDLC levels of drug-naive and first-episode patients with depressive disorder with those of the control subjects. We also analyzed its latent related factors containing sex, age, educational background, and depression severity through further multiple comparisons. In addition, correlation analysis was conducted to recognize the relevance of serum lipid level and Self-rating Depression Scale (SDS) standard score of patients with depression, providing a novel idea and a theoretical principle for the pathogenesis and therapeutic strategies for depression.

MATERIALS AND METHODS

Participants

A total of 150 depressive patients were recruited from the Affiliated Kailuan Mental Health Center, North China University of

From the *Department of Neurology, Affiliated Hospital of North China University of Science and Technology; and †Department of Clinical Medicine, Tangshan Vocational and Technical College, Tangshan; ‡Department of Psychiatry, The Sixth Hospital of Hebei Province, Baoding; and §School of Psychology and ||Institute of Mental Health, North China University of Science and Technology, Tangshan, China.

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Reprints: Jie Yuan, MD, Institute of Mental Health, North China University of Science and Technology, No. 21 Bohai Avenue, Caofeidian New Town, Tangshan 063210, Hebei, China (e-mail: jie_yuan123456@163.com).

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Science and Technology, Tangshan, Hebei, China, diagnosed from June 2014 to November 2015. The inclusion criteria were as follows: (1) met the *Chinese Classification of Mental Disorders, Third Edition* (*CCMD-3*) criteria for depressive disorder, (2) no history of antipsychotic drug treatment, and (3) first episode with total course less than 3 years. Meanwhile, the general exclusion criteria were as follows: (1) a history of organic brain disease, CVD, gastrointestinal diseases, or renal diseases; (2) a history of other mental disorders; (3) taking lipid-lowering agents, diuretics, and oral contraceptive within 2 weeks; (4) pregnant and lactating women; and (5) a history of alcohol and drug abuse. In addition, 158 sex- and age-matched control subjects (male/female, 96/62), ranging in age from 34 to 60 years (mean ± SD, 47.02 ± 12.74), were recruited from health examination centers of North China University of Science and Technology Affiliated Hospital. All participants signed informed consent, and this study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. As the control subjects, 158 healthy volunteers' demographic data are shown in Table 1.

General Survey

Data of all patients were collected on sex, age, education (primary, junior, senior, university degrees, and above), occupation (unemployed, worker, farmer, student, leader, staff, medical personnel, and self-employed), marital status (spinsterhood, married, divorce, and widowed), course of disease, and a family history of any mental illness.

Measurement of Blood Cholesterol Levels

Five milliliters of venous blood samples was collected from all participants on an empty stomach for 12 hours followed by centrifugation to get the upper layer of the serum. Measurements of plasma lipid profile such as TC, triglyceride (TG), HDLC, and LDLC were determined by automatic biochemistry analyzer (Hitachi, Tokyo, Japan) using blood lipid detection kit (Beijing North Institute of Biological Technology, Beijing, China). Non-HDLC was calculated by the formula: non-HDLC = TC − HDLC.

Assessment of Depressive Symptoms

Zung's SDS was applied to measure the severity of depression of all patients according to previous reports.[14–16] The SDS was a 4-item scale ranking from 1 to 4, in which those with scores of 0.5 or less was considered as not depressed, scores from 0.5 to 0.59 as slightly to moderately depressed, scores between 0.6 and 0.69 as moderately to severely depressed, and scores of 0.70 or greater as extremely depressed. Total raw scores were expressed as cumulative scores of each item, whereas standard scores were represented as the integer portion of the product of total raw scores multiplied by 1.25. Moreover, the index of depression severity was the raw scores divided by 80, ranging from 0.25 to 1.0. The test was performed when patients were hospitalized and receiving treatment. Throughout the phase of initial drafting, each item in *CCMD-3* was compared with the corresponding item in the CCMD-2R, and the descriptive definitions were based on the clinical descriptions and diagnostic guidelines of the *International Classification of Diseases* (*ICD*) system. The diagnostic criteria also refer to the research criteria of *ICD-10* and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Therefore, we believed that despite differences in the diagnostic criteria the actual differences of the major depressive diagnosis for *CCMD-3* and *Diagnostic and Statistical Manual of Mental Disorders* or *ICD* were slight. In addition, *CCMD-3* was more suitable for Chinese patients.

TABLE 1. Demographics of Control Subjects

Variables		n
Sex	Males	88
	Females	70
Age, y	①≤30	19
	②31–40	29
	③41–50	46
	④51–60	37
	⑤≥61	27
Education	①Primary	17
	②Junior	59
	③Senior	58
	④College	24

Statistical Analysis

All data entry and analyses were conducted with SPSS version 17.0 (SPSS Inc, Chicago, Ill). Measurement data are expressed as means ± SD, whereas enumeration data are represented as number of cases and percent. Independent-samples *t* test and analysis of variance as well as least significant difference-t were performed to compare non-HDLC levels. The correlation between SDS standard scores and blood cholesterol levels was assessed by partial correlation analysis. The predictive effect of forecasting variables on non-HDLC levels was estimated by stepwise multiregression analysis. Statistical significance level was set at $\alpha = 0.05$.

RESULTS

Demographic Data

One hundred fifty patients with depressive disorder aged 18 to 77 years (mean ± SD, 45.81 ± 13.20 years) including 83 males (55.3%) and 67 females (44.7%) with 0 to 3 years (mean ± SD, 0.97 ± 1.12 years) of illness duration were included in this study. When patients were grouped by education levels, it was found that 16 (10.7%) received primary education, 56 (37.3%) received junior education, 55 (36.7%) received senior education, and 23 (15.3%) received college education. Subjects were classified into subgroups containing 90 workers (60%), 11 farmers (7.3%), and 30 teachers and medical personnel (20.0%), as well as 19 unemployed (12.7%), according to occupation. Marital status was classified into 3 groups: 11 single (7.3%), 122 married (81.3%), and 17 divorced or widowed (11.4%). Regarding family histories of mental illness, 24 patients (16.0%) have been reported to have a family history, whereas the remaining 126 ones (84. 0%) did not have any family history. In addition, patients with slight to moderate depression, moderate to severe depression, and major depression were 30 (20.0%), 63(42.0%), and 57 (38.0%), respectively.

Comparison of Non-HDLC Levels in Depressive Patients With Normal Subjects

Relative to the control group, patients with depression displayed significantly decreased serum non-HDLC, with 3.78 ± 1.05 and 3.45 ± 0.97 mmol/L, respectively ($P < 0.01$).

Comparison of Non-HDLC Levels of Depressive Patients in Demographic Variables

There were no significant differences of serum non-HDLC from patients with depression in illness duration, occupation, marital status, and family histories of mental illness (all $P > 0.05$). However,

significant differences were observed in sex, age, education background, and symptom severity (all $P < 0.05$). As shown in Table 2, multiple comparisons demonstrated that the non-HDLC levels were markedly increased in the 51- to 60-year age group as compared with those 50 years or younger and 61 years or older, in the low education group as compared with the high education group, and in patients with slight to moderate depression.

Correlation Analysis of SDS Score and Blood Cholesterol Levels

Partial correlation analysis showed that SDS scores of patients were negatively correlated with TC, TG, LDLC, and non-HDLC (all $P < 0.05$), but did not significantly correlate with HDLC ($P > 0.05$; Table 3), while keeping constant the other variances such as sex, age, and education background.

Multivariate Analysis

The following discrete variables were included as dummy variables: sex, education background, and age, as shown in Table 4, whereas stepwise multiregression analysis was used to estimate the relationship between sex, education background, age, and SDS scores (independent variables) and serum non-HDLC levels (dependent variable). The results indicated that the SDS standard score negatively forecast serum non-HDLC levels ($\beta = -0.682$, $P < 0.05$). Linear regression equation was non-HDLC levels = $-0.682 \times$ SDS standard score (Table 5).

DISCUSSION

Depression is a chronic psychiatric disorder with a high recurrence rate, leading to an increasing morbidity and mortality of CVDs and cerebrovascular diseases and severely affecting its prognosis.[1] The association between the emergence of depression and the increased proportion of calcified plaque coronary volume has been reported using coronary computed tomography angiography after modulation for demographics and other risk factors.[17] Similarly, Lee et al[18] found that depressive symptoms were observably correlated with carotid intima-media thickness in middle-aged or elderly women among 7554 Koreans with no history of CVD. These studies support a potential link between depression and atherosclerosis. Moreover, non-HDLC level is an all-around reflection of atherogenic lipid metabolism, which plays a decisive role in the developments of atherosclerosis.

TABLE 3. Correlation Analysis of Serum Lipid Level and SDS Standard Score in Depressive Patients

Serum Lipid Level, mmol/L	*r*	*P*
TC	−0.513	<0.001
TG	−0.244	0.003
HDLC	0.042	0.62
LDLC	−0.43	<0.001
Non-HDLC	−0.673	<0.001

In this study, the serum non-HDLC levels of male patients were slightly higher than those of females, whereas patients with relatively low degree of education had a comparatively high non-HDLC level. Meanwhile, the elevated non-HDLC levels were observed in patients aged 51 to 60 years compared with those of other age groups. Previous studies have provided evidence that abnormal non-HDLC level is a specific risk factor for the development of metabolic syndrome in males instead of females.[19] In a large study with 7825 adult participants older than 20 years from the United States, similar evidence showed that the mean age of participants with elevated non-HDLC (187.2 ± 1.4 mg/dL) was 52.9 years.[20] Nonetheless, there was some evidence inconsistent with our findings. For example, Dai et al[21] showed that females had a greater prevalence of high non-HDLC than did males in children and adolescents. Furthermore, a pooled analysis of lipid parameters demonstrated that postmenopausal women had higher levels of LDLC as well as TG and lower levels of HDLC compared with premenopausal women, resulting in the increased incidence of CVDs and cerebrovascular diseases. These unfavorable changes were associated with reduced estrogen level induced by ovarian failure leading to abnormal lipid metabolism.[22]

Our study found that patients with depression had lower levels of non-HDLC in comparison with the control subjects. Depression severity was negatively corrected with non-HDLC level. The reason we thought was depression improved the incidence of atherosclerosis, thereby reflecting the concentration of total atherogenic cholesterol, leading to the elevated serum non-HDLC levels. Park et al[23] showed that TG levels were negatively correlated with suicidal ideation; however, they did not measure serum non-HDLC levels. Kale et al[24] mentioned this correlation, but several

TABLE 2. Comparison of Serum Non-HDLC Level in Demographic Variables in Patients With Depression (Mean ± SD)

Factors		n		Non-HDLC, mmol/L	*P*	Multiple Comparisons
Sex	Male	83		3.61 ± 0.93	0.019	
	Female	67		3.24 ± 0.97		
Age, y	① ≤30	18		2.92 ± 0.67	0.012	① < ② < ⑤ < ③ < ④
	② 31–40	28		3.35 ± 0.78		
	③ 41–50	44		3.45 ± 1.07		
	④ 51–60	35		3.87 ± 1.03		
	⑤ ≥61	25		3.36 ± 0.88		
Education	① Primary	16		3.87 ± 0.92	0.027	① > ② > ③ > ④
	② Junior	56		3.63 ± 0.87		
	③ Senior	55		3.26 ± 0.91		
	④ College	23		3.17 ± 1.19		
Depression severity	Slight to moderate	30	SDS 55.07 ± 2.95	4.54 ± 0.88	<0.001	① > ② > ③
	Moderate to severe	63	67.14 ± 2.88	3.48 ± 0.57		
	Major	57	79.25 ± 6.43	2.84 ± 0.84		

TABLE 4. Sex, Education Level, and Age Dummy Variables in Patients With Depression

Original Variables		Dummy 1	Dummy 2	Dummy 3	Dummy 4	Dummy 5
Sex	Male*		0			
	Female		1			
Age, y	≤30	1	0	0		0
	31–40	0	1	0		0
	41–50	0	0	1		0
	51–60*	0	0	0		0
	≥61	0	0	0		1
Education	Primary*		0	0	0	
	Junior		1	0	0	
	Senior		0	1	0	
	College		0	0	1	

*Control of this variable.

studies showed opposite results. For example, Liang et al[25] demonstrated that elevated cholesterol and non-HDLC levels in Chinese cohort were associated with increased depressive symptoms. Similarly, Beydoun et al[26] found that high non-HDLC/HDLC levels were associated with increased depressive symptoms in a large cohort, particularly in females. Another study elucidated that increased non-HDLC levels were correlated with higher HAMD scores in acute ischemic stroke patients.[27] Moreover, major depressive patients with suicide attempts and suicidality had lower non-HDLC levels and higher HDLC levels.[28]

The present findings also indicated that patients with slight to moderate depression had higher serum non-HDLC levels, whereas the SDS standard scores were negatively correlated with non-HDLC levels. The reason we thought was depression improved the incidence of atherosclerosis, thereby reflecting the concentration of total atherogenic cholesterol, leading to the elevated serum non-HDLC levels. In addition, the results of stepwise multiple regression analysis showed that serum levels of non-HDLC were negatively predicted by standard scores of SDS, after controlling for sex, age, and degree of education. In other words, the higher SDS standard scores, the lower the non-HDLC levels. It has been proved that non-HDLC had a positive correlation with LDLC. Both of them were suitable as crucial predictors of CVDs and cerebrovascular diseases. In addition, non-HDLC seemed to be an alternative marker to LDLC because it was not influenced by TG levels.[29] Our study was directly supported by the results of Persons et al[30] showing that the decreased LDLC was associated with an elevated prevalence of depression.

The association of depressive symptom and non-HDLC levels might arise from functional differences of serotonin in genetics. As is well known, non-HDLC level is the remainder by subtracting HDLC from TC. In this study, a strong positive correlation between non-HDLC and TC was observed; however, the correlation between non-HDLC and HDLC was not statistically significant. Conformably, an inverse correlation between TC and depression has been reported according to a meta-analysis.[31] Troisi[32] has speculated that as a major myelin sheath component on the cytomembrane cholesterol plays a crucial role in the growth, function, and stability of synapses; thus, the reduction of TC on brain membranes induces the decreased viscosity of membrane lipids, thereby diminishing the binding affinity of 5-hydroxytryptamine receptor agonist, which eventually leads to depression resulting from a decreasing serotonin. This hypothesis has been supported by neuroendocrinology study indicating that TC levels are positively related with the function of 5-hydroxytryptamine receptor.[33] Some preliminary studies have further testified the relationship between TC and depression. For instance, Suna et al[34] showed that electroconvulsive therapy successfully enhanced the serum lipid levels containing TC, LDLC, and HDLC. It is necessary to continue further research on the complicated relation between function of central serotonin and blood lipid levels in basic and clinical aspects.

Limitation

Lipid-based etiology for some types of depressive illness is not focused on this study, and this section will be our next research emphasis.

Above all, the present study manifested that depressive symptom of patients with depression was correlated with non-HDLC levels, implying that the pathologic basis of atherosclerosis in patients with depression should be highly concerned contributing to eliminate latent risks of CVDs. Last but not least, the effect of pharmaceuticals on depressive symptoms and atherosclerosis should be taken into consideration during treatment for depression.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

TABLE 5. Stepwise Multiple Regression Analysis of Serum Non-HDLC Level in Depressed Patients With Different Predictive Variables

The Order of Input Variables	Multiple Correlation Coefficient	R^2	$\triangle R^2$	F	$\triangle$F	B	β
Intercept						7.993	
SDS standard scores	0.682	0.465	0.465	128.755*	128.755*	−0.066	−0.682

*$P < 0.001$.

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