Characteristics of carotid atherosclerosis in elderly patients with type 2 diabetes at different disease course, and the intervention by statins in very elderly patients

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ABSTRACT

Introduction: Chronic complications of diabetes have become the leading cause of death in elderly patients with diabetes. Carotid atherosclerosis, one of the major complications, was evaluated and the effects of atorvastatin on carotid atherosclerosis in very elderly patients with type 2 diabetes were observed.

Materials and Methods: Patients were divided into three groups: (i) disease course <5 years; (ii) disease course 5–10 years; (iii) disease course >10 years, and carotid atherosclerosis was evaluated. The very elderly patients were treated with statins, and the effect was observed.

Results: Carotid intima-media thickness values, plaque instability and levels of homocysteine, cystatin, and C-reactive protein in diabetes patients were significantly higher than those in the healthy control group, whereas levels of C-peptide and estimated glomerular filtration rate in the patients were significantly lower. In patients with type 2 diabetes for >10 years, intima-media thickness values and plaque instability were obviously higher than those in patients with type 2 diabetes for <5 years, while levels of fasting C-peptide and estimated glomerular filtration rate were lower than those in patients with type 2 diabetes for <5 years. In the very elderly patients, after statins treatment, intima-media thickness values, levels of homocysteine and C-reactive protein were significantly reduced, as well as the number of unstable plaques.

Conclusions: In the elderly patients with type 2 diabetes, carotid atherosclerosis-related factors increased obviously, and renal function declined obviously, which were closely related to the disease course. Atorvastatin significantly reduced homocysteine and C-reactive protein, and delayed and reversed the progress of carotid atherosclerosis in very elderly patients with type 2 diabetes.

INTRODUCTION

Chronic complications of diabetes have become the leading cause of death in elderly patients with diabetes mellitus. Carotid artery thickening, one of the major complications of diabetes, is regarded as a sign of early atherosclerosis[1], and a 'window' for systemic arterial disease[2]. In the present study, the characteristics of carotid atherosclerotic plaques in elderly patients with type 2 diabetes and the effect of atorvastatin on carotid atherosclerotic plaques in very elderly patients with type 2 diabetes were observed. Intima-media thickness (IMT), plaque stability, fasting C-peptide, C-reactive protein (CRP), homocysteine (Hcy), cystatin and other indexes were also measured to provide a theoretical basis for prevention and treatment of macrovascular complications in elderly patients with type 2 diabetes.

METHODS

Study protocol

There were 240 patients including 116 men and 124 women with type 2 diabetes, aged >65 years. They were enlisted from

the clinic and ward of the Geriatrics Department, Linyi People's Hospital, Linyi, China, from June 2013 to August 2016, in which there were 106 very elderly patients with type 2 diabetes (≥80 years), including 47 men and 59 women.

Patients with one of the following were included: (i) glycosylated hemoglobin (HbA1c) ≥6.5%; (ii) fasting plasma glucose ≥7.0 mmol/L; (iii) a 2-h oral glucose tolerance test glucose level ≥11.1 mmol/L; (iv) 2-h post-load plasma glucose ≥11.1 mmol/L; (v) diabetes symptoms (such as polyuria, polydipsia, polyphagia an weight loss) and random blood glucose level ≥11.1 mmol/L; and (vi) normal glucose level after taking hypoglycemic agents.

Exclusion criteria were as follows: (i) secondary hyperglycemia; (ii) various acute and chronic inflammation, connective tissue diseases, autoimmune diseases or malignant tumors; (iii) allergy to atorvastatin calcium; (iv) severe cardiovascular and cerebrovascular diseases, such as acute cerebrovascular accident, acute myocardial infarction or congestive heart failure; (v) active liver disease; (vi) severe renal impairment (creatinine clearance <30 mL/min); (vii) myopathy; or (viii) taking vitamin B$_1$, vitamin B$_{12}$, folic acid, diuretics, antiepileptic drugs, niacin, methotrexate, cyclosporin, clarithromycin or itraconazole.

The study protocol was approved by the Medical Ethics Committee of Linyi People's Hospital (KY2015052), and informed consent for all participants was obtained. The study design is shown in Figure 1.

Research method

Based on the disease course, patients were divided into three experimental groups: (i) disease course <5 years; (ii) disease course lasting for 5–10 years; (iii) disease course lasting for >10 years; there were 80 patients in each group. In addition, 80 healthy people were enlisted from the physical examination center at Linyi People's Hospital, with the same age and sex distribution of the patients with type 2 diabetes. Carotid plaque and blood-related parameters were measured. In the enlisted elderly patients with type 2 diabetes, patients aged ≥80 years were randomly assigned to two groups: (i) the treatment group; and (ii) control group ($n = 53$). In the treatment group, patients were treated with statins, and the patients were given a 2-week washout period (stopping administration of statins for 2 weeks). All patients were treated with insulin aspart and insulin glargine subcutaneously. The treatment group was treated with atorvastatin calcium tablets (Lipitor; Pfizer Pharmaceutical Co., Ltd., New York, New York, USA) 20 mg once daily, orally administered before bedtime; the control group was treated with insulin aspart and insulin glargine subcutaneously without statins. The treatment lasted for 6 months. The aforementioned indexes were measured before and after treatment.

After 1 month, liver function and kidney function were tested, and serum creatinine levels were measured. When the level of aminotransferase increased to triple the upper limit of the normal range, serum creatinine increased >20% of the normal upper limit or creatinine levels reached double the upper limit of the normal range, the treatment was terminated.

Observing indicators
Carotid IMT and plaque detection
A color Doppler ultrasound imaging device (LOGIQ S6; GE Healthcare, Waukesha, Wisconsin, USA) were used with the probe frequency of 6–12 MHz.

The IMT of the carotid artery is the vertical distance from the interface of the outer membrane and the medial layer to the interface between the intima and the lumen; that is, the thickness of the middle and inner layers of the vessel wall.

The measurement of IMT was carried out in the three locations bilaterally, in the common carotid, at the bifurcation and in the internal carotid artery. The mean IMT was taken as the carotid IMT. If there was a plaque present in the location, the measure was carried out nearby.

Assessment criteria for carotid atherosclerosis: IMT ≥ 1.0 mm was considered as carotid artery intimal thickening; IMT ≥ 1.3 mm, with or without the localized arterial wall thickening in the lumen >50% of the nearby IMT or a visible intrusion into the lumen of at least 0.5 mm, was considered as a plaque.

For the Crouse score, the maximum thickness of each isolated plaque was added regardless of plaque length.

For the evaluation of plaque stability, plaques with equal or strong echo were regarded as stable; plaques with weak or mixed echo were regarded as unstable plaques, and the number of unstable plaques was recorded.

Test for blood samples
After 8–12 h of fasting, venous blood of 5 mL was taken, and tested using a Cobas 8000 analyzer (Roche Diagnostics, Shanghai, China) for the following items: (i) HbA1c; (ii) serum Hcy; (iii) C-peptide; (iv) serum cystatin; (v) serum uric acid; (vi) serum creatinine and urea nitrogen; (vii) CRP; and (viii) estimated glomerular filtration rate (eGFR). The Cockcroft–Gault formula was applied as follows: for men (140 − age) × bodyweight (kg) × 1.23/serum creatinine (μmol/L); for women (140 − age) × bodyweight (kg) × 1.04 / serum creatinine (μmol/L).

Statistical analysis
SPSS 17.0 statistical software (SPSS Inc., Chicago, Illinois, USA) was used for analysis. Measurement data with homogenous variance were analyzed using Student's *t*-test, and measurement data with heterogenous variance were analyzed using Student's *t*-test; $P < 0.05$ was considered statistically significant.

RESULTS
General information
The general information of the participants is shown in Table 1. There was no significant difference in the clinical data of the diabetes patients in the three groups, and no significant
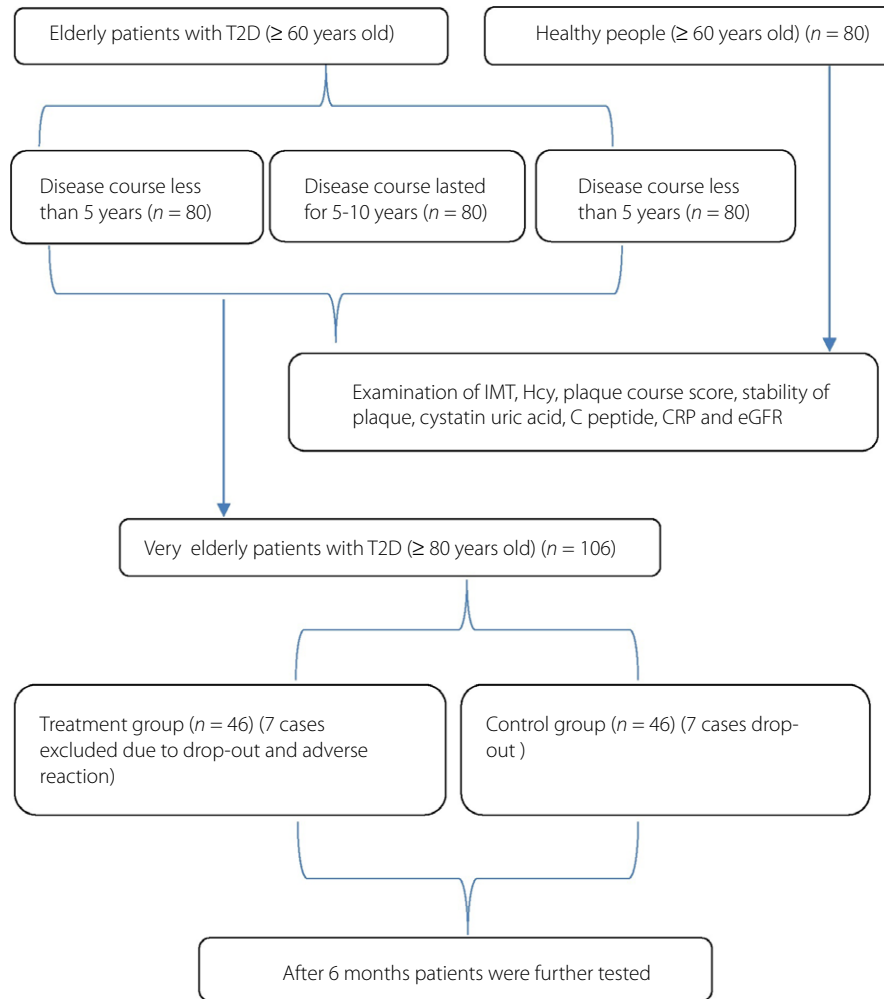
Figure 1 | Study protocol and participants. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; IMT, intima-media thickness; T2D, type 2 diabetes.

difference in the age, sex and general condition between the healthy control group and the diabetes patients.

There was no significant difference in the clinical data between the treatment group and control group of very elderly patients with type 2 diabetes (Table 2).

Characteristics of carotid atherosclerosis in elderly patients with type 2 diabetes at different disease course and the related factors

The IMT value in the diabetes group was significantly higher than that in the healthy control group ($P < 0.05$), and the IMT value in the patients with diabetes for >10 years was significantly higher than that in the patients with diabetes for <5 years ($P < 0.05$), but is of no significant difference compared with patients with diabetes lasting for 5–10 years. The Crouse score in patients with diabetes was significantly higher than that in the healthy control group ($P < 0.05$), but there was no significant difference among the three diabetes groups.

In the diabetes groups, the plaque instability was significantly higher than that in the healthy control group ($P < 0.05$). In the patients with diabetes for >10 years, the plaque instability was significantly higher than that in patients with diabetes for <5 years ($P < 0.05$), but there was no statistical difference compared with the group with diabetes lasting for 5–10 years. The levels of serum Hcy and serum cystatin in patients with diabetes were significantly higher than those of the healthy control group ($P < 0.05$), but there was no significant difference among the three diabetes groups. In patients with diabetes, eGFR was significantly lower than that in the healthy control group ($P < 0.05$), and in patients with diabetes for >10 years, eGFR was significantly lower than that in patients with diabetes for <5 years ($P < 0.05$), but showed no statistical difference compared with diabetes lasting for 5–10 years. There was no significant difference on serum uric acid levels between the diabetes patients and the healthy control group. The level of fasting serum C-peptide in patients with diabetes was significantly

Table 1 | Clinical data of diabetes patients and the healthy control group

Index	Disease course <5 years (n = 80)	Disease course lasting for 5–10 years (n = 80)	Disease course > 10 years (n = 80)	Healthy control (n = 80)	P-value
Sex, female (%)	50	53.75	51.25	52.5	>0.05*
Age (years)	78.01 ± 7.14	78.53 ± 7.29	77.45 ± 7.05	77.85 ± 7.1	>0.05*
FBG (mmol/L)	10.38 ± 2.98	10.91 ± 2.62	10.74 ± 2.82	5.35 ± 0.70	>0.05**
TG (mmol/L)	1.63 ± 0.76	1.64 ± 0.78	1.66 ± 0.68	1.30 ± 0.42	>0.05**
TC (mmol/L)	4.74 ± 1.13	4.52 ± 0.99	4.58 ± 1.00	4.07 ± 0.88	>0.05**
LDL-C (mmol/L)	3.30 ± 0.92	3.20 ± 0.93	3.22 ± 0.90	2.85 ± 0.64	>0.05**
HDL-C (mmol/L)	1.14 ± 0.27	1.15 ± 0.27	1.14 ± 0.29	1.32 ± 0.29	>0.05**
Hypertension, n (%)	53.75 (43)	58.75 (47)	56.25 (45)	0	>0.05**
Hyperlipidemia, n (%)	48.75 (39)	47.5 (38)	43.75 (35)	11.25 (9)	>0.05**
Smoking, n (%)	8.75 (7)	11.25 (9)	10 (8)	8.75 (7)	>0.05*
HbA1c	9.03 ± 2.07	8.98 ± 1.98	9.15 ± 1.95	5.21 ± 0.80	>0.05**
Treated by statins, n (%)	60 (48)	52.5 (42)	56.25 (45)	0	>0.05**
Body mass index	24.43 ± 2.61	24.07 ± 2.6	24.52 ± 2.76	23.9 ± 2.83	>0.05*

There was no significant difference between the three diabetes groups (**$P > 0.05$$); there was no significant difference between the four groups (*$P > 0.05$). FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 2 | Clinical data of very elderly patients with type 2 diabetes in the treatment group and the control group

Parameters	Treatment group (n = 46)	Control group (n = 46)	P-value
Sex, female (%)	27 (58.7%)	25 (54.35)	>0.05
Age (years)	82.86 ± 2.91	83.78 ± 3.69	>0.05
Disease course (years)	7.88 ± 5.48	7.86 ± 5.40	>0.05
Body mass index	24.46 ± 2.61	24.16 ± 2.73	>0.05
Hypertension, n (%)	21 (45.65%)	23 (50%)	>0.05
Smoking	7 (15.22)	6 (13.04)	>0.05

There was no significant difference between the two groups ($P > 0.05$).

lower than that in the healthy control group ($P < 0.05$), and in the patients with diabetes for >10 years, it was significantly lower than that in the other two diabetes groups ($P < 0.05$). In the patients with diabetes, the level of serum high-sensitivity C-reactive protein was higher than that in the healthy control ($P < 0.05$), but there was no significant difference between the three groups of diabetes patients. All the results are shown in Table 3.

Effect of statins on atherosclerosis and the related factors in very elderly patients

In the two groups of very elderly patients with diabetes, there was no statistical difference in IMT value, Crouse score and plaque instability before treatment; after being treated with statins, the IMT value and the number of unstable plaques were reduced significantly ($P < 0.05$), but the Crouse score showed no change. Before treatment, there was no significant difference in serum Hcy level between the two groups, whereas after they were treated with statins, the Hcy level was reduced significantly ($P < 0.05$). Also, in the two groups, there was no statistical difference in cystatin level, eGFR, serum uric acid level and

fasting serum C-peptide before treatment, and also there was no significant change after treatment. In addition, in the two groups, there was no significant difference on high-sensitivity C-reactive protein level before treatment, whereas after treatment in the treatment group, the high-sensitivity C-reactive protein level decreased significantly ($P < 0.05$). Also, there was no significant difference between the two groups before treatment in the HbA1c level, but after 6 months of treatment, HbA1c decreased significantly in the treatment group and in the control group ($P < 0.05$). All the results are shown in Table 4.

Adverse reactions and loss to follow up

In the present study, there were seven cases lost to follow up in the control group of the very elderly patients with type 2 diabetes for various reasons, whereas in the treatment group there were three cases that withdraw due to elevated liver enzymes more than triple the normal level (after stopping administration, the liver enzyme levels become normal) and four cases lost to follow up. Therefore, a total of 92 patients met the study requirements.

Table 3 | Characteristics of carotid atherosclerosis at different disease course and the related factors

Index	Disease course <5 years (n = 80)	Disease course lasting for 5–10 years (n = 80)	Disease course >10 years (n = 80)	Healthy control group (n = 80)
IMT (mm)	1.27 ± 0.10	1.29 ± 0.11	1.32 ± 0.12**	1.21 ± 0.11*
Crouse score	4.10 ± 1.08	4.17 ± 1.11	4.28 ± 1.06	2.61 ± 0.84*
No. unstable plaques (n)	3.11 ± 1.37	3.28 ± 1.38	3.39 ± 1.38**	1.86 ± 1.23*
Hcy (µmol/L)	15.10 ± 4.15	15.20 ± 4.41	15.16 ± 4.30	12.51 ± 3.31*
Serum uric acid (µmol/L)	349.78 ± 113.93	355.67 ± 98.34	359.11 ± 112.88	325.20 ± 86.83
C-peptide (ng/mL)	1.15 ± 0.39	1.09 ± 0.39	0.85 ± 0.34***	2.27 ± 0.43*
CRP (mg/L)	4.27 ± 2.07	4.25 ± 1.48	4.71 ± 1.99	2.87 ± 1.56*
Serum cystatin (mg/L)	1.17 ± 0.43	1.19 ± 0.48	1.29 ± 0.47	0.93 ± 0.37*
eGFR (mL/min/1.73 m^2)	99.11 ± 18.06	92.99 ± 18.66	88.94 ± 17.19**	112.92 ± 17.65*

*$P < 0.05$, compared with the three groups of diabetic patients; **$P < 0.05$, compared with the patients with diabetes for <5 years; ***$P < 0.05$, compared with the patients with diabetes for <5 years and those lasting for 5–10 years. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; IMT, intima-media thickness.

Table 4 | Effect of statins on atherosclerosis and related factors

Index	Treatment group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
IMT (mm)	1.31 ± 0.12	1.25 ± 0.11*	1.30 ± 0.11	1.28 ± 0.10
Crouse score	4.13 ± 0.95	3.94 ± 1.03	4.09 ± 1.10	3.98 ± 1.06
No. unstable plaques (n)	3.26 ± 1.29	2.65 ± 1.30*	3.15 ± 1.32	3.13 ± 1.38
Hcy (µmol/L)	16.22 ± 5.34	13.74 ± 4.54*	15.91 ± 5.19	14.15 ± 4.15
Serum uric acid (µmol/L)	355.59 ± 133.97	350.97 ± 131.72	341.3 ± 119.07	338.57 ± 120.23
C peptide (ng/mL)	1.11 ± 0.30	1.12 ± 0.26	1.10 ± 0.28	1.04 ± 0.29
CRP (mg/L)	4.55 ± 1.61	3.81 ± 1.63*	4.30 ± 1.48	4.12 ± 1.59
Serum cystatin (mg/L)	1.19 ± 0.43	1.17 ± 0.44	1.18 ± 0.47	1.14 ± 0.43
eGFR (mL/min/1.73 m^2)	94.53 ± 16.16	91.71 ± 16.43	97.38 ± 17.30	95.5 ± 15.51
HbA1c (%)	8.96 ± 1.73	7.05 ± 1.35*	8.98 ± 1.75	6.91 ± 1.14**

*$P < 0.05$, in treatment group, compared with before treatment; **$P < 0.05$, in the control group, compared with before treatment. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; Hcy, homocysteine; IMT, intima-media thickness.

DISCUSSION

With the aging of the population, diabetes in elderly patients has become a hot issue. According to statistical studies, the risk of atherosclerosis in patients with diabetes was two- to fourfold higher than non-diabetes patients[3,4]. Microvascular complications in diabetes are the main reason for death and disability in patients with diabetes, and therefore preventing the occurrence and delaying the progression of microvascular complications in diabetes is very important. IMT thickening is an independent risk factor for cardiovascular and cerebrovascular events[5].

We chose the carotid IMT, Crouse score, and plaque stability as the risk factors and indicators for microvascular complications in elderly patients with type 2 diabetes. Type 2 diabetes was divided into three disease courses; that is, 5, 5–10 and 10 years, and the changes of the size and stability of the plaques were observed. It was found that the IMT value and Crouse score of elderly patients with type 2 diabetes were significantly higher than the

healthy control group, and the value of IMT also increased corresponding to the disease course. The IMT value increased significantly higher in the patients with type 2 diabetes for >10 years than the patients with type 2 diabetes for <5 years, but there was no significant difference between the patients with type 2 diabetes of 5–10 and 10 years. This result showed that systemic atherosclerosis increased corresponding to the increase of disease course. In addition, with the increase of disease course, plaque stability was also gradually reduced, manifesting as increased hypoechoic plaques and mixed echo plaques, which could lead to more cardiovascular and cerebrovascular events.

In the very elderly patients with type 2 diabetes, the carotid IMT value decreased and the plaque stability increased after treatment with atorvastatin calcium. Although the Crouse score was not statistically different, it showed a decreasing trend, which showed that atorvastatin could not only stabilize plaque, but also reverse plaque formation.

C-reactive protein is a non-specific inflammatory response protein[6,7], and it is an inflammation marker for atherosclerotic plaque[8]. A study has confirmed[9] that serum C-reactive protein level was closely related to the occurrence of cardiovascular and cerebrovascular events, as well as the severity and prognosis.

In the present study, it was found that serum C-reactive protein levels in elderly patients with type 2 diabetes were significantly higher than the healthy control group, suggesting that in diabetes patients, the inflammatory response was significantly stronger than that in the healthy people, and inflammation was closely related to diabetes, but as the duration of diabetes increased, the level of inflammatory response did not increase.

After atorvastatin calcium therapy for 6 months, the C-reactive protein level was significantly decreased in the very elderly patients with type 2 diabetes, showing that atorvastatin has a definite anti-inflammatory effect.

In addition, the plasma Hcy levels in elderly patients with type 2 diabetes were significantly higher, suggesting that Hcy plays an important role in the development and progression of diabetic macroangiopathy, and is an important factor in clinical treatment. However, with the continuation of disease course, Hcy level does not increase. Supplementation of folic acid and vitamin B_{12} can reduce Hcy levels, but does not significantly relieve vascular disease.

In the present study, it was found that atorvastatin can significantly reduce the levels of serum Hcy in very elderly patients with type 2 diabetes, and it played an important role to stabilize plaques, maintain the homeostasis of blood vessels, prevent vasospasm and thrombosis, and reduce cardiovascular and cerebrovascular events.

Cystatin C is a very important endogenous marker that reflects the state of renal function in humans[10]. In the present study, it was found that cystatin C and the glomerular creatinine clearance rate were significantly consistent. With the duration of diabetes, eGFR gradually decreased, and cystatin C levels slowly rose, suggesting that renal function deteriorated corresponding with the development of diabetes. After treatment with atorvastatin for 6 months, cystatin C and eGFR levels showed no obvious improvement, suggesting that atorvastatin had no obvious effect on very elderly patients with type 2 diabetes.

Uric acid is the metabolic product of purine, and it can increase and finally lead to hyperuricemia when there is a disorder of purine metabolism or uric acid excretion. In the present study, it was found that serum uric acid level in elderly patients with type 2 diabetes was not significantly different from that in the healthy control group, and atorvastatin could not significantly reduce uric acid. This is possibly due to the small sample size, and therefore in the future study the sample size should be increased.

C-peptide and insulin are both peptides resulting from the decomposition of proinsulin[11]. C-peptide cannot be inactivated by liver enzymes, and is not influenced by exogenous insulin and insulin antibodies. Therefore, it could reflect the function of pancreatic β-cells more accurately[12]. In the present study, it was found that with the development of diabetes, the fasting C-peptide level decreased significantly, possibly as a result of the malfunction of pancreatic β-cells, with significant difference. However, in the very elderly patients with type 2 diabetes, atorvastatin had no effect on the fasting C-peptide levels, suggesting that atorvastatin had no effect on pancreatic β-cell function.

In short, in elderly diabetes patients, there is usually disorder of lipid metabolism, and also glucotoxicity and lipotoxicity can influence each other, both leading to the accelerated development of atherosclerotic lesions; that is, with the progress of diabetes, there are more and more plaques formed, and the stability becomes lower and lower, with more Inflammatory mediators to be released. Therefore, in elderly diabetes patients, cardiovascular and cerebrovascular events are common. In addition, the function of pancreatic β-cells gradually fails, the level of fasting C-peptide gradually decreases and renal function gradually decreases.

Plaque regression and stabilizing plaques have become the key to treating diabetic macrovascular complications, and they become more urgent with the development of diabetes.

Atorvastatin can reduce serum Hcy and C-reactive protein levels, with functions of anti-inflammation, stabilizing plaque and plaque regression, and therefore it could improve the prognosis in very elderly patients with type 2 diabetes, with a low incidence of adverse drug reactions, high safety and good compliance.

In summary, the conditions of carotid atherosclerotic plaques in elderly patients with diabetes mellitus are associated with various factors, such as the disease course of diabetes, dyslipidemia, inflammatory factors, oxidative stress and renal dysfunction. Atorvastatin could improve the blood lipid profile, and also has a significant effect on carotid atherosclerotic plaque, C-reactive protein and homocysteine levels in very elderly patients with diabetes mellitus. In the future study, we will further explore the related factors and effective treatment based on this understanding.

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DISCLOSURE

The authors declare no conflict of interest.

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