Diabetes and carotid artery disease: a narrative review

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Abstract: Diabetes mellitus (DM) has been linked to an increased prevalence and severity of carotid artery disease, as well as polyvascular disease. Carotid disease is also associated with obesity and abnormal peri-organ and intra-organ fat (APIFat) deposition (i.e., excess fat accumulation in several organs such as the liver, heart and vessels). In turn, DM is associated with APIFat. The coexistence of these comorbidities confers a greater risk of vascular events. Clinicians should also consider that carotid bruits may predict cardiovascular risk. DM has been related to a greater risk of adverse outcomes after carotid endarterectomy or stenting. Whether modifying risk factors (e.g., glycaemia and dyslipidaemia) in DM patients can improve the outcomes of these procedures needs to be established. Furthermore, DM is a risk factor for contrast-induced acute kidney injury (CI-AKI). The latter should be recorded in DM patients undergoing carotid stenting since it can influence both short- and long-term outcomes. From a pathophysiological perspective, functional changes in the carotid artery may precede morphological ones. Furthermore, carotid plaque characteristics are increasingly being studied in terms of vascular risk stratification and monitoring short-term changes attributed to treatment. The present narrative review discusses the recent (2019) literature on the associations between DM and carotid artery disease. Physicians and vascular surgeons looking after patients with carotid disease and DM should consider these links that may influence outcomes. Further research in this field is also needed to optimise the treatment of such patients.

Keywords: Diabetes; carotid artery disease; stroke; vascular risk; epicardial fat; non-alcoholic fatty liver; carotid bruits

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Introduction

There has been a considerable increase in the literature related to diabetes mellitus (DM) and carotid artery disease (*Table 1*). This trend reflects current interest in this topic. In this narrative review, we focused on the recent (2019; last accessed 3 November 2019) literature (in PubMed) with the aim to highlight some key issues regarding the links between DM and carotid disease. This association has considerable clinical relevance for both physicians and surgeons.

Treatment issues will not be addressed since they are well covered by recent guidelines and some of the other reviews in this special issue (1,2).

Does DM increase the risk of developing carotid disease?

It is well established that DM is associated with an increased risk of vascular events (1). Nevertheless, more recent studies

Table 1 Number of entries on PubMed 1969–2019 under "carotid diabetes" (last accessed 3 Nov 2019; https://www.ncbi.nlm.nih.gov/pubmed/?term=carotid+diabetes)

Year	Number of entries
2019	416
2009	302
1999	125
1989	38
1979	7
1969	4

are also of interest.

DM, stroke and vascular risk

DM increases the risk of ischaemic stroke in the general population (3) and can also aggravate the severity of extracranial atherosclerotic disease (4). Moreover, as far back as 2010, the European Society of Vascular Surgery (ESVS) "carotid" guidelines (5) emphasised the increased vascular event risk associated with DM. Updated recommendations are provided in the more recent (2018) and comprehensive ESVS guidelines (2).

Glycaemic control and carotid disease

In a cross-sectional study [n=2,215 patients with type 2 DM (T2DM)], glycaemic control [expressed as time in range (TIR)] was associated with carotid intima-media thickness (cIMT) (6). For the normal cIMT group (n=1,944) age was 59.5±11.8 years and 53.2% were males; for the abnormal cIMT group (n=271) the corresponding values were: 67.0±9.6 years and 63.5% were males. TIR was defined as glucose levels in the range of 3.9–10.0 mmol/L (70–180 mg/dL) (assessed by continuous subcutaneous glucose monitoring for 3 days) (6). Compared with patients with a normal cIMT, those with a mean cIMT ≥1.0 mm had significantly lower TIR (P<0.001). In particular, each 10% increase in TIR was related to a 6.4% lower risk of abnormal cIMT (6).

Similar findings were observed in another study involving 1,065 patients with neurological asymptomatic carotid atherosclerosis (median follow up: 11.8 years) (7). DM was diagnosed in 335 (31.5%) of the participants; most had T2DM (95.3%). In this study, the adjusted hazard ratio (HR) for every 1% increase in glycated haemoglobin (HbA_{1c}) levels was 1.31 (P<0.01) for cardiovascular (CV) mortality and 1.21 (P<0.01) for all-cause mortality, respectively (7).

Severity of carotid stenosis in patients with DM and risk of adverse outcomes

The severity of carotid stenosis in patients with DM may confer an increased risk of adverse outcome. In the study by Hoke *et al.* (7), described above, there were 4 groups of patients: no DM and <50% carotid stenosis, DM and <50% carotid stenosis, no DM and ≥50% carotid stenosis and DM and ≥50% carotid stenosis. Only 21% of the diabetic patients with asymptomatic carotid narrowing ≥50% survived. In contrast, 40% of those without DM and asymptomatic carotid narrowing ≥50% survived. Also, 62% of the patients without DM and with asymptomatic carotid artery narrowing <50% were still alive after a median follow-up of 11.8 years (P<0.01 for trend). This high risk associated with DM remained significant after adjusting for several established CV risk factors in a multivariable regression analysis (7). The increased mortality in those with DM was attributed to higher all-cause and CV mortality.

Changes in cIMT and carotid function indices start early in life

The harmful effects of DM on the carotid arteries seem to start early in life since an increased cIMT has been reported among children (mean age =12.15±2.59 years) with type 1 DM (T1DM) (8). This finding may reflect the influence of several predictors of vascular risk factors that were identified in these patients. Changes in arterial function and aortic IMT were also observed in this population (8). These findings are supported by a meta-analysis involving 20 cIMT studies and 4 carotid-femoral pulse wave velocity studies (9). The trend may be initiated even earlier since a link between gestational DM, maternal obesity, child lean body mass and weight gain in childhood and cIMT has been reported (10).

Renal events and cIMT

As expected, there is evidence supporting that resistant hypertension increases the risk of developing complications in those with T2DM (11). The same study (the Rio de Janeiro type 2 diabetes cohort study) also showed that

cIMT and the presence of carotid plaques predicted CV events and renal outcomes, but not mortality or other microvascular complications (12).

Multisite arterial disease and cIMT

Multisite atherosclerosis was assessed in CV disease (CVD)-free participants (n=1,675; 51% males, mean age: 64 years) from the Multi-Ethnic Study of Atherosclerosis (MESA); 33.4% had metabolic syndrome (MetS) and 15.9% had DM (13). The involvement of several arterial beds was recorded: coronary arteries (as coronary calcium), abdominal aorta (as aortic calcium), carotids (as cIMT ≥1 mm) and peripheral artery disease (PAD) [as ankle brachial index (ABI), <1 or ≥1.4]. The number of atherosclerotic sites identified was significantly (P<0.0001) higher in the participants with DM (mean ± SD =1.67±1.15) and MetS (1.49±1.12) *vs.* neither MetS nor DM (1.09±1.09) (13). CVD rates/1,000 person-years ranged from 3.5, 8.2, and 10.0 in those with 0 arterial sites positive to 35.1, 79.6 and 103.4 in those with four arterial sites positive among neither DM nor MetS, MetS and DM groups, respectively (13).

PAD and cIMT

PAD has been associated with increased cIMT. In a study involving patients with diabetic foot, more patients with PAD had cIMT ≥0.71 mm (79.65% *vs.* 38.89%; P<0.001) and internal carotid arteries (ICA) plaques (66.37% *vs.* 11.11%; P<0.001) than those without PAD (14). This study is of interest since it includes data on carotid plaques. According to recent guidelines, attention has drifted away from the cIMT to carotid plaque presence and area (1). The reason for this change is that plaque presence and area are likely to reflect more rapid changes in the carotid arteries. A recent comprehensive review as well as an editorial discussing the value of measuring carotid plaque area and its other characteristics are available (15,16).

The importance of carotid plaque was demonstrated in a study where CV events in patients with T2DM without manifest CVD were associated with greater median carotid plaque area [30.4 (16.1–92.2) *vs.* 19.5 (9.5–40.5) mm^2, P=0.01] (17). Similarly, in another study, the only variable predicting CV events among patients with DM and chronic kidney disease was the number of carotid and femoral arterial territories with plaque at baseline [HR 1.782, 95% confidence interval (CI): 1.393–2.278] (18). Furthermore, in a cross-sectional analysis involving 3,815 Chinese community-dwelling adults, T2DM, hypertension and decreased estimated glomerular filtration rate (eGFR) were independently related to the presence, number and total area of carotid plaque (19).

PAD is often undiagnosed in asymptomatic patients with T1DM and may coexist with carotid artery disease (20). It is relevant to consider that medial artery calcification can be found in up to 47% of patients with T1DM (20). Therefore, the ABI may underestimate the prevalence of PAD (20). This information would be clinically relevant since it may influence patient management. Furthermore, PAD may be a part of a polyvascular disease in some patients with all forms of DM.

A link between asymptomatic carotid artery stenosis (ACAS) and PAD has also been reported; this association may be influenced by age and hypercholesterolaemia (21).

Carotid function and cIMT

It is also relevant to consider that functional changes in the carotid artery may precede morphological ones (22). Indeed, an increase in cIMT in patients with DM can be accompanied by abnormalities in function (e.g., carotid wave speed, carotid artery distensibility and carotid-femoral pulse wave velocity) (23,24).

Carotid plaque characteristics and DM

Patients with T1DM have different carotid plaque types compared with individuals without T1DM (25). This includes an increased frequency of echogenic and extensively calcified plaques. This finding needs to be confirmed but it may well represent a trend for calcification in these patients. Whether, this difference represents an increased risk of vascular events remains unclear but worthy of further investigation (26).

Comments

There is evidence of a link between "glycaemia" and carotid pathology (as represented by cIMT and some function indices) and the risk of vascular events (including kidney function). Although this relationship appears to be time-related, it starts "early" in children with T1DM. Another message is "always look for polyvascular disease" when you see carotid disease. Polyvascular disease is associated with a greater risk of vascular events.

There is considerable discussion regarding plaque area

vs. cIMT in terms of predicting vascular risk and also for monitoring short-term changes attributed to treatment.

Finally, we always need to consider the overall high vascular risk associated with DM (1,26).

DM and carotid endarterectomy (CEA) and carotid artery stenting (CAS)

In the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial (748 operations; follow-up: 13 years), previous myocardial infarction (MI) (HR 2.045, 95% CI: 1.108–3.777, P=0.022), DM (HR 2.111, 95% CI: 1.183–3.767, P=0.011) and symptomatic patients [previous stroke or transient ischaemic attack (TIA); HR 2.045, 95% CI: 1.018–4.109, P=0.044] were independently associated with major adverse CV and cerebrovascular events (MACCE) (27).

A recent analysis of the effect of best medical therapy (BMT; 162 patients) *vs.* carotid surgical revascularization (CRevasc; 247 patients) + BMT in patients with ACAS (>70% stenosis) was carried out (mean follow-up: 60.7±37.5 months) (28). Ipsilateral stroke and any stroke at 1 and 5 years were comparable between the 2 groups. However, patients with a history of DM and remote stroke treated with BMT only were at a high risk for future stroke (7.2%/year). CRevasc + BMT patients with DM and contralateral >50% carotid stenosis who were smokers had the highest risk for stroke (28).

In a meta-analysis of 18 studies (17,106 patients), DM (HR 1.68; 95% CI: 1.00–2.83; I^2=76.7%), among other factors (e.g., dyslipidaemia, chronic kidney disease, female gender, smoking, hypertension, and baseline stenosis >70%) were associated with a significant increased risk of restenosis after CRevasc (29).

Another study included 16,739 CEA patients; 58% had ACAS (30); there were patients with no DM (69%), non-insulin-dependent DM (NIDDM) (20%) and insulin-dependent DM (IDDM) (11%). Among ACAS patients, after adjustment, IDDM was associated with a higher 30-day stroke/death (primary end point) compared with non-DM patients [odds ratio (OR) 2.3, 95% CI: 1.5–3.4; P<0.001]. In contrast, those with NIDDM experienced rates similar to those of non-DM patients (2.1% *vs.* 1.5%; P=0.1) (31). Among symptomatic patients, after adjustment, those with IDDM and NIDDM experienced similar rates of the primary end point as those without DM. The high primary end point rates in ACAS patients with IDDM may limit any benefit from CEA (30).

MetS may precede T2DM (31,32). Therefore, it is relevant to consider the relationship of MetS with carotid artery disease. Among a consecutive cohort of 752 patients undergoing CEA (n=314) and CAS (n=438), 296 (39.4%) participants had MetS (33). The authors selected a definition of MetS that included body mass index (BMI) (33) because they could not access to waist circumference measurements used by more widely recognized definitions of MetS (32). Patients with MetS had a significant increased risk in 30-day mortality, major adverse events (MAE) and restenosis rates after CEA or CAS (MAE: 5.3% *vs.* 2.7%; death: 0.7% *vs.* 0.0%; restenosis: 1.7% *vs.* 0.2%; P<0.05). MAE and restenosis rates were still significantly different at 36 months, for both CEA and CAS. Among the diagnostic characteristics of MetS, fasting serum glucose, high-density lipoprotein cholesterol (HDL-C) and BMI were associated with increased complications both at 30 days and within 36 months (33).

A prospective study included 606 non-diabetic and 296 diabetic (83 were insulin-dependent) patients (3). The 30-day cumulative TIA/stroke rate was significantly higher in the diabetic group (2.6% *vs.* 5.7%, P=0.02) (3). Mortality was also significantly higher in this group (0.2 *vs.* 1.7%, P=0.01). In multivariate analysis, among several factors, the use of insulin (OR 2.47, 95% CI: 1.61–4.68; P=0.01) and higher HbA_{1c} levels in those with DM (OR =1.28, 95% CI: 1.05–1.66, P=0.03) increased the risk of all-cause death and stroke (3).

Patients (n=17,800) from the Premier Healthcare Database who underwent CAS were retrospectively analysed. The group on statins (n=12,416; 70%) had more symptomatic patients (41% *vs.* 31%; P<0.001) and significantly more comorbidities, including hypertension, DM, coronary artery disease (CAD), dyslipidaemia, history of congestive heart failure, history of stroke, history of MI and PAD (all P<0.05) (34). Despite this disadvantage, after adjustment for confounders, statin use was associated with a 64% reduction in death (OR 0.36, 95% CI: 0.27–0.47; P<0.001) and 18% reduction in stroke/death (OR 0.82, 95% CI: 0.68–0.99; P=0.03) (34).

A Korean study divided CEA patients into those with T2DM (n=265) and those without DM (n=410) (35). MAEs were defined as fatal or non-fatal stroke or MI or all-cause mortality. MAEs were assessed perioperatively and within 4 years after CEA. Multivariate analysis showed that DM was not associated with MAEs during the perioperative period (35). In contrast, within 4 years after CEA, DM was an independent risk factor for MAEs overall (HR 1.62,

95% CI: 1.06–2.48; P=0.026) and stroke (HR 2.55, 95% CI: 1.20–5.41; P=0.015) (35).

In a retrospective review of CEA, CAS, endovascular and open aortic aneurysm repair as well as other procedures (36), 366 patients (34.8%) had perioperative hyperglycaemia defined as ≥1 glucose value >180 mg/dL (10.0 mmol/L) within 72 h of surgery. This was associated with a greater 30-day mortality (5.7% *vs.* 0.7%; P<0.01) and an increased risk of acute kidney failure (4.9% *vs.* 0.9%; P<0.01), postoperative stroke (3.0% *vs.* 0.7%; P<0.01) and surgical site infections (5.7% *vs.* 2.6%; P=0.01). These patients were more likely to require reoperation (6.3% *vs.* 1.8%; P<0.01) or readmission (12.3% *vs.* 7.9%; P=0.02) (36). Multivariable logistic regression demonstrated that perioperative hyperglycaemia was related to a higher 30-day mortality and negative postoperative outcomes, including MI, stroke, kidney failure and wound complications (36).

In a survey (37) of adults hospitalised between 2007 and 2011 in the U.S., 128,664 patients (aged ≥45 years) underwent CEA or CAS; of those, 41,120 had DM. Uncomplicated DM was not associated with higher odds of perioperative outcomes. In contrast, DM with chronic complications was a significant risk factor in those undergoing CEA (perioperative infection (OR 2.45, 95% CI: 1.29–4.65), longer hospital stay [β (regression coefficient indicating number of days): 2.05, 95% CI: 1.90–2.20] and mortality (OR 1.48, 95% CI: 1.01–2.16) compared with patients without DM. Those with DM and chronic complications undergoing CAS had significantly increased odds of acute kidney injury (OR 3.17, 95% CI: 2.31–4.35) and longer hospital stay (β: 1.98, 95% CI: 1.58–2.38) compared with patients without DM (37).

In contrast with the results described above, another study (38) showed that T2DM even without clinical evident CVD was associated with a greater risk of MACE (fatal or non-fatal stroke, MI and all-cause mortality). In patients with T2DM (n=2,006; aged >50 years) without clinical evident CVD, the risk of MACE was significantly (P<0.001) greater in those with both longer duration of DM (≥10 years) and significant carotid artery stenosis (50–69% stenosis), compared with those with shorter duration and/or non-significant carotid artery stenosis (38).

The increased risk of perioperative events in patients with DM was supported by the findings of a meta-analysis published in 2016 (39). This meta-analysis included ten CEA, three CAS studies and one study where both CEA and CAS were carried out [total =16,264 patients; 26% (n=4,204) had DM] (39).

One reason for the greater risk of carotid-related complications in patients with DM may be that they have more carotid plaques with calcification and lipid-rich necrotic core compared with non-diabetic patients [as visualized by magnetic resonance imaging (MRI)] (40). However, this potential interpretation requires confirmation.

Comments

There is convincing evidence that DM confers a greater risk of adverse outcomes after CEA or CAS, especially if DM is associated with complications. This is clearly illustrated by the inclusion of DM in the NSQIP (National Surgical Quality Improvement Program) registry that predicts adverse outcomes (30-day adverse events: stroke, MI or death) after CEA for ACAS or symptomatic carotid stenosis (41). The OR in the prediction model for non-insulin dependent DM was 1.41 (95% CI: 1.10–1.81; P=0.007) and for insulin dependent DM, the corresponding values were 1.55 (95% CI: 1.15–2.08; P=0.004) (41).

There is a need to establish whether modifying risk factors (e.g., glycaemia and dyslipidaemia) in patients with DM can improve outcomes related to CRevasc. In this context, some of the evidence discussed above seems encouraging. It is also important to establish if "statin loading" pre-CEA and/or pre-CAS (or current longer-term statin use) confers any benefits in patients (including those with DM) (1,2,42-46). Undoubtedly, vascular surgeons involved in carrying out CEA or CAS procedures need to be aware of the specific risks associated with DM.

Carotid disease is associated with obesity and excess fat deposition in other organs

Epicardial fat thickness (EFT)

EFT (assessed by transthoracic echocardiography) and cIMT (assessed by ultrasonography) were recorded in 76 T2DM patients without clinical atherosclerotic CVD and 30 age- and sex-matched controls (47). Patients with DM had significantly higher EFT and cIMT than controls (6.23±1.27 *vs.* 4.6±1.03 mm, P<0.001 and 0.77±0.15 *vs.* 0.58±0.08 mm, P<0.001, respectively). Stepwise regression analysis showed that cIMT, duration of T2DM, triglyceride levels and BMI were the independent predictors of EFT, with cIMT as the most important predictor (P<0.001). These findings are of interest since EFT is a predictor of cardio-metabolic disease (47).

Similar results for EFT, cIMT and presence of carotid plaque were reported by others (48). Furthermore, compared with a T2DM normoalbuminuric group, EFT and cIMT were significantly higher in those with T2DM and microalbuminuria (P<0.05 for all) (49). In logistic regression analysis, cIMT (OR 3.15, 95% CI: 1.5–36.3, P=0.024) was independently related to the presence of microalbuminuria in these patients (49).

Fatty liver

Liver steatosis (as assessed by fatty liver index) was associated with carotid and coronary (but not femoral atherosclerosis) and with CV mortality risk (as assessed by the 10-year Framingham Risk Score) (50). In another study, after adjusting for several variables, logistic regression demonstrated that HbA_{1c} levels and fatty liver were independent predictors of cIMT (OR 1.426, 95% CI: 1.084–1.876, P=0.011 and 4.718, 95% CI: 1.083–20.542, P=0.039, respectively) (51). This study was conducted in lean (BMI 23.3±4.6 and 22.4±4.4 kg/m^2) adolescents with T1DM and with or without increased cIMT (n=110; mean age: 14.2±0.7 years; mean duration of T1DM: 6.0±0.3 years) (51). Mean visceral fat and liver size measured ultrasonographically were significantly higher in adolescents with increased cIMT (51).

Perivascular fat

A multivariable regression model showed that age (P<0.0001), perivascular adipose tissue (PVAT) (P<0.0001) and smoking (P=0.04) were independently associated with the severity of ICA stenosis (52). PVAT [expressed as extra-media thickness (EMT) to BMI ratio, EMT/BMI] was significantly increased in those with ≥50% carotid stenosis compared with those with <50% carotid stenosis whether they had DM (28.5±5 *vs.* 24.7±4, P<0.0001) or not (28.8±6 *vs.* 26.1±3.8, P<0.001) (52).

In another study, the density of carotid perivascular fat was measured by computed tomography angiography (CTA) in 94 patients (52 asymptomatic and 42 symptomatic for stroke and TIA) with unilateral ICA stenosis ≥50–99% (53). Symptomatic patients (16.7% had DM) had higher mean pericarotid fat density (–66.2±19.2 *vs.* –77.1±20.4, P=0.009) compared with asymptomatic patients (32.7% had DM). In contrast, for non-stenotic ICAs, there was no significant difference between pericarotid fat density in symptomatic compared with asymptomatic patients (53). These findings suggest that inflammation associated with symptomatic carotid plaques extends beyond the vessel lumen and can be identified using CTA imaging (53).

Neck circumference was also significantly and independently associated with common carotid IMT, thus suggesting a possible effect of PVAT on atherosclerosis (54). Perhaps neck circumference should be measured more often and considered as an index of local excess fat?

Perivascular inflammation and local adiponectin levels may influence carotid intraplaque inflammatory activities (55,56). These studies included patients with DM.

Obesity, visceral adiposity and MetS

Obesity and MetS are linked with vascular event risk as well as an increased probability of developing T2DM (31,32). Therefore, some recent studies are worth a mention.

A Japanese community-based study (n=1,241 participants) compared metabolically healthy obese (MHO), metabolically unhealthy obese (MUO) and non-obese (BMI <25.0 kg/m^2) participants in terms of the presence of carotid plaque (57). Multivariable analysis showed that MHO (OR 1.564, 95% CI: 1.102–2.222, P=0.012) and MUO (OR 1.857, 95% CI: 1.226–2.811, P=0.003), as well as age ≥65 years, male sex, hypertension and DM were independently associated with carotid plaque formation (57).

Another Japanese study (n=7,750) involving middle-aged participants without CVD undergoing health check-ups also found that obesity-related indices (i.e., BMI, % body fat, visceral fat area and waist circumference) were positively associated with cIMT (58). Visceral fat area was assessed by CT (58).

Another study involved subjects (731 adults; median age: 47 years) free of CVD but who were at risk of developing DM (59). Visceral adiposity index (estimated based on waist circumference, BMI, triglyceride and HLD-C values) (P=0.0392) but not the homeostatic model assessment of insulin resistance (P=0.37) was associated with cIMT, independently of established CV risk factors (59).

Comments

Some years ago, we coined the term APIFat since several authors used the term "ectopic" fat to describe excess fat accumulation in several organs (60). Actually, fat is present within and "around" many organs under healthy conditions; the problem is excessive pathological fat deposition (e.g., in the obese and those with DM). This excessive fat accumulation is often associated with abnormal function

which can be harmful. It follows that any excessive fat deposition is not "ectopic" since it is present in a usual location rather than in one where there is usually no fat at all. The word "ectopic" signals a factor that occurs outside its usual location (60).

The APIFat phenomenon includes several organs and, based on the above literature, the carotid arteries are not spared (60-62). This relationship may be relevant since there is evidence that APIFat is associated with adverse outcomes in various organs and also with vascular risk (60-62). For example, non-alcoholic fatty liver disease (NAFLD) and excess EFT are associated with an increased risk of vascular events and other conditions such as DM, MetS and obesity (60-63). Based on the literature above, the increased risk of vascular events in patients with carotid pathology may include a complex interaction of several factors. In this context, it is relevant that even ACAS is associated with an increased risk of vascular events (64).

All these associations are in need of further research to confirm their clinical relevance and consider potential diagnostic and treatment options. Among new potential measurements that may reflect perivascular fat, EMT may deserve further exploration (65).

Other links with carotid disease

CV autonomic neuropathy in normoalbuminuric patients with long-term T1DM is associated with increased generalised arterial calcification (including the carotid arteries) (66). It has also been proposed that hypertension, smoking and DM, can destabilize atheromatic plaques and enhance their calcification (67).

cIMT is negatively correlated with endothelial-dependent flow-mediated vasodilation, as well as with the circulating levels of endothelin-1 (a vasoconstrictor and activator of platelet function) and vascular endothelial growth factor (68,69). These variables can be abnormal in patients with DM.

Associations between lipid variables and carotid disease will be the subject of another review within this series of articles (70). However, it is worth mentioning that elevated levels of lipoprotein (a) [Lp(a)] may increase the risk of carotid plaque presence (71,72). This finding is interesting since the circulating levels of this lipoprotein are mainly genetically determined and new treatment options that can considerably lower Lp(a) levels are being developed (72,73). Furthermore, we need to consider that the new proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors also lower Lp(a) as well as LDL-C levels (72,73). Interestingly, there is evidence of an inverse relationship between Lp(a) levels and risk of T2DM [greater risk of T2DM at low Lp(a) levels] (74).

Increased cIMT was also associated with ocular ischaemia and mild non-proliferative diabetic retinopathy (NPDR) in patients with T2DM. This finding, if confirmed, supports the hypothesis that cIMT may be an early predictor of mild NPDR (75).

Carotid bruits

The role of carotid bruits is worth a mention. There is evidence from a meta-analysis and a review that the presence of carotid bruits predicts CV risk (76,77). For example, in a meta-analysis of 4 trials comparing patients with and without carotid bruits, the OR for MI was 2.15 (95% CI: 1.67–2.78) and for CV death 2.27 (95% CI: 1.49–3.49) (76). However, such conclusions are not without some limitations (78).

More specifically related to DM, in 2003, the Fremantle Diabetes Study (79) reported, based on a community-based sample, reported that in the first 2 years, first stroke (n=45/1,181; 3.8%) was strongly predicted by the presence of carotid bruits after adjusting for CV risk factors and potential confounders (HR 6.7; 95% CI: 3.0–14.9; P<0.001). This relationship was not sustained on a more prolonged follow-up (79). As expected, age and diastolic blood pressure were also determinants of stroke in the first 2 years (79). Age, atrial fibrillation/flutter, and microalbuminuria were additional independent predictors of stroke at 2 years (79).

Carotid bruits may be absent in patients with ICA occlusion. Yet these patients are likely to have many vascular risk factors (including DM) and atherosclerotic disease at other sites (80).

Contrast-induced acute kidney injury (CI-AKI)

CAS could be associated with CI-AKI (81). This factor did not seem to be recorded when CEA *vs.* CAS were compared in terms of outcomes (81). CI-AKI is relevant because it can influence both short- and long-term outcomes (82-84). Moreover, DM is a risk factor for CI-AKI (85). In addition, the use of metformin should be considered in patients with DM receiving a contrast medium (86).

Concluding comments

Based on the above evidence, there is more to carotid disease than just "local" arterial pathology, especially if DM is also present. It is therefore not surprising that there has

been a huge increase in the "carotid diabetes" literature (see *Table 1*).

Moreover, there is a need for the better understanding of the role of perivascular fat in patient outcomes. In this context, it is of interest that evidence shows that perivascular fat surrounding various arteries has different properties (87-89). Therefore, it is possible that carotid perivascular fat has to be specifically studied. To this "regional specificity" of perivascular fat, we need to add the possibility that different arteries may show variation in their receptor populations (90) and DM may affect that pattern. In addition, vascular risk factors may not affect all arteries equally (91). We still have a lot to learn!

Physicians and vascular surgeons involved in looking after patients with carotid disease and DM have to consider several factors that will influence patient outcomes. There is also an urgent need for further research to optimise the assessment and treatment of these patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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