

Change of Plasma Oxidized Low-Density Lipoprotein Level Predicts Clinical Outcome at 90 Days for Patients with Acute Ischemic Stroke

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Research Article

Keywords: oxidized low density lipoprotein, acute ischemic stroke, infarct volume, clinical outcomes

Posted Date: April 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-395099/v1>

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Abstract

Objectives: To investigate the relationship between change of plasma oxidized low-density lipoprotein (oxLDL) level and clinical outcomes in patients with acute atherosclerosis related ischemic stroke.

Methods: We recruited acute ischemic stroke patients within 3 days after onset consecutively. Plasma oxLDL level were measured on the second day after admission and before discharge. Initial stroke severity was assessed by the National Institutes of Health Stroke Scale(NIHSS) scores, and infarct volume was measured using diffusion weighted imaging (DWI) by ITK-SNAP software. Clinical outcomes were evaluated by neurological improvement at discharge and favorable functional prognosis at 90 days.

Results: 207 patients were enrolled into this study. Compared with mild change of oxLDL level group, patients with significant change oxLDL level group were more likely to have higher ratio of neurological improvement at discharge(55.07% vs 14.49%) and favorable functional prognosis at 90 days(91.30% vs 55.07%). The DWI volumes in patients with different oxLDL level change groups were no statistical difference. In multivariable logistic regression, the degree of oxLDL level change was related with neurological improvement at discharge and favorable functional prognosis at 90 days. Compared to patients with mild change of oxLDL level, patients with significant change were more likely to have neurological improvement at discharge(OR=7.21,95%, 3.09-16.80, $p < 0.01$) and favorable functional prognosis at 90 days (OR=6.67, 95%CI, 2.15-20.73, $p < 0.01$).

Conclusions: The degree of oxLDL level change is related to the neurological improvement at discharge and favorable functional prognosis at 90 days for patients with acute atherosclerosis related ischemic stroke, but not with infarct volume.

Introduction

Atherosclerosis is the most common pathological mechanisms of stroke[1]. Oxidized low-density lipoprotein (oxLDL) is the major product of lipid oxidative stress, with pro-inflammatory properties, has been identified to mediate vascular endothelial cell dysfunction, activate platelet and accelerate foam cell formation, resulting in the development of vulnerable atherosclerotic plaques eventually[1]. Therefore, oxLDL may be the trigger for atherosclerosis and contribute to clinical events as result[4-6]. Studies demonstrated that oxLDL in the acute phase was not only related to poor functional outcome after stroke[2, 7], but also can predict recurrent stroke in patients with minor stroke or transient ischemic attack independently, particularly atherosclerosis related ischemic stroke, namely in large-artery atherosclerosis subtype and small-artery occlusion subtype[8]. However, the level of oxLDL is fluctuant in circulation. Study showed that it increased to peak level at the third day, and decreased gradually to the premorbid state [9]. To date, previous studies just focused on oxLDL at the acute stage of stroke[7, 8, 10], only limited research has been conducted on relationship between the change of oxLDL level with the prognosis of stroke. For this purpose, we measured oxLDL level at different stages to investigate its change with the prognosis of stroke in patients with acute atherosclerosis related ischemic stroke.

Methods

Study Population

This study was approved by the ethics committee of Shanghai Fifth People's Hospital. Written informed consent was obtained from all the patients or their representatives. We enrolled prospectively acute ischemic stroke patients within 3 days after onset consecutively. According to the purpose of this study, only large artery atherosclerotic and small-artery occlusion cerebral infarction (In accordance with Trial of Org 10172 in Acute Stroke Treatment criteria[11]) were included into our analysis. Patients who met any one of the following criteria were excluded: history of stroke, no cerebral MRI, cardioembolism, other determined etiology cerebral infarction and undetermined etiology.

Basic Clinical Data Collection

Demographic and clinical data were collected on admission by neurologists face-to-face, including age, sex, hypertension, diabetes mellitus and other health conditions. Fasting venous blood samples to test for circulating ox-LDL level, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and other laboratory tests were obtained within 24 hours admission and before discharge.

DWI Volumes

We followed the methods of Yang et al. 2021[12]. All patients underwent multimodal MR imaging within 96 hours of admission. MR imaging examinations were performed using 3.0-tesla (Magnetom Skyra, Siemens, Germany). The imaging parameters were as follows: repetition time of 2800 milliseconds, echo time of 74 milliseconds, matrix number 220*220mm, voxel size 1.4*1.4*8mm³, interslice gap 0.8 mm, and 2 b values of 0 and 1,000 s/mm². Acute cerebral infarction lesions were defined as presence of increased signal on DWI, but with corresponding low signal on the apparent diffusion coefficient (ADC) maps. ITK-SNAP software (Version 3.8.0) was used to measure acute infarct volumes indicated by DWI[13] (<http://www.itksnap.org/pmwiki/pmwiki.php>). The images were independently rated by 2 blinded stroke neurologists (Chen Li and Xiaoli Yang). A subset of images were reviewed by them to assess inter-rater agreement, and inter-rater reliability was 0.88. The average infarct volume of two neurologists was used for analysis.

Outcome assessment

Initial stroke severity was assessed by the NIHSS scores at the time of presentation and at the time of discharge[14]. According to a common consensus of neurological practitioners, stroke severity was divided into three grade: mild, NIHSS score ≤ 4 ; moderate, $5 \leq \text{NIHSS} < 10$; severe, $\text{NIHSS} \geq 10$. Compared with the NIHSS score at the time of presentation, NIHSS of 0 or ≥ 4 points of remission at discharge was defined as neurological improvement[15], and ≥ 2 -point increase was defined as neurologic worsening[16]. modified Rankin scale (mRS) score was used to evaluate functional outcome at 90 days, where 0–2 was defined as a favorable outcome and 3–6 was defined as a poor outcome.

Measurement of circulating OxLDL

Human oxLDL ELISA Kit (Elabscience) was used to measure the ox-LDL directly in human fasting venous plasma samples obtained on the second day after admission and before discharge (10-14 days after stroke onset). The samples were centrifuged (2000g for 5 minutes) immediately after collection, and plasma samples were stored in -80 refrigerator. The assay was a sandwich ELISA and measurements were conducted according to the manufacturer's guidelines.

Statistical Analyses

SPSS 21.0 software was used for statistical analyses. According to the change of oxLDL difference, the patients were divided into three groups on average. For each demographic and clinical feature, normal distribution continuous variables were presented as mean \pm standard deviation, and abnormal distribution continuous variables were presented as median (interquartile range). Student t test or ANOVA for normally distributed parameters, Wilcoxon or Kruskal–Wallis test for nonparametric variables were used as appropriate. Categorical variables were expressed as frequency (percentage) and χ^2 test or Fisher exact test was used. The association between oxLDL level change and clinical outcome was performed by logistic regression. For all regression models, age, sex and variables showing a $p < 0.1$ on the respective univariate analyses were included into models. A p value 0.05 was considered significant.

Results

Baseline Characteristics of Study Patients

207 patients were included into this study. According to the change of oxLDL level difference, the patients were stratified into 3 groups on average: Δ tertile 1 ($\leq 33.33\%$, mild change), the difference ≤ 36.23 pg/mL; Δ tertile 2 (moderate change, $33.34\% - 66.66\%$), the difference was 36.23 pg/mL - 60.63 pg/mL; Δ tertile 3 (significant change, $\geq 66.67\%$), the difference ≥ 60.63 pg/mL. There were no significant differences in age, hypertension, diabetes mellitus, LDL-C and total cholesterol in patients with different oxLDL level change groups ($P > 0.05$). Patients with mild change of oxLDL level group were more likely to have a higher prevalence of tobacco use, but p value was 0.05 (Table 1).

Table 1. Demographic and baseline clinical characteristics of patients with different oxLDL changes group

	Δ tertile1(mild change)	Δ tertile2(moderate change)	Δ tertile3(significant change)	p value
	≤ 36.23 pg/mL	36.23 pg/mL -60.63pg/mL	≥ 60.63 pg/mL	
Age, y	65.04 \pm 12.17	65.97 \pm 10.88	68.74 \pm 10.20	0.13
Male, n (%)	51 \square 73.91 \square	45 \square 65.22 \square	46 \square 66.67 \square	0.50
Alcohol use, n (%)	21 \square 30.43 \square	14 \square 20.29 \square	10 \square 14.49 \square	0.07
Tobacco use, n (%)	34 \square 49.28 \square	20 \square 28.99 \square	26 \square 37.68 \square	0.05
History of disease, n (%)				
Diabetes Mellitus, n (%)	21 \square 30.88 \square	31 \square 44.93 \square	24 \square 34.78 \square	0.21
Hypertension, n (%)	52 \square 76.47 \square	55 \square 79.71 \square	50 \square 72.46 \square	0.61
TC, mmol/L	4.12 \pm 1.09	4.30 \pm 0.96	4.28 \pm 1.07	0.55
TG, mmol/L	1.34(0.84,1.82)	1.40(0.94,1.88)	1.32(1.02,1.93)	0.59
HDL-C, mmol/L	1.01(0.83,1.23)	1.00(0.84,1.30)	1.00(0.87,1.24)	0.97
LDL-C, mmol/L	2.69 \pm 1.04	2.74 \pm 0.85	2.84 \pm 0.91	0.63
Homocysteine, μ mol/L	14.45(10.50,19.10)	13.75(11.70,16.38)	15.10(11.30,18.60)	0.87

Clinical Course and Outcomes of Groups in Different oxLDL Level Change Groups

Comparisons of clinical course and outcome features between different oxLDL level change groups are presented in Table 2. Patients with significant change of oxLDL level (Δ tertile3) were more likely to have lower ratio of severe neurological function impairment on admission (14.49% vs 37.68%) and lower neurologic worsening at discharge(15.94% vs 46.38%) compared with patients with mild change group(Δ tertile1). Furthermore, with the gradual increase of oxLDL level difference, the proportion of good functional prognosis gradually increased(55.07% vs 84.06% vs 91.30%, $p < 0.01$). The median DWI volumes in patients with different oxLDL changes groups were 4.21cm³, 3.08 cm³, and 2.38 cm³ respectively, although presented reduced, no statistical difference(Table 2).

Table 2. Clinical Course and Outcomes of Groups in Different oxLDL Level Change Groups

	Δ tertile 1(mild change)	Δ tertile 2(moderate change)	Δ tertile 3(significant change)	p value
	≤ 36.23 pg/mL	36.23pg/mL-60.63pg/mL	≥ 60.63 pg/mL	
NIHSS Score at Admission (median)	6(2.5,8.5)	4(2,5)	3 \times 2,4 \times	<0.01
Neurological Impairment Severity				<0.01
Mild, NIHSS score ≤ 4	23(33.33)	28(40.58)	40(57.97)	
Moderate, NIHSS score5-9	20(28.99)	35(50.72)	19(27.54)	
Severe, NIHSS score ≥ 10	26(37.68)	6(8.70)	10(14.49)	
DWI Volumes(cm³)	4.21(1.17,9.58)	3.08(1.27,4.73)	2.38(1.59,8.68)	0.62
Median Onset-to-MRI time (hour)	74.20(52.05,99.00)	68.50(45.75,88.75)	66.00(32.25,97.00)	0.49
Clinical Response at Discharg				<0.01
Neurological Improvement	10 \times 14.49 \times	29 \times 42.03 \times	38 \times 55.07 \times	
No Significant Neurological Change	27 \times 39.13 \times	23 \times 33.33 \times	20 \times 28.99 \times	
Neurologic Worsening	32 \times 46.38 \times	17 \times 24.64 \times	11 \times 15.94 \times	
mRS score at day 90	1 \times 0,3 \times	1 \times 1,2 \times	1 \times 0,1 \times	<0.01
Favorable Functional Prognosis	38 \times 55.07 \times	58 \times 84.06 \times	63 \times 91.30 \times	<0.01

Association Between Different oxLDL Changes Groups and Clinical Outcomes

We investigated the association between different oxLDL level change groups and clinical outcomes. Change of oxLDL level was related with neurological improvement, neurologic worsening at discharge and favorable functional prognosis at 90 days. Compared to patients with mild change of oxLDL level, patients with significant change were more likely to have favorable functional prognosis at 90 days (OR=6.67, 95%CI, 2.15-20.73, p <0.01) and neurological improvement at discharge(OR=7.21,95%, 3.09-16.80, p <0.01), in addition, the possibility of neurologic worsening were also lower(OR=0.25,95%, 0.10-0.62, p<0.01). The neurological impairment severity on admission was correlated with neurologic worsening and favorable functional prognosis, but not with neurological improvement at discharge(Table 3).

Table3.Variables which were found independent predictors of clinical outcome in multivariate analysis

	Neurological Improvement		Neurologic Worsening		Favorable Functional Prognosis	
	Estimate (95% CI)	p value	Estimate (95% CI)	p value	Estimate (95% CI)	p value
Infarct volume((cm³)	—		1.04 [1.02,1.07]	<0.01	0.95 [0.92,0.98]	<0.01
Neurological impairment severity	—			0.03		<0.01
Mild(NIHSS score≤4)			0.45 [0.19,1.08]	0.07	11.75 [3.95,34.98]	<0.01
Moderate(NIHSS score5-9)			0.29 [0.12,0.73]	<0.01	6.24 [2.29,16.95]	<0.01
Severe(NIHSS score≥10)			Reference		Reference	
Quartiles of oxLDL change				0.01		<0.01
ΔTertile 1(mild change)	Reference	<0.01	Reference		Reference	
ΔTertile 2(moderate change)	3.97 [1.71,9.23]	<0.01	0.55 [0.25,1.25]	0.16	2.78 [1.05,7.42]	0.04
ΔTertile 3(significant change)	7.21 [3.09,16.80]	<0.01	0.25 [0.10,0.62]	<0.01	6.67 [2.15,20.73]	<0.01
Homocysteine			—		0.96 [0.92,1.00]	0.06
Male	0.51(0.26,0.98)	0.05	—		—	
LDL-C	1.44(1.02,2.04)	0.04	0.65 [0.44,0.96]	0.03	—	

Discussion

The major findings of our study were that the degree of oxLDL level change is related to the neurological improvement at discharge and favorable functional prognosis at 90 days for patients with acute atherosclerosis related ischemic stroke, but was not correlated with infarct volume on DWI.

Previous researches demonstrated that oxLDL level in the acute phase was not only related to poor functional outcome after stroke[2, 7], but also can predict recurrent stroke in patients with minor stroke or transient ischemic attack independently. However, the level of oxLDL is fluctuant in circulation. Study showed that it increased to peak level at the third day, and decreased gradually to the pre-morbid state [9]. To date, previous studies just focused on oxLDL at the acute stage of stroke[7, 8, 10], only limited

research has been conducted on relationship between the change of oxLDL level with the prognosis of stroke. Our study extended previous studies, and firstly reported that significant change of oxLDL level is related with favorable functional prognosis at 90 days for patients with acute atherosclerosis related ischemic stroke.

The mechanism of these association between oxidative lipoprotein markers and prognosis of stroke remains unclear. The potential reasons were as follows. Firstly, oxLDL as the result of oxidative modification of low-density lipoprotein, has pro-inflammatory and pro-atherosclerotic properties by inducing endothelial dysfunction[17]. Endothelial dysfunction may contribute to the blood-brain barrier (BBB) impairment, leading to the permeability of the BBB increased, circulatory immune cells permeate and infiltrate the surrounding brain parenchyma. These immune cells secrete pro-inflammatory cytokines, deteriorating the injurious damage following stroke as result[18]. Which was confirmed by many studies, because they all showed a positive relationship between oxLDL level and severe neurological deficits in patients with acute ischemic stroke [19-22]. Secondly, endothelial dysfunction and continuous neuroinflammation state caused by oxLDL may accelerate atherosclerosis progression, promote the formation of unstable plaque, contributing to clinical events onset[4-6]. Studies suggested that there was a significant correlation between plasma and plaque oxLDL level[23], and high plasma levels of oxLDL were correlated with the vulnerability to rupture of atherosclerotic lesions [23, 24]. Therefore, oxLDL can be used as a biomarker of atherosclerotic plaque stability [25]. Given the volatility of oxLDL levels in the cycle[9]. We only recruited acute ischemic stroke patients within 3 days after onset in order to ensure the initial level of oxLDL is its peak level. In our study, Compared to patients with mild change of oxLDL level, patients with significant change were more likely to have favorable functional prognosis at 90 days (OR=6.67, 95%CI, 2.15-20.73, $p < 0.01$) and neurological improvement at discharge(OR=7.21,95%, 3.09-16.80, $p < 0.01$).Therefore, the more the level of oxLDL decreased, the more likely the plaque tends to be stable, and the more likely the neurological function will be improved.

We found the change of oxLDL level is not related with infarct volume on DWI. The median DWI volumes in patients with different oxLDL changes groups were 4.21cm^3 , 3.08cm^3 , and 2.38cm^3 respectively, although presented reduced gradually, no statistical difference. Nai-Wen Tsai et al [26]demonstrated the oxLDL level in acute phase was positively correlated with infarct volume. Uno et al [20] evaluated oxLDL levels and ischemic lesions in acute stroke, and confirmed that a persistent plasma oxLDL elevation was associated with enlargement of the ischemic lesion in the early phase after acute ischemic stroke. But as far as we know, we are the first to explore the relationship between change of oxLDL level and infarct volume on DWI.

Our study had some limitations. First , Our sample size is relatively small, so in view of the biological characteristics of oxLDL, we only focus on acute ischemic stroke associated with atherosclerosis, namely large artery atherosclerotic and small-artery occlusion cerebral infarction. Secondly, we recruited acute ischemic stroke patients within 3 days after onset , the initial oxLDL level was not the time of stroke onset. What's more, our oxLDL level for the second time was before discharge(10-14days after stroke

onset), it has not reached the level before the stroke onset[9] , so the change of oxLDL level was between acute phase and subacute phase, but not the acute phase and premorbid state.

Despite all this, we evaluated changes of plasma oxLDL level and their impact on stroke prognosis over time, and confirmed that significant change of oxLDL level is related to the neurological improvement at discharge and favorable functional prognosis at 90 days for patients with acute ischemic stroke associated with atherosclerosis, but is not correlated with infarct volume on DWI.

These findings shed new light on oxLDL level as a therapeutic target in improving functional outcomes after acute ischemic stroke.

Abbreviations

oxidized low-density lipoprotein: oxLDL; low-density lipoprotein cholesterol: LDL-C

high -density lipoprotein- cholesterol: HDL-C; diffusion weighted imaging: DWI; blood-brain barrier:BBB

apparent diffusion coefficient: ADC; National Institutes of Health Stroke Scale: NIHSS

Declarations

Ethics statement

This study was performed according to the principles of the Declaration of Helsinki, and was approved by the ethics committee of Shanghai Fifth People's Hospital. Written informed consent was obtained from all the patients or their representatives.

Consent for publication

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by grants from Shanghai Municipal Commission of Health and Family Planning (20184Y0178), Shanghai Minhang District Health and Family Planning Commission for

constructing big disciplines (2020MWDXK01), Minhang District High Level Specialist Backbone Physician Training Plan (2020MZYS09), Beijing Bethune Public Welfare Foundation AX083CS.

Authors' contributions

XY and CL measured acute infarct volumes. TW rated MR imaging, disagreement was resolved by consensus with WL. WS measured circulating OxLDL level. DH, YL, SZ, LS were responsible for collecting data. XY and DW analyzed data. XY wrote the article, DW and WL polished the final manuscript. All authors read and approved the final manuscript.

Acknowledgment

We sincerely thank the patients, families, general practitioners, and hospital colleagues who participated into our study.

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