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Blood pressure is a risk factor for progression of diabetic retinopathy in normotensive patients with type 2 diabetes: correlation with carotid intima-media thickness

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Objective. Carotid atherosclerotic lesions have been described more frequently in patients with diabetes and microvascular disease than in those with uncomplicated diabetes. In this study, we investigated the role of blood pressure as a risk factor of diabetic retinopathy in normotensive patients with type 2 diabetes. We also assessed the correlation of carotid intima-media thickness with both blood pressure and diabetic retinopathy.

Methods. The study group consisted of 140 normotensive patients (68 males and 72 females) with type 2 diabetes and diabetic retinopathy. Carotid intima-media thickness was evaluated using high-resolution B-mode ultrasonography. Diabetic retinopathy was assessed and graded, using colored fundus photography and fundus fluorescein angiography, as either non-proliferative or proliferative.

Results. Patients with proliferative diabetic retinopathy showed a higher systolic and diastolic blood pressure ($p<0.01$). Carotid intima-media thickness was higher in patients with proliferative than non-proliferative diabetic retinopathy ones (1.094±0.142 vs. 0.842±0.134 mm, respectively; $p<0.001$) Carotid intima-media thickness showed positive correlation with both systolic ($p<0.001$) and diastolic blood pressures ($p<0.01$). No significant differences were found between males and females in any of the studied parameters.

Conclusion. Our study proves that both systolic and diastolic blood pressures are important risk factors for the progression of retinopathy in normotensive patients with type 2 diabetes. We also demonstrate that carotid intima-media thickness, as a marker of atherosclerosis, is strongly correlated with both blood pressure and diabetic retinopathy in those patients.

Key words: blood pressure, type 2 diabetes, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, carotid intima-media thickness

The long term vascular complications of diabetes mellitus account for the majority of morbidity and mortality in patients with diabetes (Dodson et al. 1995). The relationship between micro- and macro-vascular diseases in diabetes mellitus was investigated in previous research work. Carotid intima-media thickness (IMT) was found to be higher in patients with type 1 diabetes and proliferative retinopathy compared to those without retinopathy (Yokoyama et al. 1993). Also in type 2 diabetes, carotid IMT was proven to be higher in patients with non-proliferative retinopathy compared to those without retinopathy (Visona et al. 1995). The aim of this work was to investigate the role of blood pressure as a risk factor of diabetic retinopathy in normotensive

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patients with type 2 diabetes. The correlations of carotid intima-media thickness with both blood pressure and diabetic retinopathy were also assessed.

Subjects and Methods

Subjects. The study group included 140 patients with type 2 diabetes (68 males and 72 females). All of them were non-smoking with normal renal function. Their ages ranged from 40 to 62 years with a mean of 51.2±4.7 years. The duration of their diabetes ranged from 3 to 10 years with a mean of 7.2±3.1 years. Body mass index (BMI) ranged from 23.5 to 38.7 kg/m^2 with a mean of 30.6±4.1 kg/m^2. Blood pressure assessment was done three times, in the sitting position, under standard conditions. The mean systolic (SBP) and diastolic blood pressures (DBP) of the three measurements were recorded. All patients included in the study were normotensive (BP < 135/85).

The study protocol was approved by the ethical committees and review boards of each participating institution. All the patients and control subjects who participated in the study provided written informed consents.

Carotid IMT measurement. Ultrasonography of the carotid arteries was performed using high-resolution color-coded Sonoline Elegra (Siemens) scanner equipped with 7.5 MHz linear imaging transducer. Common carotid IMT measurement and the detection of atherosclerotic lesions were done using gray scale B-mode imaging. The measurement of the IMT was made in the 2 cm segment proximal to the dilation of the carotid bulb and always in a plaque free area (Fig. 1). For each patient, three measurements were performed on each side. All results are the mean of the two sides (Bonora et al. 1997). Previous reports suggest that cardio-vascular events are rare in subjects with mean carotid IMT measurements below 0.6 mm (Chambless et al. 1997). Forty age, sex and weight matched normal subjects were included in the study as a control group for carotid IMT measurement by ultrasonography.

Assessment of retinopathy. Colored fundus photography and fundus fluorescein angiography (FFA) were done to assess and grade the retinopathy using Topcon 50 XS fundus camera. FFA was done using the conventional technique. Then with the exciter and barrier filters activated, sequential photography was done using 400 ASA black and white films. All patients included in the study group had diabetic retinopathy which was classified into either non-proliferative or proliferative one. Non-proliferative cases revealed changes ranging from few retinal microaneurysms to retinal microangiopathies and venous changes (Fig. 2). Proliferative cases revealed more extensive retinal ischemic changes in addition to neovascularization (Fig. 3).

Statistical analysis. Statistical analysis of the results was done using student t-test with p value < 0.05 to be considered significant. Correlation between carotid IMT and other parameters in the study group was done using the correlation coefficient. Multiple regression analysis was used to evaluate the independent association of risk factors with carotid IMT in the study group.

Results

The study group included 66 patients with non-proliferative (NPDR) and 74 patients with proliferative diabetic retinopathy (PDR). Patients with PDR showed a higher systolic blood pressure (SBP) compared to those with NPDR (130±3 vs. 125±3 mmHg, respectively; $p<0.01$). Also diastolic blood pressure (DBP) was significantly higher in patients with PDR compared to those with NPDR (82±2 vs. 77±4 mmHg, respectively; $p<0.01$). Carotid IMT was significantly higher in the study group compared to the control group (0.978±0.233 vs. 0.620±0.103 mm, respectively; $p<0.0001$) and it was significantly higher in patients with PDR compared to those with NPDR (1.094±0.142 vs. 0.842±0.134 mm, respectively; $p<0.001$). Carotid intima-media thickness showed positive correlation with both SBP ($p<0.001$) and DBP ($p<0.01$), diabetes duration ($p<0.01$), but not with age or BMI. No significant differences were found between males and females in any of the studied parameters. The results among the study group and their statistical significance are presented in Table 1 and Table 2.

Discussion

Type 2 diabetes exposes the vasculature to the onslaught of several factors, namely hyperglycemia, hypertension, dyslipidemia, hemostatic changes, and inflammation (Juhan-Vague et al. 2002). The association of the above factors with macro-vascular disease and with diabetic retinopathy is well known (van Leiden et al. 2002). Carotid IMT has been shown to correlate well with general atherosclerotic status (O'Leary et al. 1999). Measurement of the far wall IMT of the common carotid artery has become an important endpoint of atherosclerosis in cardiovascular clinical trials (Lehmann

Fig. 1. Measurement of carotid intima-media thickness (IMT) by ultrasonography.

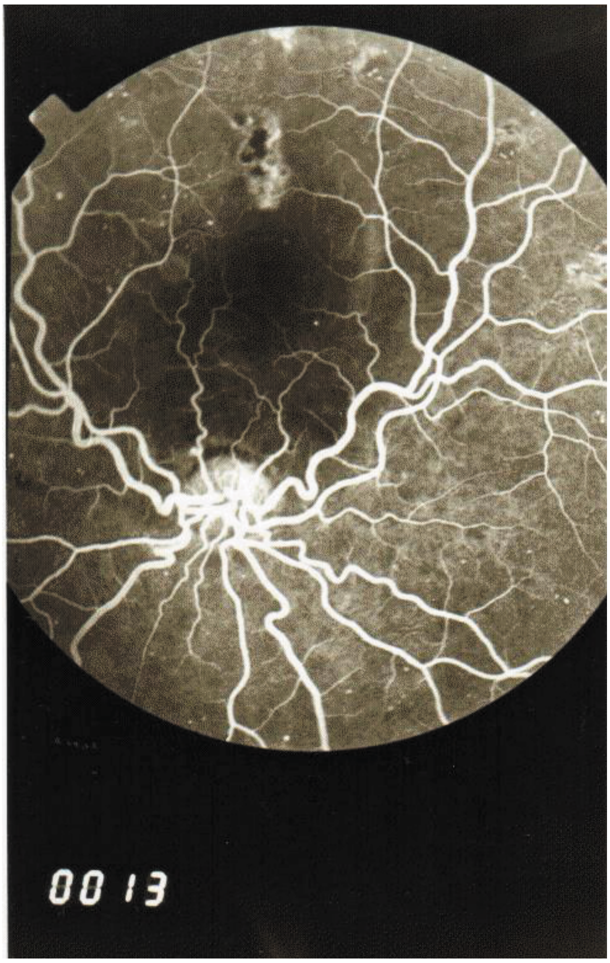

Fig. 2. Non-proliferative diabetic retinopathy by fundus fluorescein angiography.

Fig. 3. Proliferative diabetic retinopathy by fundus fluorescein angiography.

et al. 1997). Epidemiological studies have found that an increase of 0.1 mm in maximum common carotid IMT was associated with an 11% increase in the risk of myocardial infarction (Salonen and Salonen 1993; Guvener et al. 2000).

Diabetic retinopathy is one of the leading causes of blindness all over the world. Management of such serious microvascular complication of diabetes depends on reliable methods of screening and grading of retinopathy (Dodson et al. 1995). Higher carotid IMT has been reported in patients with diabetes and microvascular disease. Yokoyama et al. (1993) reported higher carotid IMT in patients with type 1 diabetes and proliferative retinopathy compared to those without retinopathy. Visona et al. (1995) have proved that in type 2 diabetes, carotid IMT is higher in patients with non-proliferative retinopathy compared to those without retinopathy.

Our study confirmed that carotid IMT was significantly higher in the study group compared to the control one. In the studied group, no significant differences were found between males and females, regarding any of the studied parameters. These results are consistent with previous reports (Yokoyama et al. 1993; Yamasaki et al. 1994; Visona et al. 1995; Jarvisalo et al. 2002).

In our study, patients with PDR showed a higher SBP compared to those with NPDR. DBP was also significantly higher in patients with PDR compared to those with NPDR. Carotid IMT was significantly higher in patients with PDR compared to those with NPDR. Previous research works have reported a higher carotid IMT in patients with type 1 (Dodson et al. 1995) and type 2 (Yokoyama et al. 1993) diabetes complicated by retinopathy, compared to those without, retinopathy. But our study demonstrates that in patients with type 2 diabetes, there is a strong correlation between carotid IMT, as a marker of atherosclerosis, and the degree of retinopathy. Carotid IMT showed positive correlation with diabetes duration ($p<0.01$), SBP ($p<0.001$), DBP ($p<0.01$), but not with age or BMI. These results are consistent with data reported by Williams and Pickup (1999) and also by the UK prospective Diabetes Study group (1998).

Our findings are also consistent with the results of the Atherosclerosis Risk in Communities (ARIC) study (Klein et al. 2002) and The Chennai Urban Rural Epidemiology Study (CURES-2) (Rema et al. 2004). Also, Ogawa et al. (2009) proved that IMT is greater in Japanese patients with long term early onset type 1 diabetes mellitus with proliferative retinopathy than in those without retinopathy.

However, Yun et al. (2011) could not establish any significant association between carotid IMT and retinopathy among Korean patients with type 2 diabetes after adjusting for cardiovascular risk factors. Also, the Multi-Ethnic Study of Atherosclerosis did not reveal significant association between diabetic retinopathy and measures of carotid artery disease; including IMT (Kawasaki et al. 2011).

Our study proves that SBP and DBP are important risk factors for the progression of retinopathy in type 2 diabetes, even in normotensive patients. This proves the strong relationship between diabetic macro- and microvascular disease. It also emphasizes the value of tight blood pressure control in these patients. The study also demonstrates that carotid IMT, as a marker of atherosclerosis, is strongly correlated with both blood pressure and DR.

Many researchers have tried to explain the relationship between micro-angiopathy and macro-vascular disease in diabetes mellitus. The presence of common

Table 1

Comparison between patients with non-proliferative diabetic retinopathy (NPDR) and those with proliferative diabetic retinopathy (PDR).

Variable	NPDR	PDR	p-value
Number of patients	66	74	
Age (years)	49.8 ± 6.4	52.4 ± 6.9	NS
Diabetes duration (years)	6.8 ± 2.8	7.8 ± 3.5	NS
BMI (kg/m2)	30.2 ± 5.4	29.6 ± 6.7	NS
SBP (mmHg)	125 ± 3	130 ± 3	<0.01*
DBP (mmHg)	77 ± 4	82 ± 2	<0.01*
Carotid IMT (mm)	0.842 ± 0.134	1.094 ± 0.142	<0.001*

Data are presented as mean ± SD. BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, IMT – intima-media thickness. *PDR vs. NPDR

Table 2

Correlation between carotid intima-media thickness (IMT) and other parameters in the study group

Variable	Carotid IMT p-value
Age	NS
Diabetes duration	<0.01*
Body mass index (BMI)	NS
Systolic blood pressure (SBP)	<0.001*
Diastolic blood pressure (DBP)	<0.01*
Diabetic retinopathy (DR)	<0.0001*

pathogenic mechanisms in both micro- and macro-vascular diabetic complications has been suggested by de Kreutzenberg et al. (2011). Diabetes mellitus induces abnormalities in the expression of various cytokines and vasoactive peptides such as transforming growth factor beta (TGF-beta), tumor necrosis factor alpha (TNF-alpha), angiotensin II and endothelin-1; as reported by Feener and King (1997). Pfeiffer et al. (1996) reported elevated plasma levels of TGF-beta 1 in patients with type 2 diabetes. They suggested that these high levels might contribute to the occurrence of diabetic vascular complications. Smulders et al. (1999) found that fasting homocysteine level correlates with macro-vascular disease in normotensive type 2 diabetes mellitus, but they found no correlation with micro-angiopathy (retinopathy and microalbuminuria). Results from the EURODIAB study (Crook et al. 2001) have indicated that elevated plasma sialic acid, a marker of the acute phase response, is strongly related to the presence of microvascular complications, especially retinopathy and nephropathy, in patients with type 1 diabetes. However it did not show correlation with coronary heart disease.

The insulin resistance state in type 2 diabetes shows a multitude of metabolic abnormalities that could cause vascular dysfunction. Non-esterified fatty acid levels increase long before hyperglycemia and impair insulin effect on glucose uptake in skeletal muscle and the vascular endothelium. This could lead to detrimental effects on the vasculature, as reported by Steinberg and Baron (2002).

References

Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R, Falezza G, Muggeo M: Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients. Relationship with insulin resistance. Diabetes Care 20, 627-631, 1997. http://dx.doi.org/10.2337/diacare.20.4.627

Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX: Association of coronary heart disease risk factors incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 146, 483-494, 1997. http://dx.doi.org/10.1093/oxfordjournals.aje.a009302

Crook MA, Pickup JC, Lumb PJ, Giorgino F, Webb DJ, Fuller JH; EURODIAB IDDM Complications Study Group: Relationship between plasma sialic acid concentration and microvascular and macrovascular complications in type 1 diabetes: The EURODIAB Complications Study. Diabetes Care 24, 316-322, 2001. http://dx.doi.org/10.2337/diacare.24.2.316

de Kreutzenberg SV, Coracina A, Volpi A, Fadini GP, Frigo AC, Guarneri G, Tiengo A, Avogaro A: Microangiopathy is independently associated with presence, severity and composition of carotid atherosclerosis in type 2 diabetes. Nutr Metab Cardiovasc Dis 21, 286-293, 2011.

Dodson P, Gibson J, Kritzinger E: Clinical retinopathies. London, Chapman and Hall, pp. 225-239, 1995.

Feener EP, King GL: Vascular dysfunction in diabetes mellitus. Lancet 350 Suppl 1, Sl9-13, 1997. http://dx.doi.org/10.1016/S0140-6736(97)90022-2

Guvener N, Tutuncu NB, Oto A, Erbas T: Major determinants of carotid intima-media thickness in type 2 diabetic patients: age and body mass index. Endocr J 47, 525-33, 2000. http://dx.doi.org/10.1507/endocrj.47.525

Jarvisalo MJ, Putto-Laurila A, Jartti L, Lehtimaki T, Solakivi T, Ronnemaa T, Raitakari OT: Carotid artery intima-media thickness in children with type 1 diabetes. Diabetes 51, 493-498, 2002. http://dx.doi.org/10.2337/diabetes.51.2.493

Juhan-Vague I, Morange PE, Alessi MC: The insulin resistance syndrome: implications for thrombosis and cardiovascular disease. Pathophysiol Haemost Thromb 32, 269-273, 2002. http://dx.doi.org/10.1159/000073579

Kawasaki R, Cheung N, Islam FM, Klein R, Klein BE, Cotch MF, Sharrett AR, O'Leary D, Wong TY; Multi-Ethnic Study of Atherosclerosis: Is diabetic retinopathy related to subclinical cardiovascular disease? Ophthalmology 118, 860-865, 2011. http://dx.doi.org/10.1016/j.ophtha.2010.08.040

Klein R, Sharrett AR, Klein BE, Moss SE, Folsom AR, Wong TY, Brancati FL, Hubbard LD, Couper D; ARIC Group: The association of atherosclerosis, vascular risk factors, and retinopathy with diabetes: the atherosclerosis risk in communities study. Ophthalmology 109, 1225-1234, 2002. http://dx.doi.org/10.1016/S0161-6420(02)01074-6

Lehmann ED, Riley WA, Clarkson P, Gosling RG: Non-invasive assessment of cardiovascular disease in diabetes mellitus. Lancet 350 Suppl 1, Sl14-19, 1997. http://dx.doi.org/10.1016/S0140-6736(97)90023-4

Ogawa Y, Uchigata Y, Iwamoto Y: Progression factors of carotid intima-media thickness and plaque in patients with long-term, early-onset type 1 diabetes mellitus in Japan: simultaneous comparison with diabetic retinopathy. J Atheroscler Thromb 16, 821-828, 2009. http://dx.doi.org/10.5551/jat.1701

O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid artery intima-media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Eng J Med 340, 14-22, 1999. http://dx.doi.org/10.1056/NEJM199901073400103

Pfeiffer A, Middelberg-Bisping K, Drewes C, Schatz H: Elevated plasma levels of transforming growth factor-beta 1 in NIDDM. Diabetes Care 19, 1113-1117, 1996. http://dx.doi.org/10.2337/diacare.19.10.1113

Rema M, Mohan V, Deepa R, Ravikumar R; Chennai Urban Rural Epidemiology Study-2: Association of carotid intima-media thickness and arterial stiffness with diabetic retinopathy: the Chennai Urban Rural Epidemiology Study (CURES-2). Diabetes Care 27, 1962-1967, 2004. http://dx.doi.org/10.2337/diacare.27.8.1962

Salonen JT, Salonen R: Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation 87 (Suppl), II56-65, 1993.

Smulders YM, Rakic M, Slaats EH, Treskes M, Sijbrands EJ, Odekerken DA, Stehouwer CD, Silberbusch J: Fasting and post-methionine homocysteine levels in NIDDM. Determinants and correlations with retinopathy, albuminuria and cardiovascular disease. Diabetes Care 22, 125-132, 1999. http://dx.doi.org/10.2337/diacare.22.1.125

Steinberg HO, Baron AD: Vascular function, insulin resistance and fatty acids. Diabetologia 45, 623-634, 2002. http://dx.doi.org/10.1007/s00125-002-0800-2

UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317, 703, 1998. http://dx.doi.org/10.1136/bmj.317.7160.703

van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Polak BC: Blood pressure, lipids, and obesity are associated with retinopathy: the hoorn study. Diabetes Care, 25, 1320-1325, 2002. http://dx.doi.org/10.2337/diacare.25.8.1320

Visona A, Lusiani L, Bonanome A, Belramello G, Confortin L, Papesso B, Costa F, Pagnan A: Wall thickening of common carotid arteries in patients affected by non-insulin dependent diabetes mellitus: relationship to microvascular complications. Angiology 46, 793-799, 1995. http://dx.doi.org/10.1177/000331979504600905

Williams G, Pickup J: Hypertension in diabetes. Handbook of Diabetes 2nd Edition. Oxford: Blackwell Science Ltd, pp. 144-146, 1999.

Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kajimoto Y, Morishima T, Kamada T: Atherosclerosis in carotid artery of young IDDM patients monitored by ultrasound high-resolution B-mode imaging. Diabetes, 43, 634-639, 1994. http://dx.doi.org/10.2337/diab.43.5.634

Yokoyama H, Yoshitake E, Otani T, Uchigata Y, Kawagoe M, Kasahara T, Omori Y: Carotid atherosclerosis in young-aged IDDM associated with diabetic retinopathy and diastolic blood pressure. Diabetes Res Clin Pract 21, 155-159, 1993. http://dx.doi.org/10.1016/0168-8227(93)90063-B

Yun YW, Shin MH, Lee YH, Rhee JA, Choi JS: Arterial stiffness is associated with diabetic retinopathy in Korean type 2 diabetic patients. J Prev Med Public Health 44, 260-266, 2011. http://dx.doi.org/10.3961/jpmph.2011.44.6.260