Am J Transl Res 2022;14(5):3113-3120
www.ajtr.org /ISSN:1943-8141/AJTR0136657

Original Article

Ultrasonic characteristics and influencing factors of atherosclerosis in diabetic patients

Yanyan Zhao, Shibin Lin, Kailiang Chen, Die Chen, Jineng Lai

Department of Ultrasound, The First Affiliated Hospital of Hainan Medical University, Haikou 570102, Hainan Province, China

Received June 23, 2021; Accepted March 5, 2022; Epub May 15, 2022; Published May 30, 2022

Abstract: Objective: The purpose of this research was to observe the characteristics of atherosclerosis in diabetic patients by ultrasound and analyze the factors influencing the development of atherosclerosis in these patients. Methods: Ninety diabetic patients treated in our hospital from January 2019 to December 2019 were enrolled in this retrospective analysis. The transcranial Doppler ultrasound (TCD) and carotid ultrasound were used to determine the presence of intracranial (stenosis) and extracranial (plaque) atherosclerosis. The differences in characteristics of different lesions and risk factors for the development of atherosclerosis were compared. Results: Ultrasound examination of the 90 enrolled patients showed that 5 (5.56%) had only intracranial artery stenosis, 30 (33.33%) had only extracranial atherosclerosis, 20 (22.22%) had intracranial artery stenosis combined with extracranial atherosclerosis, and 35 (38.89%) had no lesions. The intracranial stenosis rate (27.78%) was significantly higher than that of extracranial carotid stenosis or occlusion (2.22%) ($P < 0.001$). Logistic regression analysis revealed that the duration of diabetes mellitus and concomitant hypertension were independent risk factors for intracranial and extracranial atherosclerosis ($P < 0.05$). Compared with the control group, the study group showed reduced carotid plaque, decreased inflammatory response, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) as well as elevated high-density lipoprotein cholesterol (HDL-C) ($P < 0.05$). Conclusion: Diabetic patients have a higher incidence of atherosclerosis, which is related to the duration of the diabetes mellitus and concomitant hypertension, so the monitoring of these patients needs to be strengthened. In addition, the administration of atorvastatin can better improve hyperlipidemia and slow down the development of atherosclerosis.

Keywords: Atherosclerosis, diabetic patients, ultrasound, atorvastatin

Introduction

Diabetes mellitus is an endocrine/metabolic disorder caused by insufficient insulin secretion or insulin resistance, characterized by chronic hyperglycemia. With the general aging of society and the acceleration of lifestyle changes, the incidence of diabetes mellitus shows an increasing trend. According to a survey done in 2017, there were about 425 million diabetic patients worldwide, of whom 114 million are in China, ranking highest in the world. Some scholars predict that by 2045, there will be 700 million people with diabetes mellitus worldwide [1-3].

Intracranial and extracranial atherosclerotic lesions are the main causes of ischemic stroke. Clinical studies have found that diabetes mellitus is a vital risk factor for the development of intracranial and extracranial complex lesions; if clinical screening and interventions can be implemented in the early stages, intracranial and extracranial macrovascular lesions will be greatly reduced, which is helpful for the treatment of diabetes mellitus [4, 5]. Ultrasound is noninvasive and inexpensive. Previous studies have pointed out that transcranial Doppler ultrasound (TCD) can detect intracranial arterial stenosis in diabetic patients, whereas carotid ultrasound can differentiate and diagnose carotid atherosclerosis, but there is no relevant study on the influencing factors of diabetic atherosclerosis [6, 7]. In this study, the ultrasonic characteristics of and influencing factors for atherosclerosis in 90 diabetic patients were analyzed to provide clinical reference for improving the prognosis of diabetic patients.

Materials and methods

General data

In this retrospective study, ninety diabetic patients treated in our hospital from January 2019 to December 2019 were enrolled, including 43 males and 47 females, aged 55-80 years old, with a mean age of (56.5±11.8) years, duration of disease from 3 months to 14 years, and a median duration of (8.29±1.22) years. The 90 enrolled patients were divided into the intracranial and extracranial atherosclerosis group (n=55) and the non-lesion group (n=35) according to the presence or absence of atherosclerosis. According to a random number table method, 35 cases were divided into study group and 20 cases were divided into control group. The objective was to analyze the risk factors of intracranial and extracranial atherosclerosis and the effectiveness of aspirin + atorvastatin intervention.

Inclusion criteria: (1) patients who met World Health Organization diagnostic criteria for diabetes (1999) [8]; (2) patients who could cooperate with the study; (3) patients with complete clinical data; (4) patients aged ≥ 18 years old; (5) the study was approved by ethics committee of the First Affiliated Hospital of Hainan Medical University (No. NCT01536847); (6) patients who signed an informed consent form.

Exclusion criteria: (1) patients with comorbid psychiatric disorders; (2) pregnant or lactating women; (3) patients with other severe complications of diabetes; (4) patients with severe hepatic or renal dysfunction; (5) patients with poor compliance; (6) patients with lower limb amputation; and (7) patients with other severe organ dysfunction.

Intervention methods

Clinical diagnosis of extracranial stenosis or plaque: Ultrasonography was performed using GE Logiq 9 and PHILIPS iU22 color ultrasound Doppler with probe frequency of 5.0-12.0 MHz. Diagnosis of plaque: intima-media thickness (IMT) ≥ 1.3 mm. Arterial stenosis was defined as: diameter reduction was ≥ 50%, and extracranial transcranial stenosis or occlusion was included in the plaque group [9].

Diagnosis of intracranial stenosis: The degree of arterial stenosis was determined by color Doppler ultrasonography in 90 diabetic patients as follows: ≥ 50 as intracranial arterial stenosis, including superior cerebellar artery (SCA), bilateral middle cerebral artery (MCA), bilateral anterior cerebral artery (ACA), bilateral posterior cerebral artery (PCA), and vertebrobasilar artery. After risk factor analysis, 55 patients were placed into the study group (N=35) and the control group (N=20). All 55 patients were administered aspirin (Bayer Healthcare Co. Ltd., Approval No. J20130078, Specification: 100 mg/tablet) 0.1 g/d, and the study group was additionally treated with atorvastatin (Pfizer Pharmaceuticals Ltd., Approval No. H20-051408, Specification: 20 mg/tablet) 20 mg, once every night, for 24 weeks.

Blood biochemical indicators: After fasting for 10-12 h, 10 mL of venous blood was drawn in the morning, and 7600-200 Automatic Biochemical Analyzer (Hitachi Ltd., Tokyo, Japan) was used to measure the levels of glycated hemoglobin (HbAlc), total cholesterol (TC), fasting blood glucose (FBG), triglycerides (TG), lipoprotein a, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP) and interleukin-4 (IL-4) by the methods of chromatography, electrophoresis, and enzyme-linked immunosorbent assay.

Statistical analysis

SPSS 22.0 software was adopted for processing data. The measurement data were expressed as ($\bar{x}$±s), and the independent- and paired- *t* test was used for inter-group and intra-group comparison, respectively. The counting data were expressed as [n (%)], and chi-square test was used for comparisons. The risk factors of intracranial and extracranial atherosclerosis were analyzed by Logistic regression. $P < 0.05$ indicated a statistically significant difference [10].

Results

Comparison of medical history and biochemical indicators

Among the 90 patients, 5 (5.56%) had only intracranial artery stenosis, 30 (33.33%) had only extracranial atherosclerosis, 20 (22.22%) had intracranial artery stenosis combined with extracranial atherosclerosis, and 35 (38.89%) had no lesions. The biochemical indicators are shown in **Table 1**. Among the 90 patients, 25 (27.78%) had intracranial

Table 1. Comparison of medical history and biochemical indicators ($\bar{x}\pm s$)/ [n (%)]

Factor	Intracranial artery stenosis alone (n=5)	Extracranial carotid atherosclerosis alone (n=30)	Intracranial artery stenosis combined with extracranial carotid atherosclerosis (n=20)	No lesions (n=35)
Mean age (years)	50.19±4.33	56.54±5.01	60.22±6.50	50.11±4.34
Male	2 (40.00)	16 (53.33)	6 (30.00)	19 (54.29)
Mean duration (years)	6.29±1.11	9.98±2.11	14.01±1.21	6.23±0.98
Hypertension	4 (80.00)	18 (60.00)	10 (33.00)	6 (17.14)
Hyperlipidemia	1 (20.00)	8 (26.67)	8 (40.00)	10 (28.57)
Smoking	2 (40.00)	7 (23.33)	4 (20.00)	14 (40.00)
Alcohol consumption	1 (20.00)	4 (13.33)	2 (10.00)	11 (31.43)
FBG (mmol/L)	10.11±2.12	8.12±1.29	7.21±1.29	8.39±1.09
HbAlc (%)	9.08±1.22	8.13±1.21	9.02±1.11	9.24±0.98
TC (mmol/L)	4.89±0.87	5.30±1.11	5.23±0.98	4.78±0.79
HDL-C (mmol/L)	1.13±0.21	1.23±0.29	1.31±0.43	1.13±0.23
LDL-C (mmol/L)	3.03±0.89	3.29±0.91	3.08±0.78	3.02±0.87
TG (mmol/L)	1.77±0.21	1.54±0.19	1.41±0.21	1.34±0.19
Lipoprotein a (mg/L)	150.12±20.11	134.28±10.89	311.18±9.98	111.29±10.22

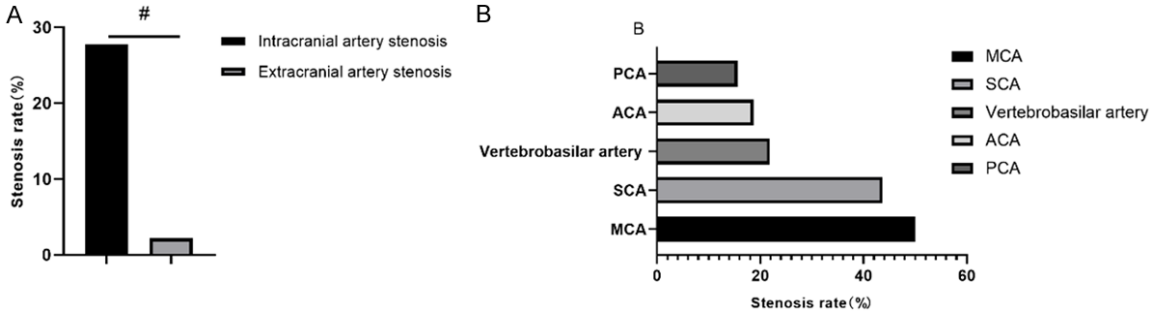

Figure 1. Comparison of arterial stenosis between different groups of patients. A: The incidence rate of intracranial and extracranial arterial stenosis; B: The stenosis rate of different intracranial arteries. #represents statistically significant difference in the same index between groups $P < 0.05$. Chi-square test was applied.

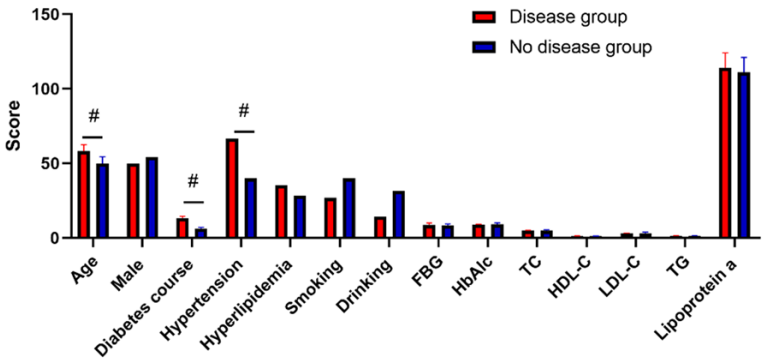

Figure 2. Comparison of medical history and biochemical indicators between the intracranial and extracranial atherosclerosis group and the non-lesion group. #indicates statistically significant difference in the same index between groups, $P < 0.05$. *t* test and chi-square test were used.

artery stenosis, which was significantly higher than the proportion of extracranial carotid stenosis or occlusion (2/90, 2.22%) (χ^2=23.05, $P < 0.001$). The most frequently involved intracranial artery was MCA (16/90, 17.78%), with a total of 32 cases (35.56%) presenting with extracranial carotid plaque or stenosis and 32 cases presenting with stenotic arteries in intracranial TCD examination, among which MCA accounted for the highest proportion (16/32, 50.00%), followed by SCA (14/32, 43.75%), vertebrobasilar artery (7/32, 21.88%), ACA (6/32, 18.75%), and PCA (5/32, 15.63%) (**Figure 1**).

Table 2. Logistic regression analysis of risk factors for intracranial and extracranial atherosclerotic lesions

Factor	AUC	OR	SE	β	95% CI	*P*
Mean age	0.6667	0.989	0.084	0.039	0.5021-0.8312	0.0645
Mean duration of diabetes	0.7807	1.096	0.078	0.098	0.6279-0.9335	0.011
History of hypertension	0.8843	3.671	0.050	0.089	0.7868-0.9818	< 0.0001

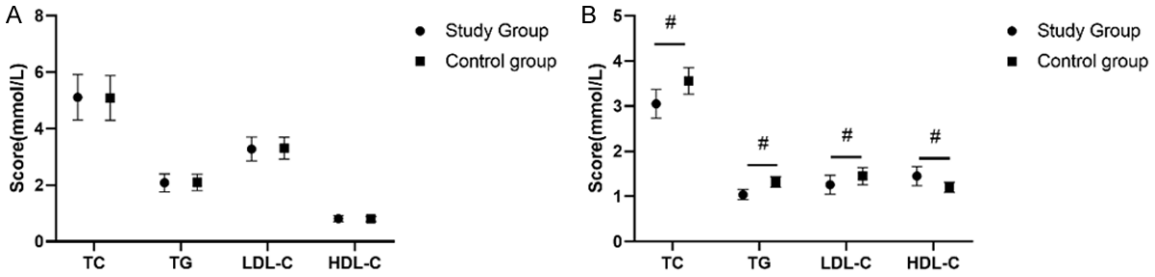

Figure 3. Changes in blood lipid levels before and after treatment between the study group and the control group. A: The levels of TC, TG, HDL-C and LDL-C before treatment; B: The levels of TC, TG, HDL-C and LDL-C after treatment. #indicates statistically significant difference in the same index between groups, $P < 0.05$. *t* test was used.

Comparison of medical history and biochemical parameters between the intracranial and extracranial atherosclerotic lesion group and the non-lesion group

The enrolled patients were divided into intracranial and extracranial atherosclerosis group and non-lesion group according to the presence or absence of atherosclerosis, and the disease history and biochemical data were compared between the groups. The results showed that the mean age, mean duration of diabetes mellitus, and incidence of combined hypertension in the intracranial and extracranial atherosclerosis group were significantly higher than those in the non-lesion group ($P < 0.05$), whereas the difference between groups was not statistically significant in terms of gender, history of hyperlipidemia, smoking, and blood biochemical parameters ($P > 0.05$) (**Figure 2**).

Logistic regression analysis of risk factors for intracranial and extracranial atherosclerosis

Logistic regression analysis was performed by backward stepwise method using mean age, mean duration of diabetes mellitus, and history of combined hypertension as variables. Multifactorial analysis showed that the duration of diabetes mellitus and the history of combined hypertension were independent risk factors for extracranial atherosclerosis ($P < 0.05$) (**Table 2**).

Changes in lipid levels before and after treatment in the study and control groups

The levels of TC, TG, HDL-C and LDL-C in the two groups before treatment were not statistically significant ($P > 0.05$). The levels of TC, TG, and LDL-C were significantly decreased, whereas the levels of HDL-C were significantly increased in the study and control groups after treatment compared with those before treatment ($P < 0.05$). The study group also showed significantly lower levels of TC, TG, and LDL-C and significantly higher levels of HDL-C compared with the control group after treatment ($P < 0.05$) (**Figure 3**).

Comparison of serum inflammatory factors between the study group and the control group

The serum levels of hs-CRP and IL-4 showed no significant difference between the two groups before treatment ($P > 0.05$). Both groups showed a significant decrease in the levels of hs-CRP and IL-4 after treatment ($P < 0.05$). The levels of the above indicators were lower in the study group than in the control group after treatment ($P < 0.05$) (**Figure 4**).

Comparison of carotid atherosclerotic plaque and IMT between the study group and the control group

Before treatment, the detection rate of carotid atherosclerotic plaque was 17 (37.78%) in the study group and 15 (33.33%) in the control

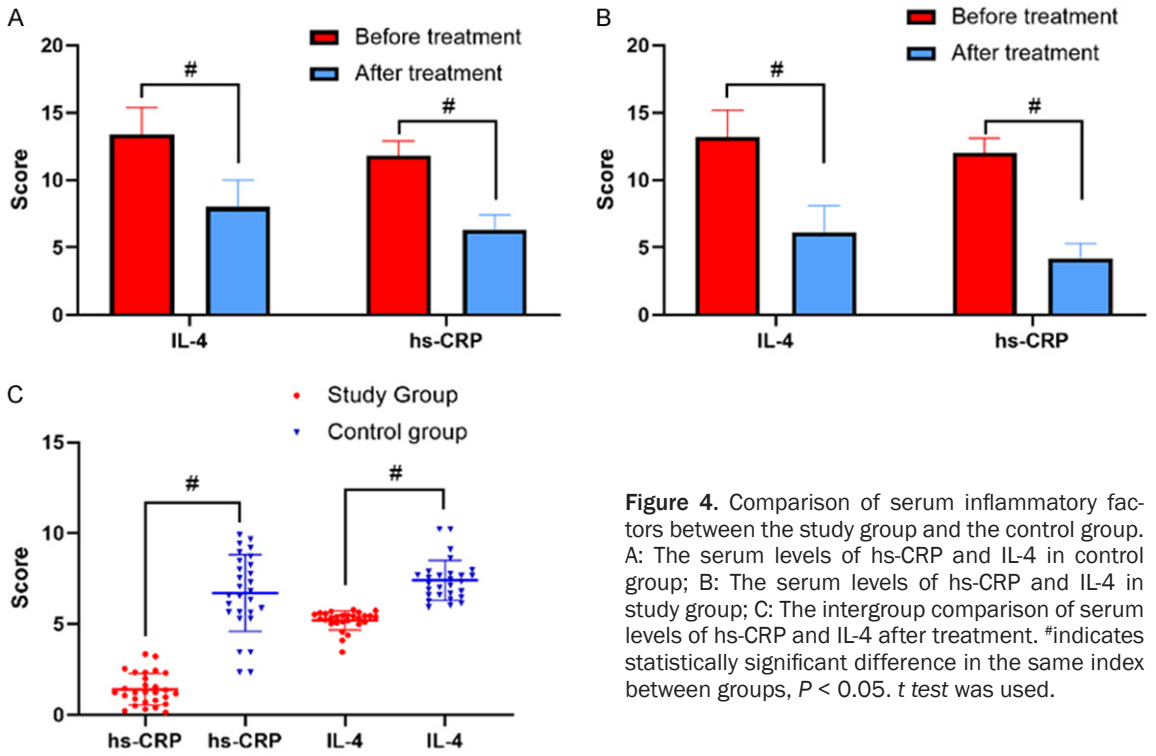

Figure 4. Comparison of serum inflammatory factors between the study group and the control group. A: The serum levels of hs-CRP and IL-4 in control group; B: The serum levels of hs-CRP and IL-4 in study group; C: The intergroup comparison of serum levels of hs-CRP and IL-4 after treatment. #indicates statistically significant difference in the same index between groups, $P < 0.05$. *t test* was used.

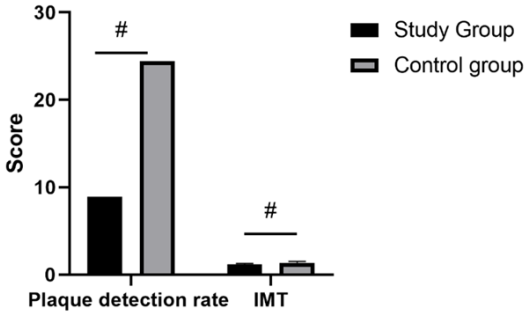

Figure 5. Comparison of carotid atherosclerotic plaque and IMT between the study group and the control group before and after treatment. #indicates statistically significant difference in the same index between groups, $P < 0.05$. *t* test was used.

group, and IMT was (1.45±0.21) mm in the study group and (1.46±0.19) mm in the control group, exhibiting no significant difference ($P > 0.05$). After treatment, the study group exhibited significantly lower detection rate of carotid atherosclerotic plaque [4 (8.89%) vs. 11 (24.44%)] and smaller IMT [(1.18±0.12) mm vs. (1.37±0.14) mm] than the control group ($P < 0.05$) (**Figures 5** and **6**).

Discussion

The incidence of diabetes mellitus has shown a year-on-year increase with the changes in dietary habits and lifestyles, and it has become a major disorder affecting populations worldwide [11, 12]. It has been found in clinical practice that long-term hyperglycemia can cause lesions in eyes, kidneys, and nerves, with a higher probability of dysfunction [13, 14]. Therefore, early detection and implementation of interventions are recommended in diabetic patients. Macroangiopathy is one of the common complications of diabetes mellitus, and it is clinically found that hyperglycemia, insulin resistance, abnormal lipid metabolism, impaired coagulation mechanisms, endothelial injury, and inflammation may be closely associated with this process [15, 16]. It has also been noted that diabetic patients have elevated blood viscosity and fibrinogen levels, leading to slow blood flow and predisposing them to thrombosis and vascular complications [17, 18].

In this study, 55 of the enrolled patients were found to have intracranial and extracranial atherosclerosis or stenosis, of which 20 (22.22%) had intracranial arterial stenosis combined with extracranial atherosclerosis, which was similar to the findings of other scholars [19]. Previous studies have confirmed that patients with diabetes mellitus can develop lipid metabolism disorders and chronic inflam-

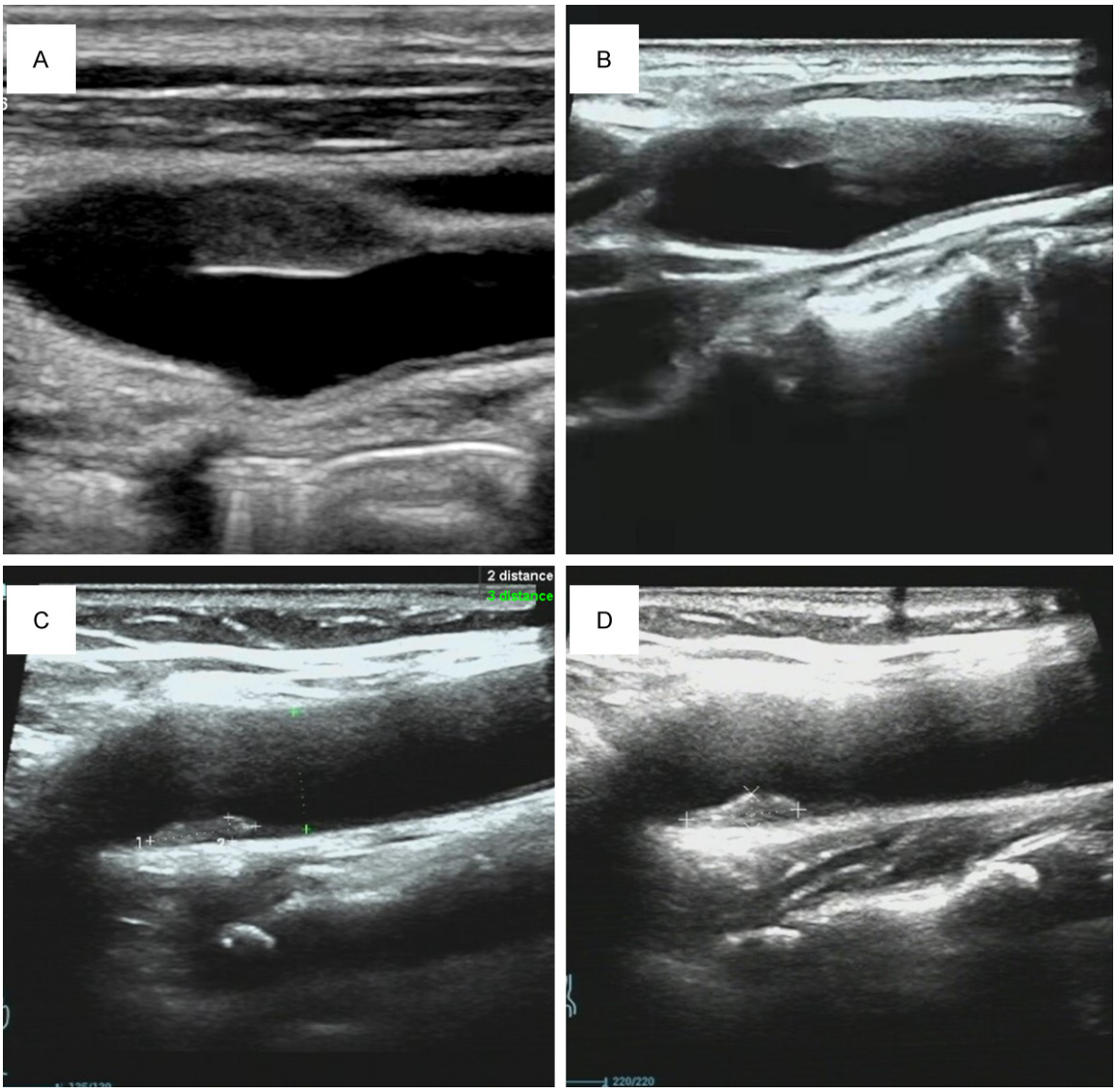

Figure 6. Changes of carotid atherosclerotic plaque in the two groups before and after treatment. In the study group, the common carotid plaque was obvious before treatment (A), and was significantly alleviated after treatment (C). In the control group, the common carotid plaque was obvious before treatment (B), and was alleviated after treatment (D).

matory lesions in the early stage, and are more prone to vascular wall calcification, which has been proved to be an important cause of atherosclerosis compared with non-diabetic patients [20]. We believe that long-term hyperglycemia may affect the wall thickness and elasticity of the common carotid artery, which may be related to hyperglycemia-induced inflammatory response *in vivo*, leading to excessive secretion of inflammatory factors and irritation to the vascular endothelium [21]. The results of this study suggested that more than half of diabetic patients had carotid atherosclerosis or stenosis, indicating that diabetic patients had a higher chance of developing stroke than normal people, thus the monitoring of diabetic patients with atherosclerotic lesions should be strengthened to prevent adverse events.

This study also analyzed risk factors for intracranial atherosclerosis in diabetic patients, and the results showed that the mean duration of diabetes and combined hypertension were independent risk factors for intracranial and extracranial atherosclerosis. This has also

been mentioned in the work of other researchers who have concluded that vascular disease in diabetic patients is a lengthy process and that vascular damage is gradually aggravated with the disease progression [22]. Some scholars conducted a long-term follow-up study on 1000 patients with carotid artery ultrasound and found that the increase rate of IMT value in diabetic patients was twice that of non-diabetic patients, confirming that diabetes accelerates the progression of carotid atherosclerosis [23]. However, some scholars believe that diabetes mellitus is not an independent risk factor for MCA stenosis, which remains controversial [24]. In this study, we conducted logistic regression analysis and found that the duration of diabetes and combined hypertension were independent risk factors for intracranial and extracranial atherosclerosis, which may be related to the fact that long-term hyperglycemia aggravates endothelial injury and accelerates the accumulation of plaque at the site of endothelial injury.

This study also revealed that the combination of aspirin and statins could reduce lipid-related indicators and improve the inflammatory status. The underlying mechanism may be that statins can improve vascular endothelial function, inhibit smooth muscle proliferation and suppress inflammatory responses, in addition to their lipid-regulating effects [25]. Statins have also been shown to be effective in slowing the progression of carotid atherosclerosis and coronary arteries and reducing the incidence of cardiovascular events, similar to the study of Gao H et al [26].

In conclusion, diabetic patients have a higher incidence of carotid atherosclerosis which is related to the duration of the disease and hypertension, so such patients should be monitored more intensively, and the administration of atorvastatin can better improve the hyperlipidemia of patients and slow down the development of atherosclerosis. This study analyzed the ultrasound characteristics of diabetic carotid atherosclerosis and listed related risk factors with detailed and reliable data, providing a reference for improving diabetic carotid atherosclerosis, which has certain innovation. The main shortcomings of this study are the lack of a large sample multicenter study and long-term follow-up.

Disclosure of conflict of interest

None.

Address correspondence to: Shibin Lin, Department of Ultrasound, The First Affiliated Hospital of Hainan Medical University, Haikou 570102, Hainan, China. Tel: +86-0898-66774347; E-mail: linshibin0909@163.com

References

[1] Pirri D, Fragiadaki M and Evans PC. Diabetic atherosclerosis: is there a role for the hypoxia-inducible factors? Biosci Rep 2020; 40: BSR20200026.

[2] Barrett TJ, Distel E, Murphy AJ, Hu J, Garshick MS, Ogando Y, Liu J, Vaisar T, Heinecke JW, Berger JS, Goldberg IJ and Fisher EA. Apolipoprotein AI) promotes atherosclerosis regression in diabetic mice by suppressing myelopoiesis and plaque inflammation. Circulation 2019; 140: 1170-1184.

[3] Josefs T, Barrett TJ, Brown EJ, Quezada A, Wu X, Voisin M, Amengual J and Fisher EA. Neutrophil extracellular traps promote macrophage inflammation and impair atherosclerosis resolution in diabetic mice. JCI Insight 2020; 5: e134796.

[4] Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, Yuan Q, Yu H, Xu W and Xie X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol 2019; 20: 247-260.

[5] La Sala L, Prattichizzo F and Ceriello A. The link between diabetes and atherosclerosis. Eur J Prev Cardiol 2019; 26: 15-24.

[6] Al-Sharea A, Murphy AJ, Huggins LA, Hu Y, Goldberg IJ and Nagareddy PR. SGLT2 inhibition reduces atherosclerosis by enhancing lipoprotein clearance in Ldlr(-/-) type 1 diabetic mice. Atherosclerosis 2018; 271: 166-176.

[7] Pennig J, Scherrer P, Gissler MC, Anto-Michel N, Hoppe N, Füner L, Härdtner C, Stachon P, Wolf D, Hilgendorf I, Mullick A, Bode C, Zirlik A, Goldberg IJ and Willecke F. Glucose lowering by SGLT2-inhibitor empagliflozin accelerates atherosclerosis regression in hyperglycemic STZ-diabetic mice. Sci Rep 2019; 9: 17937.

[8] Di Pino A and DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. Endocr Rev 2019; 40: 1447-1467.

[9] Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V and Orekhov AN. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. Int J Mol Sci 2020; 21: 1835.

[10] Haas AV and McDonnell ME. Pathogenesis of cardiovascular disease in diabetes. Endocrinol Metab Clin North Am 2018; 47: 51-63.
[11] Elfaki I, Mir R, Almutairi FM and Duhier FMA. Cytochrome P450: polymorphisms and roles in cancer, diabetes and atherosclerosis. Asian Pac J Cancer Prev 2018; 19: 2057-2070.
[12] Tian J, Liu Y, Liu Y, Chen K and Lyu S. Cellular and molecular mechanisms of diabetic atherosclerosis: herbal medicines as a potential therapeutic approach. Oxid Med Cell Longev 2017; 2017: 9080869.
[13] Lonardo A, Nascimbeni F, Mantovani A and Targher G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? J Hepatol 2018; 68: 335-352.
[14] Xia Y, Feng H, Li ZW, Tang KX, Gao HQ, Wang WL, Cui XP and Li XL. Low-dose phloretin alleviates diabetic atherosclerosis through endothelial KLF2 restoration. Biosci Biotechnol Biochem 2020; 84: 815-823.
[15] Hagensen MK, Mortensen MB, Kjolby M, Palmfeldt J, Bentzon JF and Gregersen S. Increased retention of LDL from type 1 diabetic patients in atherosclerosis-prone areas of the murine arterial wall. Atherosclerosis 2019; 286: 156-162.
[16] Zhou W, Ye SD, Chen C and Wang W. Involvement of RBP4 in diabetic atherosclerosis and the role of vitamin D intervention. J Diabetes Res 2018; 2018: 7329861.
[17] Matsuura Y, Yamashita A, Zhao Y, Iwakiri T, Yamasaki K, Sugita C, Koshimoto C, Kitamura K, Kawai K, Tamaki N, Zhao S, Kuge Y and Asada Y. Altered glucose metabolism and hypoxic response in alloxan-induced diabetic atherosclerosis in rabbits. PLoS One 2017; 12: e0175976.
[18] Rader DJ. Enhancing atherosclerosis regression in diabetic mice through apo AI (apolipoprotein AI). Circulation 2019; 140: 1185-1187.
[19] Wang Q, Zhang M, Torres G, Wu S, Ouyang C, Xie Z and Zou MH. Metformin suppresses diabetes-accelerated atherosclerosis via the inhibition of Drp1-mediated mitochondrial fission. Diabetes 2017; 66: 193-205.
[20] Tang Y, Li SL, Hu JH, Sun KJ, Liu LL and Xu DY. Research progress on alternative non-classical mechanisms of PCSK9 in atherosclerosis in patients with and without diabetes. Cardiovasc Diabetol 2020; 19: 33.
[21] Navas-Madroñal M, Castelblanco E, Camacho M, Consegal M, Ramirez-Morros A, Sarrias MR, Perez P, Alonso N, Galán M and Mauricio D. Role of the scavenger receptor CD36 in accelerated diabetic atherosclerosis. Int J Mol Sci 2020; 21: 7360.
[22] Martínez-Hervás S, Sánchez-García V, Herrero-Cervera A, Vinué Á, Real JT, Ascaso JF, Burks DJ and González-Navarro H. Type 1 diabetic mellitus patients with increased atherosclerosis risk display decreased CDKN2A/2B/2BAS gene expression in leukocytes. J Transl Med 2019; 17: 222.
[23] Ioachimescu AG. Diabetes and atherosclerotic cardiovascular disease. Endocrinol Metab Clin North Am 2018; 47: xiii-xiv.
[24] Li Y, Xiao L, Li J, Sun P, Shang L, Zhang J, Zhao Q, Ouyang Y, Li L and Gong K. MicroRNA profiling of diabetic atherosclerosis in a rat model. Eur J Med Res 2018; 23: 55.
[25] Suwanwela NC and Chutinetr A. Risk factors for atherosclerosis of cervicocerebral arteries: intracranial versus extracranial. Neuroepidemiology 2003; 22: 37-40.
[26] Gao H, Li H, Li W, Shen X and Di B. Pioglitazone attenuates atherosclerosis in diabetic mice by inhibition of receptor for advanced glycation end-product (RAGE) signaling. Med Sci Monit 2017; 23: 6121-6131.