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Original Article

Oxidative Stress is Involved in the Occurrence and Development of Lower Extremity Atherosclerotic Disease

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SUMMARY

Background: Lower extremity atherosclerotic disease (LEAD) is a common disease in elderly, and it is closely related to many risk factors. The oxidative stress is involved in the arteriosclerosis. This study aimed to investigate the changes of oxidative stress indexes in patients with LEAD, and discuss their relations with the disease severity and the complications.
Methods: Eighty-three LEAD patients and 40 subjects without LEAD (control group) were enrolled. The ankle-brachial index (ABI) was measured. The serum superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels were determined.
Results: The serum SOD and GSH-Px levels and ABI in LEAD group were significantly lower than those in control group, respectively ($p < 0.01$), while the serum MDA level in LEAD group was significantly higher than that in control group ($p < 0.01$). There was significant difference of SOD, GSH-Px, MDA and ABI among LEAD patients with different stages, respectively ($p < 0.01$), with significant difference of each index between LEAD patients with and without hypertension, with and without diabetes, and with and without hyperlipemia, respectively ($p < 0.01$). In LEAD patients, there was positive correlation between SOD and ABI and between GSH-Px and ABI, respectively, with negative correlation between SOD and MDA, between GSH-Px and MDA and between MDA and ABI, respectively ($p < 0.01$).
Conclusion: The changes of serum SOD, GSH-Px and MDA levels are involved in the occurrence and development of LEAD. These indexes are helpful for the diagnosis of the LEAD severity and the complications.

1. Introduction

Lower extremity atherosclerotic disease (LEAD) is a common disease in elderly. It is a chronic disease in which the atherosclerosis involves the lower extremity arteries and causes the arterial stenosis or occlusion. LEAD is also a manifestation of systemic arteriosclerosis in the lower extremities, and has become a common disease in vascular surgery. The main symptoms of LEAD are lower extremity cold, numbness, weakness, intermittent claudication, resting pain, ischemic ulcer, gangrene, etc.[1] LEAD is closely related to the risk factors, such as hyperlipidemia, hypertension, diabetes and smoking. Most of LEAD patients have at least one coronary artery lesion, and a smaller part of LEAD patients are complicated by carotid artery stenosis.[2] The prognosis of LEAD is poor.[3] The 5-year mortality of LEAD patients with resting pain, ulcer or gangrene is very high.[4] The main causes of death from LEAD are the coronary heart disease and cerebrovascular diseases.[5,6] The body can produce reactive oxygen species (ROS) in the process of metabolism. ROS are easy to cause damage to cells and tissues. At the same time, there is an antioxidant system in the body. ROS and antioxidant system are in a dynamic equilibrium under normal conditions. When ROS are excessive or the function of the antioxidant system is reduced, the tissues and organs are vulnerable to injury, which is called the oxidative stress.[7] Studies have shown that, the oxidative stress plays an important role in the occurrence and development of atherosclerosis. It is also confirmed that the oxidative stress level is increased in patients with arteriosclerosis obliterans.[8,9] Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) are the important indicators which reflect the oxidative stress in the body.[10] The purpose of this study was to investigate the changes of serum SOD, GSH-Px and MDA levels in patients with LEAD, and discuss their relations with the severity of LEAD and the complications.

2. Subjects and methods

2.1. Subjects

This study enrolled eighty-three LEAD patients treated in Gansu Provincial Hospital from March 2013 to March 2017. All patients had generally normal liver, kidney and cardiac functions, without hypertension. Based on the severity of LEAD by Fontaine staging, there were 10 cases (12.05%) in mild complaint stage, 34 cases (40.96%) in intermittent claudication stage, 26 cases (31.32%) in resting pain stage and 13 cases (15.66%) in intermittent claudication stage. According to the diagnosis standards of diabetes and hyperlipidemia,

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there were 16 (19.28%) and 12 (14.46%) cases with complicated diabetes and hyperlipidemia, respectively. During the same period, 40 subjects without LEAD performing physical examination in our hospital were enrolled as control. The hypertension was excluded in these 40 subjects. This study was approved by the ethics committee of Gansu Provincial Hospital. Written informed consent was obtained from all participants.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria of LEAD were as follows: i) the patients had signs and symptoms of lower extremity arterial ischemia: lower extremity cold, numbness, weakened or disappeared arterial pulsation, intermittent claudication, resting pain, ulceration or gangrene of toes or feet, etc.. ii) the result of Burger test was positive; iii) the ankle-brachial index (ABI) was less than 0.9; iv) the color Doppler ultrasound and cardiac CT angiography confirmed the LEAD. The exclusion criteria were as follows: thromboangiitis obliterans, acute arterial embolism, polyarteritis, etc..

2.3. Clinical staging of LEAD

According to the Fontaine staging, the LEAD was staged as follows: i) Mild complaint stage (stage I): the patients presented lower skin temperature, chills, slight numbness of affected limbs, or fatigue after exercise; the extremities were easy to suffer from tinea pedis infection which was not easy to control; ii) Intermittent claudication stage (stage II): the lower limb pain appeared after walking for about hundreds to tens of meters, which was usually manifested by soreness of calf muscles, or pain in other parts of lower limbs. iii) Resting pain stage (stage III): the patient had lower limb pain even without exercise, especially when the patient fell asleep at night; iv) Gangrene stage (stage IV): the limb ulceration or gangrene occurred, and was very difficult to heal.

2.4. Measurement of ABI

ABI was measured by the automatic method using a validated oscillometric device that allowed simultaneous arm-leg blood pressure measurements and using a validated and calibrated sphygmomanometer and a two-way Doppler detector with an 8 MHz probe (Bidop Es-100V3, Hadeco Medical Company, Kawasaki, Japan). The ABI was calculated by the ratio of lateral ankle artery systolic pressure to maximum bilateral brachial artery systolic pressure. The lower value of bilateral measurement results was used as the final value.

2.5. Determination of serum oxidative stress indexes

Four milliliter of fasting peripheral venous blood was taken on the morning. After centrifugation at 3000 rpm for 10 min, the serum was obtained, and was stored at -80 °C for test. The level of superoxide dismutase (SOD) was determined using the xanthine oxidase method. The level of glutathione peroxidase (GSH-Px) was determined by enzymatic reaction and glutathione consumption method. The level of malondialdehyde (MDA) was determined by thiobarbituric acid colorimetry method.

2.6. Statistical analysis

All statistical analysis was carried out using SPSS 20.0 software (SPSS Inc., Chicago, USA). The enumeration data were presented as number and rate, and were compared between two groups using χ^2 test. The measurement data were presented as mean ± standard deviation. The comparison between two groups was performed using t test, and the comparison among three or more groups was performed using one-way analysis of variance. If a significant F ratio was obtained, Tukey's post hoc test was used to detect significant differences between means. The correlations of different indexes were analyzed using Pearson correlation analysis. $p < 0.05$ and $p < 0.01$ were considered as statistically significant and highly statistically significant, respectively.

3. Results

3.1. Baseline characters between control and LEAD groups

The baseline characters of patients in control and LEAD groups were shown in Table 1. There was significant difference of diabetes, hyperlipemia, coronary artery disease, fasting blood glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol between two groups, respectively ($p < 0.05$), with no significant difference of age, gender, body mass index or chronic kidney disease between two groups ($p > 0.05$).

3.2. Comparison of oxidative stress indexes and ABI between control and LEAD groups

In LEAD group, the serum SOD and GSH-Px levels and ABI were 52.85 ± 9.15 U/ml, 167.62 ± 27.54 μg/ml and 0.41 ± 0.07, respectively, which were obviously lower than 73.16 ± 13.01 U/ml, 186.81 ± 23.78 μg/ml and 1.21 ± 0.16 in control group, respectively ($p < 0.01$). The serum MDA level in LEAD group was 7.46 ± 1.44 nmol/ml, which was obviously higher than 3.83 ± 0.51 nmol/ml in control group ($p < 0.01$) (Table 2).

3.3. Comparison of oxidative stress indexes and ABI among LEAD patients with different stages

Table 3 showed that, there was significant difference of serum SOD, GSH-Px and MDA levels and ABI among LEAD patients with mild complaint, intermittent claudication, resting pain and gangrene stage, respectively ($p < 0.01$). With the deepening of LEAD severity,

Table 1
Baseline characters between control and LEAD groups.

Parameter	Control group	LEAD group	t/χ^2	p
n	40	83		
Age (years)	62.34 ± 9.12	64.48 ± 8.57	1.270	0.206
Gender (n)			0.009	0.923
Male	24	49	0.010	0.919
Female	16	34		
BMI (kg/m^2)	24.76 ± 3.67	25.62 ± 4.62	1.030	0.305
Diabetes (n)	3	48	28.172	< 0.001
Hyperlipemia (n)	6	53	25.812	< 0.001
CKD (n)	2	6	0.221	0.639
CAD (n)	1	13	4.636	0.031
FBG (mmol/L)	5.58 ± 1.04	7.69 ± 1.12	10.013	< 0.001
TC (mmol/L)	4.36 ± 0.11	5.89 ± 0.13	64.152	< 0.001
TG (mmol/L)	1.15 ± 0.12	1.80 ± 0.11	3.685	< 0.001
LDL-C (mmol/L)	1.37 ± 0.16	2.50 ± 0.21	30.062	< 0.001
HDL-C (mmol/L)	1.21 ± 0.12	1.06 ± 0.15	5.526	< 0.001

LEAD, lower extremity atherosclerotic disease; BMI, body mass index; CKD, chronic kidney disease; CAD, coronary artery disease; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

the SOD and GSH-Px levels and ABI significantly decreased, respectively, and the MDA level significantly increased.

3.4. Comparison of oxidative stress indexes and ABI between LEAD patients with and without diabetes

Table 4 showed that, the serum SOD and GSH-Px levels and ABI in LEAD patients with diabetes were 47.32 ± 8.13 U/ml, 158.81 ± 29.73 μg/ml and 0.39 ± 0.09, respectively, which were obviously lower than 62.78 ± 10.34 U/ml, 178.65 ± 25.52 μg/ml and 0.44 ± 0.08 in LEAD patients without diabetes, respectively ($p < 0.01$). The serum MDA level in LEAD patients with diabetes was 9.34 ± 2.28 nmol/ml, which was obviously higher than 6.56 ± 1.67 nmol/ml in LEAD patients without diabetes ($p < 0.01$).

3.5. Comparison of oxidative stress indexes and ABI between LEAD patients with and without hyperlipemia

Serum SOD and GSH-Px levels and ABI in LEAD patients with hyperlipemia were 45.62 ± 10.21 U/ml, 155.32 ± 29.58 μg/ml and 0.38 ± 0.08, respectively, which were obviously lower than 64.45 ± 8.34 U/ml, 176.45 ± 25.12 μg/ml and 0.48 ± 0.06 in LEAD patients without hyperlipemia, respectively ($p < 0.01$). The serum MDA level in LEAD patients with hyperlipemia was 8.77 ± 1.49 nmol/ml, which was obviously higher than 6.21 ± 1.56 nmol/ml in LEAD patients without hyperlipemia ($p < 0.05$) (Table 5).

3.6. Correlations of oxidative stress indexes and ABI in LEAD patients

Pearson correlation analysis showed that, in LEAD patients, there was positive correlation between serum SOD level and ABI ($r = 0.741$, $p < 0.001$) and between serum GSH-Px level and ABI ($r = 0.394$, $p < 0.001$), respectively. There was negative correlation between serum SOD level and MDA level ($r = -0.628$, $p < 0.001$), between serum GSH-Px level and MDA level ($r = -0.725$, $p < 0.001$), and between serum MDA level and ABI ($r = -0.287$, $p < 0.001$), respectively (Table 6).

4. Discussion

With the improvement of people's living conditions, changes in dietary structure, progress of population aging and enhancement of vascular surgery diagnosis level, the incidence of this LEASO is rising, and it has become a common disease in vascular surgery. The etiology of LEAD is not completely clear. The vascular intima injury, lipid metabolism disorder and hemodynamic changes may play an important role in the formation of LEAD.[1] Previous epidemiological studies have found that the risk factors of LEASO include sex, age, smoking, alcohol consumption, hyperlipidemia, obesity, diabetes,

Table 2
Comparison of oxidative stress indexes and ABI between control and LEAD groups.

Group	n	SOD (U/ml)	GSH-Px (μg/ml)	MDA (nmol/ml)	ABI
Control	40	73.16 ± 13.01	186.81 ± 23.78	3.83 ± 0.51	1.21 ± 0.16
LEAD	83	52.85 ± 9.15	167.62 ± 27.54	7.46 ± 1.44	0.41 ± 0.07
t		10.002	3.778	15.455	38.637
P		< 0.001	< 0.001	< 0.001	< 0.001

[a] $p < 0.05$ compared with control group.
LEAD, lower extremity atherosclerotic disease; ABI, ankle-brachial index; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

Table 3
Comparison of oxidative stress indexes and ABI among LEAD patients with different stages.

Stage	n	SOD (U/ml)	GSH-Px (μg/ml)	MDA (nmol/ml)	ABI
Mild complaint	10	64.32 ± 10.67	181.95 ± 15.38	5.03 ± 1.05	0.66 ± 0.11
Intermittent claudication	34	58.52 ± 9.03*	177.47 ± 26.53	5.74 ± 1.32	0.44 ± 0.06*
Resting pain	26	47.37 ± 7.67*#	155.73 ± 27.83*#	8.14 ± 1.05*#	0.35 ± 0.12*#
Gangrene	13	41.53 ± 8.11*#	144.53 ± 23.48*#	12.32 ± 2.01*#%	0.17 ± 0.04*#%
F		22.572	8.644	91.616	71.635
p		< 0.001	< 0.001	< 0.001	< 0.001

* $p < 0.05$ compared with mild complaint stage; # $p < 0.05$ compared with intermittent claudication stage; % $p < 0.05$ compared with resting pain stage.
LEAD, lower extremity atherosclerotic disease; ABI, ankle-brachial index; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

Table 4
Comparison of oxidative stress indexes and ABI in LEAD patients with and without diabetes.

Group	n	SOD (U/ml)	GSH-Px (μg/ml)	MDA (nmol/ml)	ABI
Without diabetes	35	62.78 ± 10.34	178.65 ± 25.52	6.56 ± 1.67	0.44 ± 0.08
With diabetes	48	47.32 ± 8.13	158.81 ± 29.73	9.34 ± 2.28	0.39 ± 0.09
t		7.624	3.183	6.112	2.617
p		< 0.001	< 0.001	< 0.001	0.009

LEAD, lower extremity atherosclerotic disease; ABI, ankle-brachial index; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

Table 5
Comparison of oxidative stress indexes and ABI in LEAD patients with and without hyperlipemia.

Group	n	SOD (U/ml)	GSH-Px (μg/ml)	MDA (nmol/ml)	ABI
Without hyperlipemia	30	64.45 ± 8.34	176.45 ± 25.12	6.21 ± 1.56	0.48 ± 0.06
With hyperlipemia	53	45.62 ± 10.21	155.32 ± 29.58	8.77 ± 1.49	0.38 ± 0.08
t		8.601	3.451	-7.3934	5.957
p		< 0.001	< 0.001	< 0.001	< 0.001

LEAD, lower extremity atherosclerotic disease; ABI, ankle-brachial index; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

Table 6
Correlations of oxidative stress indexes and ABI in LEAD patients.

Index	SOD		GSH-Px		MDA		ABI	
	r	p	r	p	r	p	r	p
SOD	-	-	0.036	0.212	-0.628	< 0.001	0.741	< 0.001
GSH-Px	0.036	0.212	-	-	-0.725	< 0.001	0.394	< 0.001
MDA	-0.628	< 0.001	-0.725	< 0.001	-	-	-0.287	0.023
ABI	0.741	< 0.001	0.394	< 0.001	-0.287	0.023	-	-

LEAD, lower extremity atherosclerotic disease; ABI, ankle-brachial index; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

hypertension, hypercoagulability, elevated plasma fibrinogen, hyperhomocysteinemia, etc..[11,12] However, it is not clear which factors play more important role in promoting the development of LEASO. This study has investigated the changes of serum SOD, GSH-Px and MDA level in patients with LEAD, for finding whether the oxidative stress is related to the occurrence and development LEAD.

Studies have shown that ROS play a key role in the development of atherosclerosis. The body generates a variety of ROS, which participate in the occurrence and development of atherosclerosis.[13] SOD is the main active enzyme to prevent the damage of O^{2-} free radicals. It can catalyze the disproportionation of O^{2-} free radicals and eventually eliminate them.[14] It is found that when the SOD activity in body increases, the free radicals are reduced correspondingly and the oxidative damage to cells and tissues and lipids also decreases, which plays an anti-atherosclerosis role. On the contrary, when the SOD activity decreases, the free radicals cannot be scavenged effectively. This promotes the development of atherosclerosis lesions.[15] GSH-Px is one of the most important antioxidant enzymes in glutathione antioxidant system. If GSH-Px is reduced or its activity is decreased, the antioxidant capacity of the body will be severely impaired. Therefore, the lipid peroxides are increased, which damage the blood vessels and increase the probability of thrombosis.[16] Results of this study showed that, the serum SOD and GSH-Px levels in LEAD group were higher than those in control group, respectively. With the deepening of LEAD severity, the SOD and GSH-Px levels decreased, respectively. In addition, the SOD and GSH-Px levels in LEAD patients with diabetes and hyperlipemia were lower than those in LEAD patients without diabetes and hyperlipemia, respectively. This suggests that, the change of serum SOD and GSH-Px levels are related with the LEAD severity and the complications.

MDA is the end product of lipid peroxidation in body, and its level is often used to indicate the degree of peroxidation. MDA damages the function and structure of endothelial cells, and then promotes the migration and proliferation of macrophages and smooth muscle cells, increases the adhesion and activity of neutrophils, and makes platelets to aggregate more easily into the endothelium.[17] Under the action of MDA, low-density lipoprotein is transformed to oxidized low-density lipoprotein, and the macrophages constantly swallow oxidized low density lipoprotein through various receptors on the cell membrane, thus changing into foam cells and promoting the development of atherosclerosis.[18] Bayram et al.[19] have confirmed that, the level of MDA is increased significantly in patients with atherosclerosis. Khan and Baseer[20] have reported that, the serum MDA level in patients with coronary heart disease is higher than that in healthy people. In our study, the serum MDA level in LEAD group was lower than that in control group. With the deepening of LEAD severity, the MDA level increased. In addition, the MDA level in LEAD patients with diabetes and hyperlipemia was higher than that in LEAD patients without diabetes and hyperlipemia, respectively. This suggests that, the change of serum MDA level is also related with the LEAD severity and the complications.

There are certain correlations among SOD, GSH-Px and MDA. Omar and Ding[21] have found that, in patients with diabetic cataract, the serum SOD level is negatively correlated with the MDA level. Tai et al.[22] have confirmed that, in patients with type 2 diabetes, the serum GSH-Px level is negatively correlated with the MDA level. In Tang's study,[23] in patients with chronic obstructive pulmonary diseases, the level of serum SOD is positively correlated with the serum GSH-Px level. Results of this study showed that, in LEAD patients, there was positive correlation between serum SOD level and ABI and between serum GSH-Px level and ABI. In addition, there was negative correlation between serum SOD level and MDA level, between serum GSH-Px level and MDA level and between serum MDA level and ABI. However, there was no significant correlation between SOD and GSH-Px. The reason needs to be further investigated.

In conclusion, the changes of serum SOD, GSH-Px and MDA levels are involved in the occurrence and development of LEAD. These indexes are helpful for the diagnosis of the LEAD severity and the complications. This study still has some limitations. Firstly, the sample size of this study is relatively small, which may affect the results. Secondly, we do not consider other complications besides diabetes and hyperlipemia. Thirdly, we do not analyze the effects of other indexes including age, body size and blood pressure, etc.. Fourthly, we only make the Pearson correlation analysis, but not perform the logistic regression on all parameters. In further studies, these issues should be solved for obtaining more convincing results.

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Disclosure of conflict of interest

None.

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