Carotid Intima Media Thickness and Plaque in Type 2 Diabetes without Cardiovascular Disease

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Background: *Type 2 diabetes mellitus (T2DM) constitutes a major public health care problem in Thailand and worldwide. Many complications can occur, especially atherosclerotic change in the vessels leading to coronary, cerebrovascular and peripheral arterial disease.*
Objective: *Using B-mode ultrasound (US), to study the carotid intima media thickness (IMT) and carotid plaque in patients with type 2 DM without cardiovascular disease, and to identify the factors that are related to plaque formation.*
Material and Method: *This was a prospective cross-sectional study, conducted in Rajavithi Hospital between September 2016 and February 2017, of 150 patients with type 2 DM who had no history of symptomatic coronary, cerebrovascular or peripheral arterial disease. Measurement of carotid IMT and carotid plaque was performed by a single radiologist.*
Results: *There were 150 patients, 68.7% of whom were women and 31.3% men, and their mean age was 66 years (48 to 79 years old). Mean carotid IMT of the right and left common carotid artery were 0.79±0.26 mm and 0.83±0.28 mm, respectively. Plaque levels at the right and left carotid bulb were 1.46±0.69 mm and 1.37±0.61 mm respectively, while plaque levels at the right and left internal carotid artery were 1.24±2.88 mm and 1.03±0.45 mm, respectively. A total of 87.3% of subjects were associated with hypertension and 96.0% with dyslipidemia during medical treatment. A rate of less than 50% carotid stenosis was found in 26.7% of the patients, while those with more than 50.0% carotid stenosis accounted for 10.0%. There was no gender-related difference in carotid plaque formation in this study. The rate of positive carotid plaque was associated with the duration of DM (p-value = 0.004), and serum triglyceride levels (p-value = 0.004). Multivariate regression analysis indicated that significant carotid plaque was associated with receiving ACEI/ARB for treatment of hypertension (p-value = 0.029).*
Conclusion: *Carotid atherosclerosis was found in 36.7% of cases. Most of the patients in the present study were normal or had no significant carotid atherosclerosis. There were varying degrees of vessel stenosis ranging between less than 50.0% stenosis and 50.0 to 70.0%. Ten percent of patients had more than 50.0% stenosis and received aspirin to prevent future vascular events.*

Keywords: *Carotid plaque, Carotid IMT, B-mode ultrasound, Type 2 DM, Angiotensin- converting enzyme inhibitors (ACEI), Angiotensin II receptor blocker (ARB)*

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Non-communicable diseases (NCDs), including type 2 DM, hypertension, dyslipidemia, obesity, cardiovascular disease, cerebrovascular disease and cancer, are the major causes of death in Thailand and worldwide. The International Diabetes Federation estimates that there will be 552 million patients with diabetes mellitus, and a further 398 million patients at risk of developing it, by the year 2030[1]; therefore, type 2 DM constitutes a major current and future health problem. Its prevention and treatment include healthy diet, regular exercise, maintenance of optimal body weight, appropriate medical treatment, and foot care. Complications of type 2 DM usually occur after a duration of DM of more than 5 years without adequate treatment. These complications include diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, coronary vascular disease, cerebrovascular disease, peripheral arterial disease, and diabetic ulcers. Type 2 DM is usually associated with hypertension and dyslipidemia. All of these can lead to an increase in the atherosclerotic process which can result primarily from endothelial dysfunction and accumulation of fat in the vessel walls. This continuous atherosclerotic process causes narrowing of the luminal

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vessel wall[2] and clinical atherosclerotic vascular disease (ASCVD) including acute coronary syndrome (ACS), ischemic stroke, transient ischemic attack (TIA), and atherosclerotic aortic disease. Subclinical ASCVD can be diagnosed by many methods including carotid plaque by B-mode ultrasound of carotid artery, calcium score of more than 300 by non-contrast CT of coronary artery, and ankle brachial index (ABI) of less than 0.9.

B-mode US can assess carotid IMT easily because the wall of the artery is superficial and can, therefore, be imaged non-invasively, in real time and at high resolution. An increase in the IMT of the common carotid artery can be used to predict cardiovascular events[3,4]. The arterial wall may demonstrate two parallel echogenic lines that are separated by a relatively hypoechoic intermediate area on longitudinal B-mode US, and the distance between these lines is the IMT (Fig. 1). This non-invasive, high-resolution imaging technique is readily available and inexpensive. High-frequency linear transducers (>7 MHZ) are ideal for measuring carotid wall thickness, as well as for qualitatively and quantitatively analyzing plaques[5].

In the cardiovascular health study, increases in IMT of the carotid artery were associated with an increased risk of myocardial infarction and ischemic stroke in older adults without a history of cardiovascular disease. CCA IMT greater than 0.87 mm and ICA IMT greater than 0.90 mm were associated with a progressively increased risk of cardiovascular events. For each 0.20 mm increase in CCA IMT, the risk increases by approximately 27%. For each 0.55 mm increase in ICA IMT, the risk increases approximately 30.0%. IMTs of the CCA and ICA above 1.18 and 1.81, respectively, were associated with a more than 2-fold increase in the risk of a cardiovascular event over 6 years. Carotid plaque appears to be a more powerful predictor of cardiovascular risk than carotid IMT alone[6]. Carotid plaque consists predominantly of intimal thickening with foam cells, smooth muscle cells, macrophages, lipid core, and fibrous cap depending on the stage of plaque development[7]. In terms of plaque shape, surface irregularities also demonstrate markers of plaque vulnerability and are predictive of ischemic stroke[8]. Echolucent plaques are associated with higher concentrations of soft-tissue components, such as fibrofatty and hemorrhagic contents (vulnerable plaques)[9].

Fig. 1 Normal carotid artery showing site for measuring Intima-media thickness at far wall. Normal IMT should be less than 1 mm.

A consensus conference of the Society of Radiologists in Ultrasound recommended the following criteria for estimating stenosis[10]:

Normal: ICA PSV <125 cm/sec and no plaque or intimal thickening is visible.

<50.0% stenosis: ICA PSV <125 cm/sec and plaque or intimal thickening is visible.

50.0 to 69.0% stenosis: ICA PSV is 125 to 230 cm/sec and plaque is visible.

>70.0% stenosis to near occlusion: ICA PSV >230 cm/sec, visible plaque and luminal narrowing.

Near occlusion: A markedly narrowed lumen is seen.

Total occlusion: No detectable patent lumen is seen on grayscale US, and no flow is seen on spectral, power, and color Doppler US.

Objective

To study the carotid intima media thickness (IMT) and carotid plaque in patients with type 2 DM without cardiovascular disease using B-mode ultrasound (US), and to identify the factors that are related to plaque formation.

Material and Method

This prospective cross-sectional study was conducted in a single tertiary hospital center (Rajavithi Hospital, Bangkok, Thailand), and the protocol was reviewed and approved by the ethics committee of the hospital (No. 110/2559). The inclusion criteria were type 2 DM patients aged between 40 and 80 years, with or without hypertension and dyslipidemia. The exclusion criteria were patients who had coronary vascular disease, cerebrovascular disease or peripheral arterial

disease. Measurement of IMT at bilateral common carotid arteries, carotid bulb and internal carotid arteries was performed by a single radiologist using B-mode US. Detection of carotid plaque value and morphology was also attempted. In some patients with large amounts of plaque, percentage stenosis by direct measurement in a cross sectional image was performed.

Personal history data were recorded, including present and past illness, use of medications, duration of DM, cigarette smoking, and alcohol consumption. Physical examination findings included weight, height, body mass index (BMI), waist circumference, and systolic and diastolic blood pressure. Laboratory test results included fasting blood sugar, Hb A1C, blood urea nitrogen, serum creatinine, eGFR, urine microalbumin, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride.

Statistical analysis

All analyses were performed with the statistical program SPSS version 17.0. Data were presented as mean, standard deviation (SD), minimum and maximum for continuous variables, and number (%) for categorical variables. Comparison was made of continuous and categorical variables in the two groups using student t-test and Chi-square test, respectively, and binary logistic regression analysis was used to assess the relationship between risk factors and carotid atherosclerosis. A *p*-value of less than 0.05 was set for statistical significance in all tests.

Results

One hundred and fifty patients were recruited from September 6, 2016 to February 14, 2017. The mean age was 66 years (range 48 to 79 years), and the majority (68.7%) were women. The mean duration of DM was 17.97±6.84 years (range 2 to 35 years), the mean body mass index was 26.27±4.75 (range 16.03 to 39.41), and the mean waist circumference was 88.58±10.55 cm (range 63 to 111 cm). Baseline characteristics are detailed in Table 1.

One hundred and thirty-one patients (87.3%) received hypertensive drugs, 57 (38.0%) received diuretics, 25 (16.7%) received beta-blockers, 54 (36.0%) received Ca-antagonist, and 117 (78.0%) received ACEI/ARB for treatment of hypertension. One hundred and forty-four (96.0%) patients had dyslipidemia, and 140 (93.3%) received statins. Only 30 cases (20.0%) were given aspirin. Calibers of right and left bulb were 8.78±6.75 mm and 8.66±6.75 mm respectively. Mean carotid IMT of the right and left common carotid artery were 0.79±0.26 mm and 0.83±0.28 mm, respectively. Plaque levels at the right and left carotid bulb were 1.46±0.69 mm and 1.37±0.61 mm, respectively, and at the right and left internal carotid artery 1.24±2.88 mm and 1.03±0.45 mm, respectively. Plaque morphology included isoechoic (Fig. 2), calcified (Fig. 3) echolucent (Fig.4), smooth and irregular surface, and some mixed types. The data are shown in Table 2.

Table 1. Baseline characteristics of study subjects (150 cases)

Patient Characteristics	n (%)
Sex	
Female	103 (68.7)
Male	47 (31.3)
Ages (years)	65.97±6.89 (48 to 79)
40 to 59	28 (18.7)
60 to 69	71 (47.3)
70 to 79	51 (34.0)
Duration of DM (years)	17.97±6.84 (2 to 35)
BMI (kg/m^2)	26.27±4.75 (16.03 to 39.41)
Waist circumference (cm)	88.58±10.55 (63 to 111)
SBP (mmHg)	137.48±13.44 (100 to 174)
DBP (mmHg)	76.06±11.63 (70 to 97)
FPG (mg/dL)	135.20±36.81 (66 to 262)
HbA1c (%)	7.36±1.74 (1 to 13)
BUN (mg/dL)	18.27±10.74 (7 to 110)
Cr (mg/dL)	1.04±0.40 (0.5 to 4)
eGFR (ml/min/1.73m^2)	67.87±21.69 (10 to 110)
Urine microalbumin (mg/g)	95.97±354.89 (0.5 to 3,223)
Cholesterol (mg/dL)	166.21±42.03 (87 to 456)
HDL-cholesterol (mg/dL)	55.92±15.98 (24 to 102)
LDL-cholesterol (mg/dL)	94.87±31.84 (24 to 197)
Triglyceride (mg/dL)	128.59±78.42 (34 to 677)

Data were presented as number (percent), mean ± SD (min-max)

Normal or minimal intimal thickening was found in 95 cases (63.3%), less than 50.0% stenosis in 40 (26.7%), and more than or equal to 50.0% stenosis in 15 cases (10.0%). The data are shown in Fig.5. Of the 20 patients who received aspirin, only 3 had more than 50.0% carotid stenosis, so new 12 cases received aspirin in this study. Clinical characteristics of the normal and carotid atherosclerotic groups are shown in Table 3.

Of all patients, 87.3% were associated with hypertension and 96.0% were associated with dyslipedemia during medical treatment. The rate of less than 50.0% carotid stenosis was 26.7% and more than 50.0% stenosis was found in 10.0% of subjects. There was no difference between men and women. Of the 150

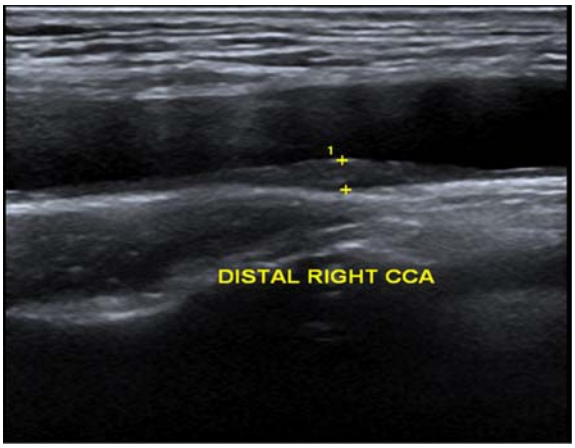

Fig. 2 Ultrasound (US) example of an isoechoic plaque.

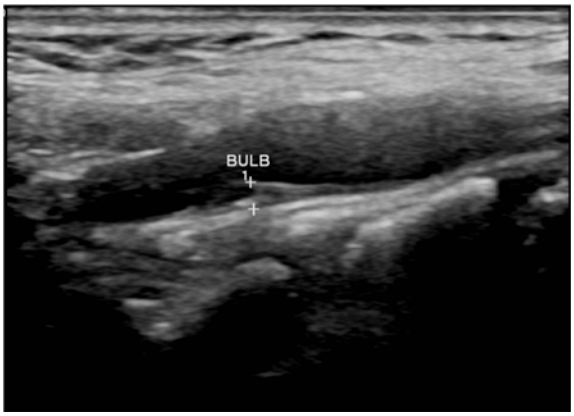

Fig. 4 Ultrasound (US) example of an echolucent plaque. The US image shows a smooth echolucent plaque in the carotid wall.

patients enrolled in the study, those with normal and carotid atherosclerosis had similar baseline characteristics with the exception of duration of DM and triglyceride. In the stenosis group, there were significantly higher DM duration and triglyceride than in the normal group. The rate of positive carotid plaque was associated with the duration of DM (*p*-value = 0.004), and levels of serum triglyceride (*p*-value = 0.004). The data are shown in Table 4. Multivariate regression analysis indicated that significant carotid plaque was associated with duration of diabetes, triglyceride levels, and receiving ACEI/ARB for treatment of hypertension, as shown in Table 4.

In the present study, the authors also found that more than half of the patients, (88 cases, 58.7%) had thyroid nodules, cystic, solid or mixed type. Most looked benign in nature, while a few appeared to be malignant.

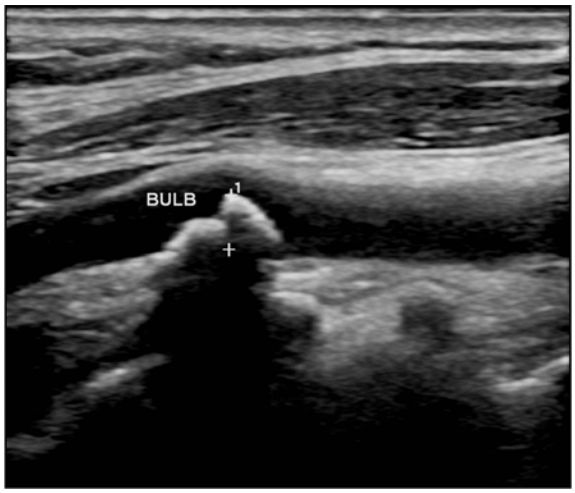

Fig. 3 Ultrasound (US) example of calcified plaque (bright area with shadowing) in the carotid artery.

Table 2. Carotid IMT plaque levels and plaque morphology by B- mode ultrasound

	Right (%) (n = 150)	Left (%) (n = 150)
CCA intima-media thickness		
Mean ± SD (mm)	0.79±0.26	0.83±0.28
Calcified	2 (1.3)	2 (1.3)
Isoecholic	148 (98.7)	143 (95.3)
Isoechoic/calcified	0 (0.0)	4 (2.7)
Isoechoic echolucent	0 (0.0)	1 (0.7)
Carotid bulb		
Mean ± SD (mm)	1.46±0.69	1.37±0.61
Calcified	25 (16.7)	18 (12.0)
Calcified/irregular border	1 (0.7)	0 (0.0)
Isoechoic	77 (51.3)	86 (57.3)
Isoechoic/calcified	45 (30.0)	46 (30.7)
Isoechoic/echolucent	2 (1.3)	0 (0.0)
Internal carotid artery		
Mean ± SD (mm)	1.24±2.88	1.03±0.45
Calcified	9 (6.0)	14 (9.3)
Isoechoic	118 (78.7)	107 (71.4)
Isoechoic/calcified	23 (15.3)	29 (19.3)

Data were presented as number (percent) and mean ± SD

Discussion

All 150 patients had a long duration of type 2 DM (median duration approximately 18 years). The median age was 66 years, and most patients had a history of hypertension and dyslipidemia that required medical

Table 3. Clinical characteristics of normal and carotid atherosclerosis groups

Characteristics	Stenosis		*p*-value
	No (n = 95)	Yes (n = 55)	
Age	65.23±6.73	67.25±7.03	0.083
Sex			
Female	64 (62.1)	39 (37.9)	0.652
Male	31 (66.0)	16 (34.0)	
Duration of DM (years)	16.92±6.82	19.78±6.54	0.013*
Waist circumference (cm)	88.80±10.79	88.20±10.23	0.738
BMI (kg/m^2)	26.37±4.97	26.10±4.37	0.733
SBP (mmHg)	136.52±12.44	139.15±14.99	0.250
DBP (mmHg)	75.89±12.73	76.36±9.55	0.809
FPG (mg/dL)	134.55±37.16	136.33±36.51	0.776
HbA1c (%)	7.24±1.64	7.55±1.89	0.295
BUN (mg/dL)	17.29±7.71	19.96±14.50	0.143
Cr (mg/dL)	1.03±0.44	1.05±0.32	0.753
eGFR (ml/min/1.73 m^2)	69.17±23.04	65.64±19.13	0.338
Urine microalbumin (mg/g)	69.02±250.07	142.53±484.96	0.223
Cholesterol (mg/dL)	161.59±31.96	174.20±54.71	0.122
HDL-cholesterol (mg/dL)	56.58±15.67	54.78±16.59	0.509
LDL-cholesterol (mg/dL)	94.96±30.92	94.73±33.65	0.966
Triglyceride (mg/dL)	115.25±56.15	151.64±103.09	0.018*

Data were presented as number (percent) and mean ± SD, * = significant at $p<0.05$

Table 4. Multivariate analysis of risk factors

Factors	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Duration of DM (years)	1.07 (1.01 to 1.24)	0.015	1.09 (1.03 to 1.15)	0.004*
Triglyceride (mg/dL)	1.01 (1.001 to 1.012)	0.012	1.01 (1.003 to 1.014)	0.004*
ACEI/ARB	3.24 (1.24 to 8.45)	0.016	3.05 (1.12 to 8.28)	0.029*

* = significant at $p<0.05$

treatment. The majority was obese with large waist circumference, and the mean common carotid artery IMT was normal (less than 1 mm). The mean carotid bulb IMT was abnormal (more than 1.3 mm), and the mean internal carotid artery IMT was also abnormal (more than 1 mm). These ultrasonographic findings were different from the findings of a study of carotid pathology in stroke patients, in which the mean CCA intima-media thickness was more than 1 mm. The mean carotid bulb IMT was more than 1.7 mm, and the mean internal carotid artery was more than 1.5 mm[11].

Eric De Groot et al[12] found that IMT measurement can accurately describe the process of arterial wall changes due to atherosclerosis, and measurement of arterial wall thickness is a surrogate marker for atherosclerosis.

Echolucent plaque in US of the carotid artery was found in three patients, one case at the left common carotid artery and two cases at the right bulb. This was vulnerable plaque associated with concentrations of soft-tissue components, such as fibrofatty and hemorrhagic contents. These asymptomatic patients with echolucent plaques were at high risk of ischemic stroke, so aspirin was given for primary prevention. Calcified and irregular border plaque was found in one case at the right bulb. Plaque surface irregularities are a marker of plaque vulnerability and are predictive of ischemic stroke, so aspirin was given to prevent future cardiovascular event or ischemic stroke. In 20 cases that received aspirin before, only 3 cases had more

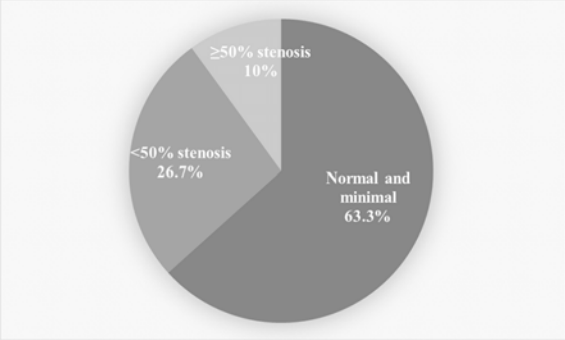

Fig. 5 Normal compared with grading carotid stenosis.

than 50.0% carotid stenosis. So the other 12 cases should receive aspirin in the present study.

The JPAD (Japanese Primary prevention of Atherosclerosis with Aspirin for Diabetes) was a prospective randomized, open-label, standard case-control trial. This study found that when given low doses of aspirin (81 to 100 mg), Japanese diabetic patients with no previous cardiovascular disease did not have their risk of cardiovascular events reduced, but suffered increase risk of gastrointestinal bleeding[13], and therefore, aspirin did not prevent plaque formation; however, it prevented arterial occlusion in cases of plaque rupture due to the antiplatelet effect. Aspirin should be given only to patients with arterial stenosis of more than 50 percent or in cases of ulcerated plaque, irregular surface, hemorrhage or vulnerable plaque. The drugs which prevent plaque formation include the statins ACEI and ARB.

Several studies have reported asymptomatic patients with echolucent plaques as being at high risk of ischemic stroke[14,15]. Nevertheless, there are conflicting studies on echogenicity, and there is no association between ischemic stroke and echogenic plaques[16]. This could be explained by the poor reproducibility of the subjective characterization of plaque echogenicity using B-mode US; however, this remains an ongoing subject of research[9].

Multivariate analysis revealed that carotid atherosclerosis in this study was significantly associated with longer duration of diabetes, higher levels of triglyceride and the usage of ACEI/ARB. Since this was a cross-sectional study, the use of ACEI/ARB cannot be postulated to have a causal relationship with atherosclerosis. The patients who received ACEI/ARB in the present study may have had more risk factors of atherosclerosis such as hypertension or diabetic nephropathy, which are indications for using ACEI/ARB. Other vessel wall imaging techniques[17] include: CT.

With multidetector and advanced software for image reconstruction, with improved spatial and temporal resolution, CT is a reliable tool for evaluating cervical carotid arterial pathology. With CT angiography, investigators can evaluate carotid stenosis and the morphology of carotid plaques. CTA is reliable and accurate (more than 70.0%, with 85.0% sensitivity and 93.0% specificity) in diagnosing severe stenosis. CTA is also highly accurate in diagnosing the degree of carotid occlusion (97.0% sensitivity and 99.0% specificity)[18]. In terms of plaque morphology, the most relevant surface alteration that may be detected on CTA is ulceration. Seba et al reported that CTA has a significantly higher diagnostic accuracy for plaque ulceration than US (93.0% vs. 37.5%, respectively); in their study, the presence of ulceration in surgery was used as the gold standard[19]. Several studies that have used CTA differentiated carotid artery plaques into three categories (fatty, mixed, and calcified lesions), according to the criteria by Schroeder et al[20]: Fatty plaques demonstrate an attenuation of <50 HU; mixed plaques are of between 50 and 119 HU; and calcified plaques are of >120 HU. However, CTA demonstrates a lower accuracy than MRI when differentiating other components (e.g., lipid core and hemorrhage)[5,19,21]. The other drawbacks of CTA include its use of radiation and iodinated contrast media, and contrast-induced nephropathy.

High-resolution MRI

There have been significant developments in receiver coil and pulse sequence design to assess carotid plaques. MRI provides information about: (1) the degree of stenosis; (2) total plaque volume; (3) plaque components; and (4) plaque surface morphology, including ulceration and fibrous cap rupture.

Using HR-MRI, it is possible to classify atherosclerotic plaques into categories defined by the American Heart Association, which have been recently adapted for MR imaging[22]. The modified American Heart Association criteria are as follows: types I-II correspond to near-normal wall thickness without calcification; type III corresponds to diffuse wall thickening or small eccentric plaque without calcification; types IV-V correspond to a plaque with a lipid-rich necrotic core surrounded by fibrous tissue with possible calcification; type VI is complex plaque

with a possible surface defect, hemorrhage, or thrombus; type VII is calcified plaque; and type VIII is fibrotic plaque without a lipid core and with possible calcification. However, only moderate inter-reader agreement between types I-II and III lesions has been reported[23].

The limitations of HR-MRI are its very high cost and lack of availability in many hospitals in Thailand; furthermore, the patients should be properly prepared; dedicated surface coil takes a long time with combined black-blood and bright-blood MR sequences being used.

Conclusion

B-mode US detection of vessel wall imaging of cervical carotid arteries was useful for identifying high-risk type 2 DM, leading to early diagnosis of carotid vascular disease, vulnerable plaque and grading carotid stenosis, which are indicators of being at high risk of future cardiovascular events and ischemic stroke. Carefully looking for plaque echogenicity, surface irregularities, and direct measurement in degree of stenosis in the case of large plaque using only B-mode US was valuable in helping these patients. The rate of positive carotid plaque was significantly associated with the duration of DM and serum triglyceride levels. Multivariate regression analysis indicated that significant carotid plaque was associated with receiving ACEI/ARB for treatment of hypertension.

What is already known on this topic?

US can assess IMT, and an increase in the IMT of the common carotid artery, bulb and internal carotid artery can be used to predict cardiovascular events or ischemic stroke.

IMT measurement can accurately describe the process of arterial wall change due to atherosclerosis.

What this study adds?

Most of these 150 type 2 DM patients had no carotid arterial disease, and only 10.0% had significant carotid stenosis. The three factors that are associated with significant carotid atherosclerosis in type 2 DM found in this study were duration of DM, triglyceride levels and receiving ACEI/ARB.

Early diagnosis of arterial disease helps to prevent its development using B-mode US screening for subclinical ASCVD leading to optimal medical therapy (OMT), preventive therapy; life style modifications should be considered before ASCVD occurs.

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Potential conflicts of interest

None.

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