Incidence of carotid artery insufficiency in patients with proliferative diabetic retinopathy

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Purpose
The aim of this work is to study the prevalence of carotid artery insufficiency by ultrasonography parameters in patients with proliferative diabetic retinopathy in Alexandria, Egypt, and also to study common carotid artery (CCA) diameter as a newly suggested marker of early carotid insufficiency.
Design
This is a descriptive cross-sectional study.
Patients and methods
The study included 100 eyes of 50 diabetic patients with proliferative diabetic retinopathy. All were apparently healthy individuals, had nonoperated eyes, and were free of renal insufficiency.
Results
Diabetic retinopathy correlated with lower CCA-peak systolic velocity, having a mean of 59.4±15.9 cm/s (P=0.020, r=–0.048); higher CCA diameter, having a mean of 7.2±0.09 mm (P=0.000, r=0.434); and higher CCA-intima-media thickness (IMT), having a mean of 0.69±0.19 mm (P=0.033, r=0.204). Diabetic retinopathy also correlated with higher plaque score (P=0.020) and higher carotid artery stenosis ranging from 4 to 50% (P=0.033). Regarding the symmetry of diabetic retinopathy, 70% of the patients (N=35) had some degree of carotid artery insufficiency (IMT>0.8 mm or carotid plaques). Asymmetric diabetic retinopathy was detected in 28 of the 50 patients. We studied the relationship among CCA diameter, CCA-IMT, and symmetry of diabetic retinopathy. Approximately half of the cases in this study (N=24) had larger CCA diameter in the worse eye and 87.5% in asymmetric diabetic retinopathy (P=0.000). Regarding CCA-IMT and symmetry, 40% of the cases in this study (N=20) had larger CCA-IMT in the worse eye and 80% in asymmetric diabetic retinopathy (P=0.005).
Conclusion
Diabetes seems to be an independent risk factor of carotid artery insufficiency, leading to worsening of diabetic retinopathy even in the absence of other known risk factors of atherosclerosis.

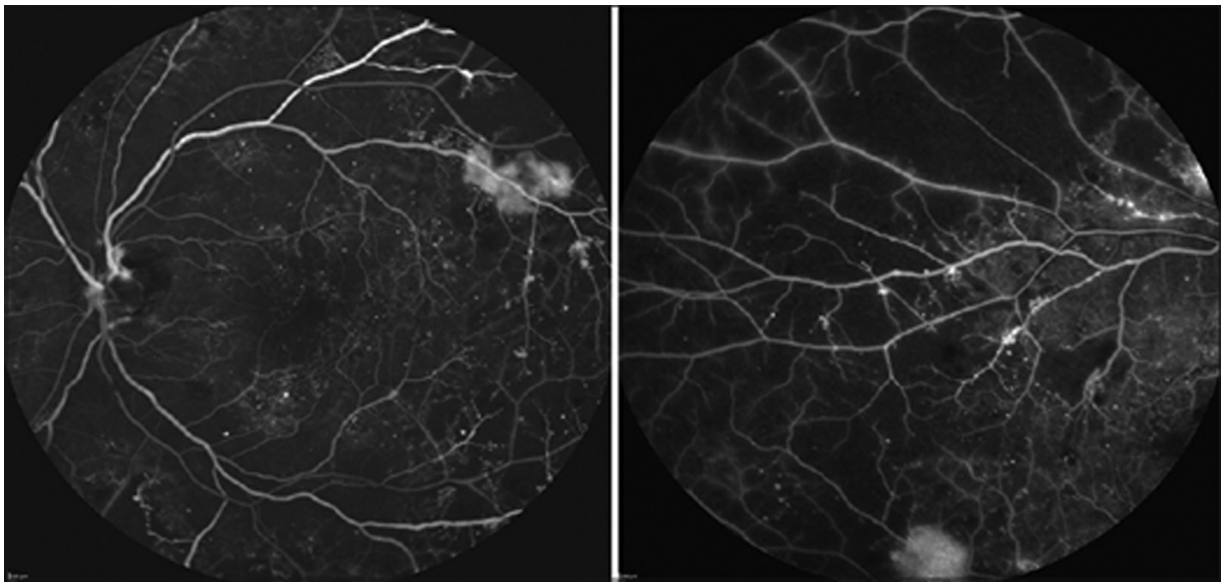
Keywords:
carotid artery insufficiency, common carotid artery diameter, intima-media thickness proliferative diabetic retinopathy

Introduction

Diabetes mellitus (DM) is a chronic disease affecting multiple organs in the body. The hallmark of the disease is hyperglycemia. The main target in most management plans is controlling hyperglycemia, in addition to ensuring the adequate delivery of glucose to the tissues of the body, and to protect against the harmful effect of hyperglycemia [1]. DM has a direct and an indirect effect on the human vasculature, which is the major source of morbidity and mortality in both type I and type II diabetes. Generally, the diabetic effect on vessels is divided into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) [2]. Figure 1 shows fluorescein angiography of a proliferative diabetic retinopathy with variable vascular diabetic changes.

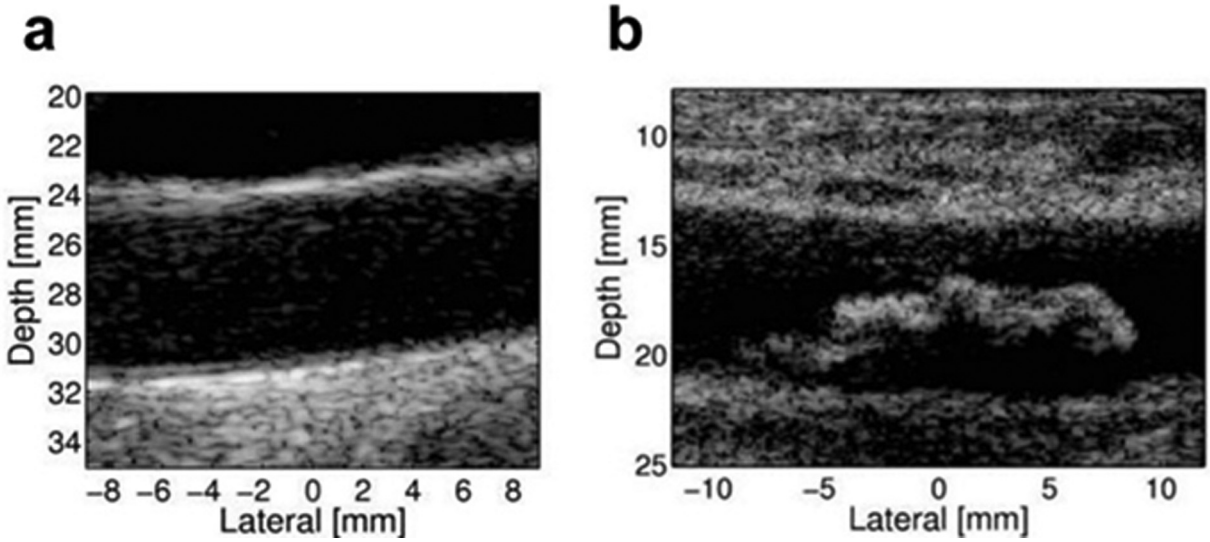
Diabetic retinopathy is a very common microvascular complication of diabetes. It is responsible for ~10 000 new cases of blindness every year in the United States alone [3]. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia.

Figure 1



Fluorescein angiography of a proliferative diabetic retinopathy. The standard 30° photograph on the left shows scattered microaneurysms throughout the macula. There is IRMA present along the superior arcade as well as leakage from an area of neovascularization. A peripheral sweep of the fluorescein angiography in the same patient shows patchy areas of hypofluorescence corresponding with extensive areas of peripheral retinal capillary nonperfusion [6].

Figure 2



B-mode imaging of the carotid artery. These images illustrate (a) a normal carotid artery and (b) a large atherosclerotic plaque protruding into the lumen of the carotid artery [7].

Diabetes increases the risk of developing cardiovascular disease. Cardiovascular disease is the primary cause of death in people with either type I or type II diabetes . The precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, but the association between them is profound [4,5].

Carotid ultrasound is a reliable imaging modality that allows noninvasive assessment of vascular anatomy and function, and is a useful and safe tool for the measurement of intima-media thickness (IMT) and other vascular parameters. This study correlated between proliferative diabetic retinopathy and carotid artery insufficiency. Figure 2 compares a normal carotid artery with an atherosclerotic one.

Patients and methods

This descriptive cross-sectional study was conducted on 100 eyes of 50 patients with proliferative diabetic retinopathy, below 50 years old, from different

socioeconomic classes and different areas in Alexandria. Approximately 40% were seen first at Alexandria University Department Ophthalmology Clinic. Smokers, patients with dyslipidemia, hypertensive patients, and any patient with renal insufficiency were excluded.

All cases were subjected to full ophthalmologic examination for the anterior and the posterior segments using slit-lamp biomicroscopy, and detailed history taking was done. The retina was photographed by ophthalmic computed tomography and fundus fluorescein angiography. Carotid artery ultrasound was performed for the common carotid artery (CCA) and the internal carotid artery (ICA). Blood samples were taken for glucose and lipid analyses.

Patient selection criteria were as follows:

(1) Diabetic regardless of the type, duration, and sex.
(2) Diabetic retinopathy reaching any degree of proliferative diabetic retinopathy in at least one eye.
(3) Age younger than 50 years, without apparent carotid artery stenosis, no dyslipidemia medication, and no renal insufficiency.
(4) No previous ophthalmologic surgery or any intervention and without any chronic treatment for the eye.

Methods

All patients were subjected to the following:

(1) Laboratory workup: fasting blood glucose test, postprandial glucose tolerance test, glycosylated hemoglobin, and lipid profile [low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides).
(2) Detailed ophthalmological examination with emphasis on the following:
    (a) Patients detailed history taking, medical history, surgical history, smoking habit, blood pressure (measured in supine position), and BMI.
    (b) Best-corrected visual acuity where decimal system was used.
    (c) Anterior segment examination using slit-lamp biomicroscopy.
    (d) Fundus examination using non-contact lens (Volk Digital Wide-Field lens), after pupillary dilatation using tropicamide 1% eye drops.
    (e) All which was done by a single trained physician.
    (f) Worse eye is considered as having different level of diabetic retinopathy; in cases of symmetric diabetic retinopathy, it is considered the eye with lower visual acuity.
    (g) All patients have proliferative diabetic retinopathy at least in one eye; patients were also compared according to symmetry of diabetic retinopathy level. Asymmetry was defined as any difference in stage according to the ETDRS classification of diabetic retinopathy.
(3) Retinal imaging, including fundus fluorescein angiography and optical coherence tomography.
(4) Carotid artery ultrasonography:
    (a) CCA diameter.
    (b) CCA maximum IMT.
    (c) End diastolic volume (EDV) for both CCA and ICA
    (d) Peak systolic velocity (PSV) for both CCA and ICA.
    (e) Plaque score: one point for every branch with plaques, regardless of the plaque number (of 6).
    (f) Stenosis percentage if present.
    (g) Difference in CCA diameter was considered if more than 0.5 mm, and CCA-IMT was considered if it was more than 0.05 mm (Table 1).

Results

Age of the cases correlated with diabetic retinopathy severity (P=0.017). Overall, 92% of the cases fell in the

Table 1 Correlation between patient parameters and severity of diabetic retinopathy

	Pearson χ^2	P value	Spearman correlation
Age group (higher)*	13.76	0.017	0.192
Duration (>10 years)*	18.43	0.002	0.347
Positive family history of uncontrolled DM*	15.39	0.009	–
BMI (higher)*	184.230	0.000	0.096
Systolic BP (higher)*	81.81	0.032	0.087
Diastolic BP (higher)*	167.73	0.000	0.106
DM type (type II)	5.25	0.386	0.035
CCA-PSV	67.46	0.123	0.021
ICA-PSV*	84.51	0.020	–0.048
CCA-EDV	26.21	0.664	0.102
ICA-EDV	27.82	0.580	–0.047
CCA diameter*	40.94	0.000	0.434
CCA-IMT*	63.91	0.033	0.204
Plaque score*	9.80	0.020	0.040
Stenosis percentage*	18.23	0.032	0.021

BP, blood pressure; CCA, common carotid artery; DM, diabetes mellitus; EDV, end diastolic volume; ICA, internal carotid artery; IMT, intima-media thickness; PSV, peak systolic velocity.
*Statistically significant correlation.

age range of 36–50 years, with mean of 45.4±5.6 years. Most cases (72%) were type II DM, but it did not correlate with diabetic retinopathy severity (*P*=0.386). Diabetic retinopathy was more severe in females (*P*=0.001), and they were the majority of the cases (82%).

Approximately 2/3 of the cases (74%) had diabetes for more than 10 years, which correlated with diabetic retinopathy severity (*P*=0.002). Interestingly, the duration of diabetes also correlated with carotid insufficiency (*P*=0.039). Overall, 68% of the patients were using insulin±oral hypoglycemic drugs (OHDs) to control the disease, which correlated with diabetic retinopathy severity (*P*=0.008).

Positive family history of uncontrolled DM was seen in 28% of the cases (*N*=14), and it correlated with diabetic retinopathy severity (*P*=0.009). Belief in diabetic risk on the eye was found in only 14 (28 eyes) cases, and it did not seem to be a protective factor against diabetic retinopathy in these cases (*P*=0.697).

Systolic blood pressure was significantly higher in worse diabetic retinopathy cases, (*P*=0.032), ranging from 100 to 160 mmHg, with mean value of 128±16 mmHg. Diastolic blood pressure also correlated with diabetic retinopathy (*P*=0.000). Its values ranged from 65 to 100 mmHg, with mean of 83±9 mmHg. In this study, 70% of the patients had BMI of more than 30 kg/m^2, which correlated with diabetic retinopathy severity (*P*=0.000).

Regarding diabetic macular edema (DME), it was present in 39% of the 100 eyes, which was more frequent and more severe with degree of diabetic retinopathy but was not statistically significant (*P*=0.541). DME positively correlated with age (*P*=0.005); all cases were between 36 and 50 years of age. DME was also more common in patients taking OHD (*P*=0.039): 53.1% of OHD group, and 32.4% of insulin group. DME also correlated with higher BMI (*P*=0.001), and was more common in females (*P*=0.047), but it should be noted that most of the cases were females (82%).

Laboratory tests had variable results. All these PDR cases were considered as having uncontrolled disease, which reflected on their laboratory results. FBG and PPGTT did not correlate with the severity of diabetic retinopathy and were high in most cases, with mean levels of 215.7±97.6 and 275.5±101.3 mg/dl, respectively. Approximately 90% of the cases had glycosylated hemoglobin more than 7%, with mean value of 9.6±2.2%, ranging from 5.4 to 13.3%, which correlated with the severity of diabetic retinopathy (*P*=0.000).

There was a positive correlation between LDL and the severity of diabetic retinopathy, with mean LDL value of 139.03±40.08 mg/dl (*P*=0.005). Triglycerides also correlated with diabetic retinopathy, with mean value of 151.9±62±mg/dl (*P*=0.005). HDL values were significantly lower in worse cases of diabetic retinopathy (*P*=0.001, *r*=−0.252), ranging from 24 to 79 mg/dl, with mean value of 43.71±10.06 mg/dl. Overall, 66% of the cases had HDL from 40 to 50 mg/dl, and 30% less than 40 mg/dl. Total cholesterol did not correlate with diabetic retinopathy (*P*=0.109). Mean value of total cholesterol was 204.5±44.4 mg/dl.

CCA-PSV ranged from 25 to 108 cm/s, with mean value of 66.7±20.4 cm/s. It did not show correlation with diabetic retinopathy (*P*=0.123). ICA-PSV ranged from 26 to 110 cm/s, with mean of 59.4±15.9 cm/s. ICA-PSV values were notably lower in higher degrees of 56, with mean value of 7.2±0.09 mm. CCA diameter was higher in worse degrees of diabetic retinopathy, and these findings were statistically significant (*P*=0.000, *r*=0.434).

CCA-IMT, a well-established ultrasonographic parameter of carotid insufficiency, ranged from 0.30 to 1.20 mm, with mean value of 0.69±0.19 mm. CCA-IMT was higher in worse degrees of diabetic retinopathy, and these findings were statistically significant (*P*=0.033, *r*=0.204).

As we are studying CCA diameter as a new ultrasonographic parameter in carotid artery insufficiency, we studied the correlation between CCA diameter and the other factors. Higher CCA diameter was found in cases with higher BMI (*P*=0.000, *r*=0.196). CCA diameter was larger in type II DM, in DM longer than 10-year duration, and in cases taking insulin (*P*=0.000, 0.045, and 0.020, respectively). Systolic blood pressure and diastolic blood pressure values also correlated with higher CCA diameter (*P*=0.000 and *P*=0.000, respectively; *r*=0.286 and 0.301, respectively).

Regarding ultrasound parameters, CCA-EDV and ICA-EDV showed negative correlation with CCA diameter, (*P*=0.000 and 0.026, respectively; *r*=−0.200, −0.315, respectively). CCA-PSV and ICA-PSV also showed significant negative correlation (*P*=0.000 and 0.050, respectively; *r*=−0.137 and −0.162, respectively).

CCA-IMT, and CCA stenosis percentage had significant positive correlation with CCA diameter, CCA-IMT (P=0.000, r=0.377), and stenosis percentage (P=0.000, r=0.112).

Plaque score in this study was calculated out of 6, and ranged from 1 to 2. Plaque score correlated with diabetic retinopathy severity (P=0.020, r=0.040). Of the 100 eyes, 27 had frank carotid plaques in their ipsilateral side. Carotid artery stenosis ranged from 4 to 50%, and it correlated with diabetic retinopathy severity (P=0.032, r=0.021).

Regarding the symmetry of diabetic retinopathy, 70% (N=35) of the patients had some degree of carotid artery insufficiency (IMT>0.8 mm or carotid plaques). Asymmetric diabetic retinopathy was detected in 28 of the 50 patients. We studied the relationship among CCA diameter, CCA-IMT, and symmetry of diabetic retinopathy. Approximately half of the cases in this study (N=24) had larger CCA diameter in the worse eye, with much higher percentage in asymmetric diabetic retinopathy (N=21, 87.5%), and this finding was statistically significant (P=0.000).

Regarding CCA-IMT and symmetry, 40% (N=20) of the cases in this study had larger CCA-IMT in the worse eye, and 80% in asymmetric diabetic retinopathy. This result was also statistically significant (P=0.005).

Conclusion

Ultrasonography parameters correlated carotid artery insufficiency with higher diabetic retinopathy. Diabetic retinopathy seems to be an independent risk factor of carotid artery insufficiency, in diabetic patients, leading to worsening of diabetic retinopathy even in the absence of other known risk factors of atherosclerosis.

Recommendations

Carotid artery ultrasound should be implemented to detect carotid artery insufficiency in selective cases of diabetic retinopathy, like asymmetric diabetic retinopathy, and in cases that are worsening despite the absence of renal insufficiency and even with good medical control.

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Nil.

Conflicts of interest

None declared.

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