

# Comparison of carotid and lower limb atherosclerotic lesions in both previously known and newly diagnosed type 2 diabetes mellitus

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Atherosclerosis, Diabetes, Epidemiology

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## ABSTRACT

**Aims/Introduction:** To compare carotid and lower limb atherosclerotic lesions, and examine if carotid atherosclerotic lesions are in line with lower limb atherosclerotic lesions, and can reflect generalized atherosclerosis in inpatients with type 2 diabetes.

**Materials and Methods:** This was an observational study carried out in 867 Chinese inpatients with type 2 diabetes, including 573 previously known and 294 newly diagnosed patients. Ultrasonographic assessments of intima-media thickness (IMT), plaques, and stenosis in the carotid and lower limb arteries were evaluated. Atherosclerotic lesions between the carotid and lower limb arteries were compared in both previously known and newly diagnosed diabetes, respectively.

**Results:** In both the known (77.3% vs 49.4%,  $P < 0.001$ ) and the newly diagnosed diabetes (55.4% vs 29.9%,  $P < 0.001$ ), the prevalence of atherosclerotic plaques was significantly higher in the lower limb arteries than in the carotid arteries. Likewise, the prevalence of stenosis was also significantly higher ( $P < 0.001$ ) in the lower limb arteries (16.9%) than in the carotid arteries (4.2%) in the established diabetes patients. However, there was no significant difference in the mean IMT between common carotid and common femoral arteries in both the previously known ( $0.90 \pm 0.24$  mm vs  $0.89 \pm 0.20$  mm,  $P = 0.675$ ) and the newly diagnosed diabetes patients ( $0.86 \pm 0.22$  mm vs  $0.85 \pm 0.16$  mm,  $P = 0.436$ ).

**Conclusions:** Carotid plaques might underestimate generalized plaques in inpatients with type 2 diabetes, as shown by its significantly lower prevalence compared with that of the lower extremity arteries. A combined carotid and lower limb ultrasound examination can improve the detection of atherosclerotic lesions in inpatients with type 2 diabetes.

## INTRODUCTION

Atherosclerotic complications are the leading causes of morbidity and mortality among patients with type 2 diabetes mellitus<sup>1,2</sup>. In addition to coronary arteries, carotid and lower extremity arteries are two other sites where atherosclerotic

lesions commonly occur<sup>2</sup>. Diabetes accelerates the progression of atherosclerosis, and increases the incidence of myocardial infarction, stroke and peripheral arterial disease<sup>2–5</sup>. Therefore, early detection of atherosclerosis in individuals with diabetes is crucial in reducing the risk of cardiovascular, cerebrovascular and amputation events.

Currently, ultrasound examination of carotid arteries is used to investigate the signs of early atherosclerotic vascular disease.

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Carotid atherosclerotic lesions are regarded as an indicator of generalized atherosclerosis. For example, previous studies showed that carotid atherosclerosis detected by ultrasonography could be an appropriate marker of atherosclerotic disease, and had been shown to independently reflect both cardiovascular and cerebrovascular events<sup>6–8</sup>. However, there is controversy whether carotid atherosclerosis detected by ultrasonography can be used as a surrogate marker of generalized atherosclerosis. For example, there are studies that showed that plaque formation in the carotid arteries was weakly associated with plaques in other peripheral arteries<sup>9,10</sup>. In particular, based on ultrasonography, studies comparing the difference of carotid and lower limb atherosclerotic lesions in type 2 diabetes are almost completely lacking.

In a previous study, we found that combining carotid and lower limb ultrasound examination could improve the detection of atherosclerotic plaques in patients with type 2 diabetes<sup>11</sup>. In the present study, we further compared the intima-media thickness (IMT) value and the prevalence of atherosclerotic plaques and stenosis between the carotid and lower limb arteries, and examined if carotid atherosclerotic lesions were in parallel with lower extremity atherosclerotic lesions in patients with type 2 diabetes using vascular Doppler ultrasonography. Given the fact that the duration of diabetes is an important risk factor for atherosclerosis of carotid and lower limb arteries in type 2 diabetes<sup>11</sup>, we divided the type 2 diabetics into previously known and newly diagnosed patients, and investigated if the characteristics of atherosclerotic lesions were different between the previously known and the newly diagnosed patients with type 2 diabetes.

## MATERIALS AND METHODS

### Participants and Study Design

The current study was a cross-sectional study and partly based on data used in our previous study<sup>11</sup>. Between May 2007 and July 2008, 917 consecutive type 2 diabetes patients who were admitted to the Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China, were observed, and valid information was available for 867 patients including 573 previously known and 294 newly diagnosed patients with type 2 diabetes in the present study. According to the World Health Organization criteria<sup>12</sup>, newly diagnosed diabetes was defined as having either fasting plasma glucose (FPG)  $\geq 7.0$  mmol/L and/or 2-h postprandial plasma glucose (2-h PPG)  $\geq 11.1$  mmol/L or a 2-h plasma glucose  $\geq 11.1$  mmol/L during a 75-g oral glucose tolerance test in patients without a history of diabetes. Previously known diabetes was defined based on self-reported physician diagnosis or use of antidiabetic agents. The definition of diabetic retinopathy, diabetic nephropathy and cardiocerebrovascular events was according to our previous study<sup>11</sup>. All participants were interviewed to obtain their history of hypertension, cardiocerebrovascular events, alcohol consumption and smoking habits, and underwent an ultrasonographic evaluation

of IMT, plaque, and stenosis in both the carotid and lower extremity arteries. The study was approved by the Ethics Committee of the hospital, and all participants gave written informed consent.

### Physical Examination and Laboratory Assays

A physical examination including weight, height and blood pressure was carried out. Body mass index (BMI) was calculated as weight divided by height squared. Hypertension was defined according to our previously described criteria<sup>11</sup>. Blood samples for plasma glucose; C-peptide; glycated hemoglobin A1c (HbA1c); renal function tests including blood urea nitrogen (BUN), serum creatinine (Scr) and blood uric acid (BUA); liver function tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and  $\gamma$ -glutamyltransferase ( $\gamma$ -GT); and lipid levels including total cholesterol (TC), total triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were obtained after an overnight fast, and 2 h after breakfast.

### Ultrasonography Measurements

Color Doppler sonography was carried out with an Acuson Sequoia 512 (Siemens Medical Solutions, Mountain View, CA, USA) scanner equipped with a 5–13-MHz linear array transducer. The ultrasonographic examination was carried out by three experienced ultrasonographers according to a standardized technique. After the participants had remained in the supine position for 5 min, the transducer was placed on the neck and lower limbs to show both vessel imaging and blood flow characteristics. At each location, IMT, atherosclerotic plaques and stenosis were recorded. Carotid arteries were examined bilaterally at the levels of the common carotid arteries, the bifurcation, the external carotid arteries, and the internal carotid arteries from transverse and longitudinal orientations. Seven locations of each lower limb artery were evaluated: common femoral artery, profunda femoris artery, superficial femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery and peroneal artery. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. The mean IMT was defined as the mean of IMT in both right and left sides of the common carotid artery or common femoral artery. Atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value or IMT of  $>1.5$  mm<sup>13</sup>. Carotid atherosclerotic plaque was defined as the presence of atherosclerotic plaques in any of the aforementioned carotid arteries segments<sup>11,14</sup>. Lower limb atherosclerotic plaque was defined as the presence of atherosclerotic plaques in any of the above-mentioned lower limb artery segments<sup>11</sup>. Based on previous literature<sup>15–17</sup>, artery stenosis in the present study was classified into three categories: normal, 1–49% diameter reduction and  $\geq 50\%$  diameter reduction. A significant artery stenosis

was defined as  $\geq 50\%$  stenosis. Both the intraobserver and interobserver reproducibility were determined using Spearman's correlation coefficient. The intraobserver correlation coefficients were 0.91–0.92 for carotid IMT and 0.92–0.94 for femoral IMT, 0.88–0.89 for carotid plaque and 0.89–0.94 for lower limb arterial plaque, and 0.87–0.94 for carotid stenosis and 0.94–1.00 for lower limb arterial stenosis, respectively. The interobserver correlation coefficients were 0.87–0.97 for carotid IMT and 0.95–0.97 for femoral IMT, 0.83–0.94 for carotid plaque and 0.89–0.94 for lower limb arterial plaque, and 0.82–0.89 for carotid stenosis and 0.83–0.89 for lower limb arterial stenosis, respectively.

### Comparison of Carotid and Lower Limb Atherosclerotic Lesions

The comparisons of carotid and lower limb atherosclerotic lesions in the present study population were based on the comparison of atherosclerotic plaques, stenosis and IMT. The comparisons of atherosclerotic plaques and stenosis were carried out at both the patient-level and vessel-level. In the vessel-level analysis, the left carotid artery, the right carotid artery, the left lower limb artery and the right lower limb artery were considered separately. In the patient-level analysis, the prevalence of plaque and stenosis between the carotid and lower limb arteries was compared. In addition to comparing the prevalence of atherosclerotic plaques, the prevalence of artery stenosis and significant artery stenosis was also compared. The comparison of IMT was carried out between the mean common carotid IMT and the mean common femoral IMT.

### Statistical Analysis

The data were analyzed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). For continuous variables, the Kolmogorov–Smirnov test was applied to examine normal distribution. Continuous variables were expressed as mean  $\pm$  standard deviation, and compared by two-sided *t*-tests or, if the data were not distributed normally, variables were expressed as median with interquartile range and the Mann–Whitney *U*-test was used. Categorical variables were expressed as percentages and using a  $\chi^2$ -test or Fisher's exact test. Linear regression was used to evaluate differences of continuous variables while adjusting for age and/or sex. Binary logistic regression was used to evaluate differences of categorical variables while adjusting for age and/or sex. A two-sided alpha level of 0.05 was considered statistically significant.

## RESULTS

### Clinical Characteristics of the Study Patients

The clinical characteristics of the 867 inpatients with type 2 diabetes are shown in Table 1. The mean age of the previously known diabetics ( $62 \pm 11$  years) was significantly older than that of the newly diagnosed diabetics ( $52 \pm 15$  years). Interestingly, after adjustment for age and sex, only the lower limb atherosclerotic lesions in the previously known type 2 diabetics

were more severe than in the newly diagnosed type 2 diabetics. The prevalence of diabetic retinopathy, diabetic nephropathy and cardiocerebrovascular events was markedly higher in the previously known diabetics than in the newly diagnosed diabetics, even after adjustment for age and sex.

### Comparison of Carotid and Lower Limb Atherosclerotic Plaques

The comparison of carotid and lower limb atherosclerotic plaques is shown in Figure 1. Patient-level analysis showed that in both the previously known diabetes group and in the newly diagnosed diabetes group, the prevalence of atherosclerotic plaques was significantly higher in the lower limb arteries than in the carotid arteries (all  $P < 0.001$ ; Figure 1a).

Vessel-level analysis showed that both in the previously known group and in the newly diagnosed diabetes group, more than 50% of the left and right lower limb arteries had atherosclerotic plaques, giving them the highest prevalence of plaque in our patient population (Figure 1b). Between 25 and 50% of the left and right carotid arteries had plaques in the previously known diabetes (Figure 1b). Less than 25% of the left and right carotid arteries were diseased in the newly diagnosed patients with diabetes, giving them the lowest prevalence of plaque in our patient population (Figure 1b).

In contrast, the prevalence of isolated carotid plaque was 6.8%, isolated lower extremity plaque 32.3%, and plaques in both the carotid and lower extremity arteries 23.1% in the newly diagnosed diabetes patients (Figure 1c). However, more patients tended to have atherosclerotic plaques in both the carotid and lower limbs (43.4%) than in either the isolated carotid (5.9%) or in the isolated lower limb arteries (33.9%) in the previously known diabetes patients (Figure 1c).

### Comparison of Carotid and Lower Limb Atherosclerotic Stenosis

Figure 2 shows the comparison of carotid and lower limb atherosclerotic stenosis. In the patient-level analysis, the prevalence of atherosclerotic stenosis was significantly higher in the lower limb arteries than in the carotid arteries in the established diabetes (Figure 2a). In contrast, the prevalence of stenosis was not significantly different between the carotid and lower limb arteries in the newly diagnosed diabetes patients (Figure 2a). In the newly diagnosed diabetes patients, the prevalence of isolated carotid arterial stenosis and isolated lower extremity arterial stenosis was 3.0 and 4.8%, and there was no stenosis in both the carotid and lower extremity arteries (Figure 2b). In the previously known diabetes, artery stenosis tended to be more often seen just in the lower limb arteries, which was much higher than in either isolated carotid arteries or in both the carotid and lower limb arteries (Figure 2b).

In the vessel-level analysis, the left lower limb artery (16.6%) had the greatest prevalence in the previously known diabetes patients, followed by the right lower limb artery (16.2%), and

**Table 1** | Characteristics and comparison between previously known and newly diagnosed type 2 diabetes patients

| Variables                            | Previously known type 2 diabetes (n = 573) | Newly diagnosed type 2 diabetes (n = 294) | P-value | P-value* |
|--------------------------------------|--|---|---------|----------|
| Male, n (%)                          | 284 (49.6%)                                | 191 (65.0%)                               | <0.001  | 0.02     |
| Age (years)                          | 62 ± 11                                    | 52 ± 15                                   | <0.001  | <0.001   |
| Duration of diabetes (months)        | 118 ± 79                                   |   | –       | –        |
| Smoking, n (%)                       | 133 (23.2%)                                | 61 (20.8%)                                | 0.503   | 0.615    |
| Alcohol, n (%)                       | 162 (28.3)                                 | 87 (29.6%)                                | 0.712   | 0.789    |
| Hypertension, n (%)                  | 308 (53.8%)                                | 115 (39.1%)                               | <0.001  | 0.242    |
| Hyperlipidemia, n (%)                | 450 (78.5%)                                | 203 (69.0%)                               | 0.227   | 0.428    |
| Body mass index (kg/m <sup>2</sup> ) | 24.79 ± 3.59                               | 25.26 ± 3.71                              | 0.079   | 0.454    |
| Waist circumference (cm)†            | 89 (83–96)                                 | 90 (84–96)                                | 0.508   | 0.537    |
| Systolic blood pressure (mmHg)       | 133 ± 18                                   | 127 ± 15                                  | <0.001  | 0.049    |
| Diastolic blood pressure (mmHg)      | 90 ± 9                                     | 81 ± 10                                   | 0.202   | 0.309    |
| Aspartate aminotransferase (U/L)†    | 19 (14–29)                                 | 26 (16.5–42.5)                            | <0.001  | 0.003    |
| Alanine aminotransferase (U/L)†      | 19 (16–24)                                 | 23 (17–32)                                | <0.001  | 0.027    |
| γ-glutamyltransferase (U/L)†         | 23 (16–40)                                 | 31 (21.5–53.5)                            | <0.001  | 0.479    |
| Blood urea nitrogen (μmol/L)†        | 5.50 (4.53–6.70)                           | 4.9 (4.0–6.3)                             | <0.001  | 0.079    |
| Serum creatinine (μmol/L)†           | 67 (56–80)                                 | 68 (56–80)                                | 0.996   | 0.734    |
| Blood uric acid (μmol/L)†            | 313 (255–371)                              | 303 (241–373)                             | 0.319   | 0.310    |
| Total triglycerides (mmol/L)†        | 1.40 (0.98–2.12)                           | 1.51 (1.07–2.13)                          | 0.081   | 0.746    |
| Total cholesterol (mmol/L)†          | 4.50 (4.00–5.30)                           | 4.90 (4.10–5.61)                          | 0.001   | 0.003    |
| High-density lipoprotein (mmol/L)†   | 1.11 (0.95–1.31)                           | 1.05 (0.89–1.23)                          | 0.001   | 0.416    |
| Low-density lipoprotein (mmol/L)†    | 2.91 (2.42–3.40)                           | 3.30 (2.57–3.99)                          | <0.001  | <0.001   |
| Fasting plasma glucose (mmol/L)†     | 7.46 (5.84–9.30)                           | 8.57 (6.79–11.33)                         | <0.001  | <0.001   |
| 2 h plasma glucose (mmol/L)          | 12.77 ± 4.44                               | 15.58 ± 5.63                              | <0.001  | <0.001   |
| Fasting C-peptide (ng/mL)†           | 1.71 (1.07–2.59)                           | 1.65 (0.88–2.43)                          | 0.616   | 0.102    |
| 2-h Postprandial C-peptide(ng/mL)†   | 3.84 (2.15–5.68)                           | 3.34 (1.9–5.48)                           | 0.105   | 0.732    |
| Glycated hemoglobin A1C (%)          | 8.82 ± 2.42                                | 10.86 ± 2.50                              | <0.001  | <0.001   |
| Mean femoral IMT (mm)                | 0.89 ± 0.20                                | 0.85 ± 0.16                               | 0.005   | 0.045    |
| Mean carotid IMT (mm)                | 0.87 ± 0.24                                | 0.79 ± 0.23                               | <0.001  | 0.849    |
| Carotid plaques, n (%)               | 283 (49.4%)                                | 88 (29.9%)                                | <0.001  | 0.135    |
| Lower limb plaques, n (%)            | 443 (77.3%)                                | 163 (55.4%)                               | <0.001  | 0.052    |
| Carotid stenosis, n (%)              | 24 (4.2%)                                  | 9 (3.1%)                                  | 0.412   | 0.425    |
| Lower limb stenosis, n (%)           | 97 (16.9%)                                 | 14 (4.8%)                                 | <0.001  | 0.010    |
| Diabetic retinopathy, n (%)          | 171 (29.8%)                                | 47 (16.0%)                                | <0.001  | <0.001   |
| Diabetic nephropathy, n (%)          | 163 (28.4%)                                | 26 (8.8%)                                 | <0.001  | <0.001   |
| Cardio-cerebrovascular events, n (%) | 132 (23%)                                  | 23 (7.8%)                                 | <0.001  | <0.001   |

Values are expressed as the mean ± standard deviation, or median with interquartile range, or percentages. †Non-normal distribution of continuous variables. The P-values were not adjusted for age and sex for trend. \*The P values were adjusted for age and sex for trend.

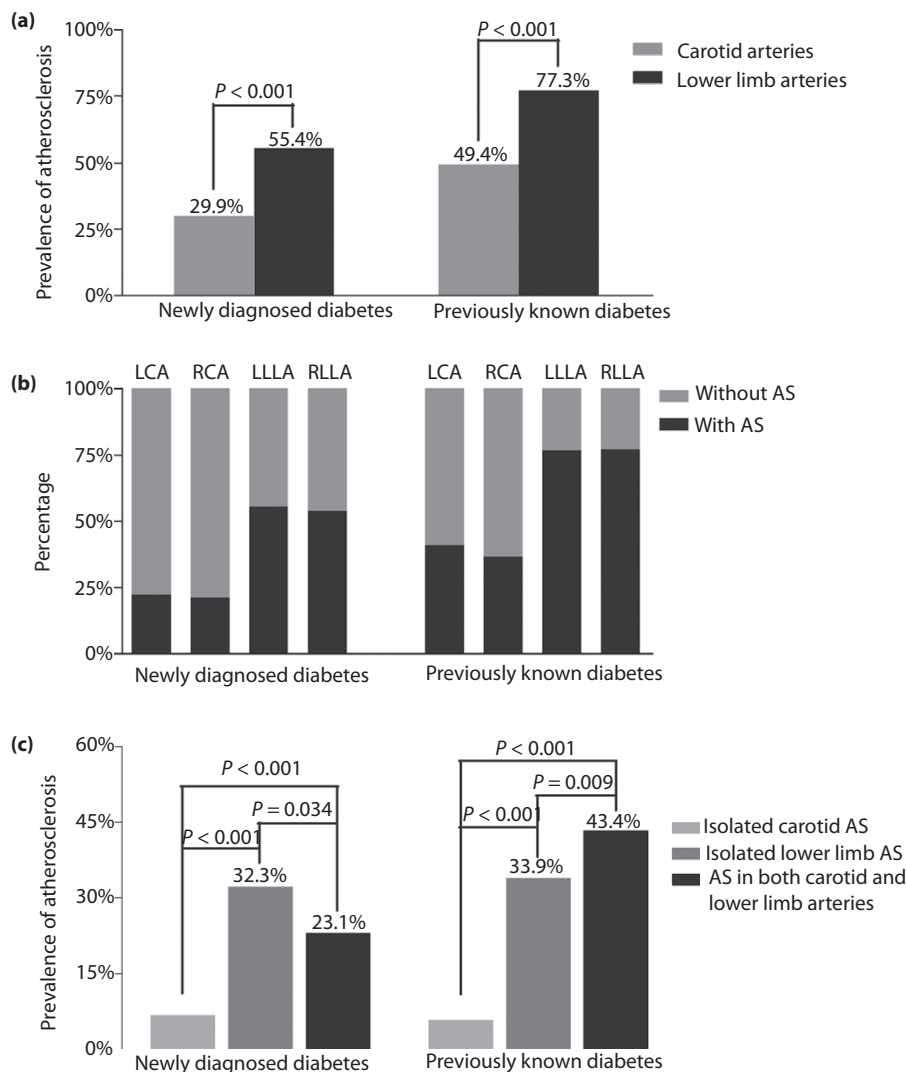
the left and right carotid artery (all 3.3%; Figure 2c). Similarly, in the newly diagnosed type 2 diabetes, the left and right lower limb artery (all 4.1%) had the greatest prevalence, followed by the left carotid artery (2.4%) and the right carotid artery (1.7%; Figure 2c).

When considering the prevalence of significant artery stenosis (≥50% stenosis) in the previously known diabetes, the left carotid artery had a prevalence of 73.7%, the left lower limb artery 71.6%, the right lower limb artery 67.8% and the right carotid artery 52.6%, respectively (Figure 2d). In contrast, in the newly diagnosed diabetes, the left and right lower limb arteries had the greatest prevalence of significant artery stenosis (all 66.7%), and there was a prevalence of significant artery ste-

nosis of 12.5% in the left carotid artery (Figure 2d). The right carotid artery had no significant artery stenosis in the newly diagnosed diabetes (Figure 2d).

#### Comparison of Mean IMT Between Common Carotid and Common Femoral Arteries

The comparison of mean IMT between common carotid and common femoral arteries is presented in Figure 3. In both the previously known diabetes group (0.90 ± 0.24 mm vs 0.89 ± 0.20 mm) and the newly diagnosed diabetes group (0.86 ± 0.22 mm vs 0.85 ± 0.16 mm), there was no significant difference between the mean common carotid IMT and the mean common femoral IMT (Figure 3).



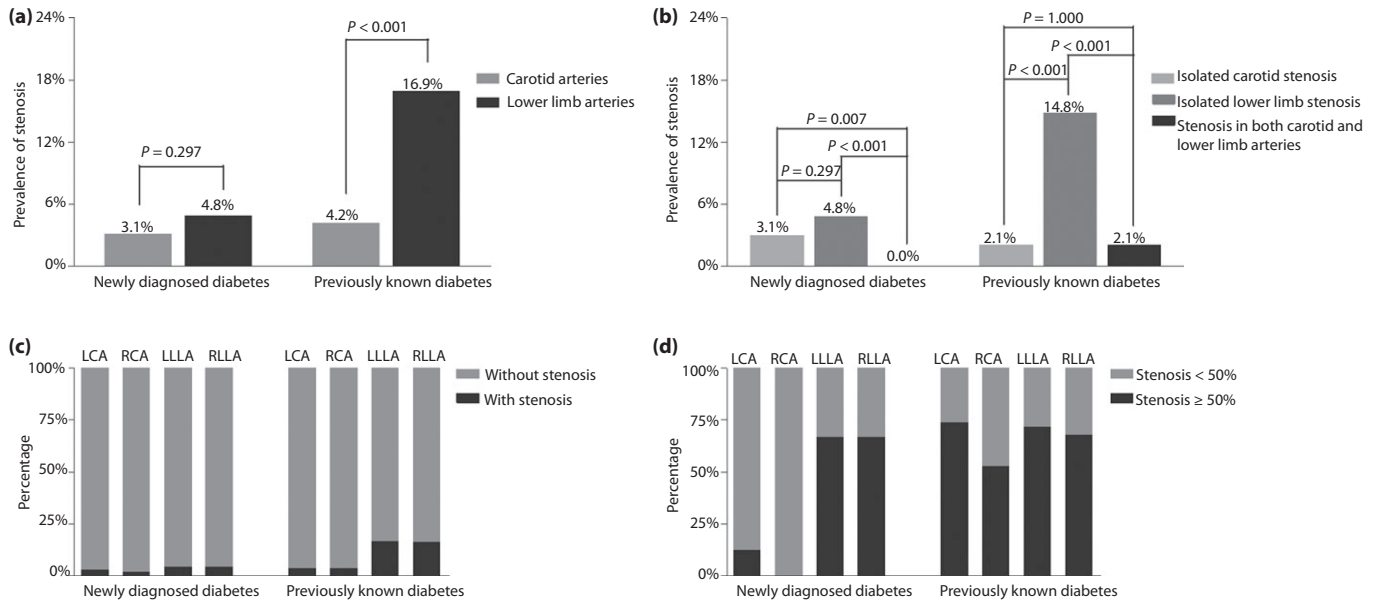
**Figure 1** | Comparison of carotid and lower limb atherosclerotic plaques in both the previously known and the newly diagnosed diabetes patients. (a) The comparison of the prevalence of atherosclerotic plaques in the carotid and lower limb arteries. (b) The comparison of the prevalence of atherosclerotic plaques in the left carotid, right carotid, left lower limb and right lower limb artery. An artery was considered normal if there was no evidence of atherosclerotic plaque present. An artery was considered “diseased” if there was evidence of any level of atherosclerotic plaque. (c) The percentage of patients with atherosclerotic plaques. The patients with plaques were divided into three groups including the patients with isolated carotid plaque, patients with isolated lower extremity plaque, and patients with plaques in both the carotid and lower extremity arteries. The *P*-values for three group comparisons were all  $<0.001$  in both the newly diagnosed diabetes patients and the previously known diabetes patients. LCA, left carotid artery; LLLA, left lower limb artery; RCA, right carotid artery; RLLA, right lower limb artery.

## DISCUSSION

Carotid ultrasonography is presently widely used as a means of assessing atherosclerotic changes in type 2 diabetes<sup>18–20</sup>. Meanwhile, carotid atherosclerosis has been commonly recognized as an indicator of general atherosclerosis because of its relationship to coronary atherosclerosis, lower limb atherosclerosis and atherosclerosis elsewhere in the circulation<sup>21–23</sup>. For example, Hulthe *et al.*<sup>24</sup> showed that the presence of atherosclerosis in the carotid arteries is known to be reflective for the extent of coronary atherosclerosis. Another previous

study found that there was a significant correlation between carotid artery disease and lower extremity arterial disease in a healthy population of elderly adults with isolated systolic hypertension<sup>25</sup>. Therefore, carotid atherosclerosis appears to mark the presence of generalized atherosclerosis.

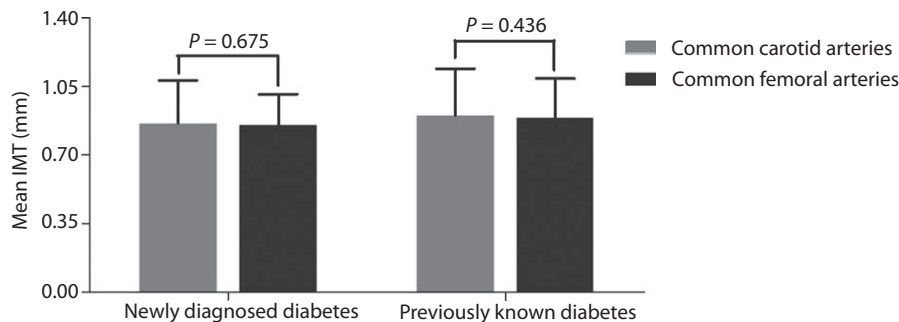
However, conflicting results have been reported for the correlation between carotid atherosclerosis and atherosclerosis elsewhere in the arterial system. Furthermore, little has been published regarding the comparison of carotid and lower limb artery atherosclerotic lesions in patients with diabetes. For



**Figure 2** | Comparison of carotid and lower limb atherosclerotic stenosis in both the previously known and the newly diagnosed diabetes patients. (a) The comparison of the prevalence of atherosclerotic stenosis in the carotid and lower limb arteries. (b) The percentage of patients with stenosis. The patients with stenosis were divided into three groups including patients with isolated carotid stenosis, patients with isolated lower extremity stenosis, and patients with stenoses in both the carotid and lower extremity arteries. The *P*-values for three group comparisons were 0.001 in the newly diagnosed diabetes patients and <0.001 in the previously known diabetes patients, respectively. (c) The comparison of the prevalence of atherosclerotic stenosis in the left carotid, right carotid, left lower limb and right lower limb artery. Artery stenosis including both 1–49% diameter reduction and ≥50% diameter reduction. (d) The comparison of the prevalence of significant atherosclerotic stenosis in the left carotid artery (LCA), right carotid artery (RCA), left lower limb artery (LLLA) and right lower limb artery (RLLA). Stenosis was considered significant if it caused ≥50% stenosis of a vessel.

example, there are studies showing that the presence of atherosclerotic plaques in the carotid arteries does not reflect atherosclerosis elsewhere in the arterial system<sup>9,10,26</sup>. This view might be further strengthened by findings from a study in which there is no correlation between the degree of lower extremity atherosclerosis and asymptomatic carotid artery stenosis >50% in male veterans with symptomatic lower limb atherosclerosis<sup>27</sup>. Furthermore, Sosnowski *et al.*<sup>28</sup> believe that the presence of femoral atherosclerotic plaque more precisely than that of the carotid plaque reflects the probability and severity of coronary artery atherosclerosis.

The present findings in a hospital-based sample of type 2 diabetes also showed that the plaque and stenosis in the carotid arteries did not indicate those in the lower extremity arteries in both the known and newly diagnosed type 2 diabetes patients, although the condition was more severe in the established patients with diabetes than in the newly diagnosed patients with diabetes. We compared the prevalence of atherosclerotic plaques and stenosis between the carotid and lower extremity arteries, based on both patient-level and vessel-level analyses. Patient-level analyses showed that in both the known and the newly diagnosed patients with diabetes, the prevalence of ath-



**Figure 3** | Comparison of mean intima-media thickness (IMT) between common carotid and common femoral arteries in both the previously known and the newly diagnosed diabetes patients.

therosclerotic plaques was markedly higher in the lower extremity arteries than in the carotid arteries.

There was a similar trend for the prevalence of stenosis in the previously known diabetes patients. In contrast, there was no significant difference in the prevalence of stenosis between the carotid and the lower extremity arteries in the newly diagnosed diabetes patients. When considering the prevalence of significant artery stenosis in the previously known diabetes patients, there was no significant difference between the lower extremity and carotid arteries. However, for the newly diagnosed type 2 diabetes, the prevalence of the significant artery stenosis was significantly higher in the lower limb artery than in the carotid artery, which showed that significant artery stenosis occurred earlier in the limb arteries in type 2 diabetes.

A previous study showed that the prevalence of carotid plaques was 28% in type 2 diabetic patients at baseline<sup>29</sup>. After a 2-year follow up, the prevalence of carotid plaques increased to 62%<sup>29</sup>. A study by Lacroix *et al.*<sup>30</sup> showed that the prevalence of carotid stenosis <60% and ≥60% was 63.6% and 4.7% in type 2 diabetic patients, respectively. The prevalence of lower extremity diseases was approximately 27% in both undiagnosed diabetes and diagnosed diabetes<sup>31</sup>. The higher prevalence of diabetic atherosclerotic lesions in the present study might be explained by the more serious condition in our studied population. Because of their more serious condition, such patients are more likely to be hospitalized, and to have a higher prevalence of atherosclerotic disease compared with the general population. In addition, it might also be explained by the different definition of atherosclerotic lesions and different measures of atherosclerosis in other studies.

Interestingly, in contrast to atherosclerotic plaques, whether in the previously known diabetes patients or in the newly diagnosed diabetes patients, there was no marked difference in the mean IMT between the common carotid and the common femoral arteries. IMT increase is an early event, and appears before plaque occurrence in the development of atherosclerosis, whereas formation of plaques represents advanced atherosclerotic lesions<sup>32</sup>. Additionally, carotid IMT is under genetic control, whereas carotid plaque is strongly influenced by environmental factors and less influenced by genetic factors<sup>32,33</sup>. Ebrahim *et al.*<sup>34</sup> have provided evidence that carotid plaque predicts cardiovascular events better than carotid IMT. Furthermore, the study by Held *et al.*<sup>35</sup> confirmed that carotid IMT was a weak predictor of events, and carotid plaques tended to predict the risk of cardiovascular death or myocardial infarction, whereas femoral artery IMT and plaques predicted the risk of revascularization. Therefore, based on the present results that carotid artery IMT value was similar to femoral artery IMT value, increased carotid IMT might represent a marker of general atherosclerosis and can be used as a way to detect early atherosclerosis risk populations, such as diabetic patients, in which prevention could be more efficient, but evaluations of plaques provided better prediction of cardiovascular events than assessments of IMT in patients with type 2 diabetes.

Thus, the present findings suggested that carotid plaque and stenosis might not represent atherosclerotic burden in type 2 diabetes, although it appears to do in general populations. However, carotid IMT might represent a marker of general atherosclerosis in type 2 diabetic patients. Different rheological conditions in the carotid and lower limb arteries could contribute to the differences presently observed.

The discrepancy between the present results and findings of other studies could be explained by the different definition of atherosclerosis and different populations studied by the researchers. The differences in study population and the methods used to assess atherosclerosis likely result in inconsistent results between studies. It is possible that carotid atherosclerosis is associated with lower limb atherosclerosis only in patients with a low risk of cardiovascular disease, but not in those with a high risk of cardiovascular disease, such as patients with diabetes. For example, in the Rotterdam Study, lower extremity atherosclerosis was defined as an ankle–arm index <0.90 in subjects aged ≥55 years<sup>21</sup>. However, based on ultrasound screening, the ankle-to-brachial index might underestimate the prevalence of peripheral occlusive disease in patients with diabetes<sup>36</sup>. More studies are required to determine whether carotid atherosclerosis reflects lower limb atherosclerosis in a population other than diabetes mellitus patients using ultrasound examination.

The present study has potential clinical significance and practical application. Our findings call into question the widespread use of carotid atherosclerotic plaques as an indicator of general atherosclerosis in patients with diabetes. The carotid plaque severely underestimates the burden of lower extremity atherosclerosis in both the previously known and newly diagnosed type 2 diabetes patients. The combination of carotid and lower extremity ultrasonography will be of considerable use in future clinical applications. Although screening the general population for lower limb atherosclerosis is currently of unproven value in effecting outcomes, it would be cost-effective in a population at high risk for atherosclerosis, such as diabetes, coronary artery disease and cerebrovascular disease patients.

Several potential limitations of the current study should be mentioned. First, the present sample was limited to inpatients with type 2 diabetes. Therefore, caution should be exercised in drawing conclusions regarding other populations, such as the general population and type 1 diabetic patients. Second, because our study design was cross-sectional, we cannot assess the evolution of the process of atherosclerosis. Finally, the present study was limited by the small sample size, and a further large-scale study to confirm our findings would be useful.

In conclusion, the present study provides evidence that carotid atherosclerotic plaques cannot reflect generalized atherosclerosis in type 2 diabetic patients, as shown by its significantly lower prevalence compared with that of the lower extremity arteries, which not only exists in previously known diabetics, but also in newly diagnosed diabetics. Carotid ultrasonography can provide important information of carotid arterial lesions,

but cannot accurately assess the presence and severity of atherosclerosis elsewhere in type 2 diabetes. It emphasizes the value of the combination of ultrasonography of carotid and lower extremity arteries in detection of early atherosclerotic lesions in patients with type 2 diabetes.

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