# Relationship between retinopathy and asymptomatic atherosclerosis determined by measurement of carotid intima-media thickness in patients with type 2 diabetes mellitus

## Karotis intima medya kalınlığı ile belirlenen semptomsuz aterosklerozun tip 2 diabetes mellituslu hastalarda retinopati ile ilişkisi

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## ABSTRACT

***Objective:*** Presence of diabetic retinopathy (DR) may be used as an early marker of atherosclerosis in type 2 diabetes mellitus (DM) patients. This study aimed to investigate the relationship between the presence of DR and carotid intima-media thickness (CIMT), which is an indicator of early atherosclerosis in patients with type 2 DM.

***Methods:*** Thirty DM patients with retinopathy (DR group), 28 DM patients without retinopathy (non-DR group), and 27 healthy controls (control group) were included in the study. CIMT was assessed using a high-resolution B-mode ultrasonography device.

***Results:*** Mean CIMT was found to be 0.9±0.17 mm in the DR group, 0.8±0.16 mm in the non-DR group, and 0.7±0.13 mm in the control group. CIMT was found to be statistically significantly higher in the DR group compared to the other 2 groups ($p<0.001$). When multivariate analysis was performed, presence of DR still remained as an independent risk factor for increased CIMT values.

***Conclusion:*** Presence of DR in type 2 DM patients is an independent risk factor in terms of increased CIMT, which is considered to be a finding of subclinical atherosclerosis. Therefore, we believe that type 2 DM patients with retinopathy should be closely followed in terms of cardiovascular events.

## ÖZET

***Amaç:*** Diyabetik retinopati (DR) varlığı tip 2 diabetes mellitus (DM) olan hastalarda aterosklerozun erken bir belirteci olabilir. Bu çalışmada tip 2 DM'li hastalarda DR varlığı ile erken ateroskleroz belirteci olarak kullanılan karoris intima-medya kalınlığı (KIMK) arasındaki ilişkiyi inceledik.

***Yöntemler:*** Bu çalışmaya retinopatisi bulunan 30 diyabetik hasta (DR grubu), retinopatisi olmayan 28 diyabetik hasta (nonDR grubu) ve 27 sağlıklı birey (kontrol grubu) alındı. Hastaların KIMK ölçümleri yüksek çözünürlüklü B-mod ultason cihazı ile yapıldı.

***Bulgular:*** Ortalama KIMK, DR grubunda 0.9±0.17 mm, nonDR grubunda 0.8±0.16 mm ve kontrol grubunda 0.7±0.13 mm olarak ölçüldü. Karoris intima-medya kalınlığı ölçümleri DR grubunda diğer iki gruba kıyasla anlamlı olarak yüksek bulundu ($p<0.001$). Çok değişkenli analiz sonucunda da DR varlığı artmış KIMK için bağımsız bir öngördürücü olarak tespit edildi.

***Sonuç:*** Tip 2 DM'si bulunan hastalarda DR varlığı subklinik aterosklerozun bir göstergesi olarak kabul edilen KIMK ile ilişkili bulunmuştur. Bu nedenle retinopatisi bulunan tip 2 DM'li hastalar kardiyovasküler olaylar açısından yakından takip edilmelidir.

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Diabetes mellitus (DM) is a major risk factor for cardiovascular system pathologies, including atherosclerosis.[1] A positive relationship has been established between major risk factors for the cardiovascular system and presence and severity of atherosclerosis; however, many individuals with these risk factors are clinically asymptomatic, which leads to difficulties in risk classification in terms of atherosclerotic diseases and detection of subclinical atherosclerosis. Presence of diabetic retinopathy (DR) may be used as an early indicator of atherosclerosis in type 2 DM patients.

Since micro- and macroangiopathies are responsible for DM-related morbidity, many risk factors including hyperglycemia and arterial hypertension also affect the cardiovascular system. It has been proposed that vascular complications of diabetes have common pathological mechanisms, including endothelial dysfunction.[2] Atherosclerosis affects large arteries earlier than medium-sized vessels. The most important changes which "emerge and are detected" in the early subclinical period of atherosclerotic disease include endothelial dysfunction as well as increased intima-media thickness (IMT), which is observed in the whole arterial bed.[3] Endothelial dysfunction and the increase in IMT can be determined by several methods, including ultrasonography. Thus, necessary therapeutic methods can be applied prior to the identification of advanced atherosclerotic involvement. Ultrasonographic methods which measure the thickness of the intima-media of superficial large arteries–including the femoral, carotid, and brachial arteries–constitute a simple, inexpensive, non-invasive, and highly reproducible technique which can show endothelial dysfunction in the asymptomatic period of the atherosclerotic process as well as widespread atherosclerosis, which develops in the same process.[4–6]

In this study, we aimed to investigate the relationship between the presence of DR and carotid intima-media thickness (CIMT), both of which possess similar pathogenetic mechanisms.

## METHODS

Fifty-eight type 2 DM patients who were evaluated for ophthalmological complications of diabetes and met the inclusion criteria were included in the study. Twenty-seven healthy patients who presented with a complaint of far-sightedness and had no ocular or systemic pathology except for presbyopia were included in the study as the control group. Twenty-seven diabetic patients who had no retinopathy were named as the non-DR group, and 31 patients who had DR were named as the DR group. Consent was obtained from all subjects included in the study. The methods of the study were approved by the ethics committee.

**Abbreviations:**

| | |
|---|---|
| *CAD* | *Coronary artery disease* |
| *CIMT* | *Carotid intima-media thickness* |
| *DM* | *Diabetes mellitus* |
| *DR* | *Diabetic retinopathy* |
| *IMT* | *Intima-media thickness* |

Exclusion criteria included chronic renal disease, hepatic disease, pulmonary disease, active infection, glaucoma, uveitis, or a history of ophthalmological surgery in the last year.

A detailed medical history including cardiovascular risk factors was obtained from each patient included in the study. Physical examination, electrocardiogram, and effort test results of the patients were found to be normal. Detailed ophthalmological and physical examinations were performed. Colored fundoscopic images were taken of all patients, and fundus fluorescein angiography was performed when necessary. Hemoglobin A1c, fasting blood glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and creatinine values were measured (Table 1).

Doppler ultrasonographic examination was performed by the same physician, who was blinded to the identity of the patient being evaluated. After patients lied down on the examination table in the supine position, their necks were supported with a pillow and their heads placed in hyperextension. LOGIC 9 ultrasonography device (GE Healthcare, Milwaukee, WI, USA) and a high-resolution linear array probe (5–12 MHz wideband) were used for the measurement of IMT of the carotid arteries. Bilateral carotid artery IMT was measured from the posterior wall, 1 cm from the bifurcation. If a plaque was present in this region, measurement was performed in the proximal segment which did not contain a plaque. Calculations were performed manually by a single operator to minimize intraobserver variability.

### Statistical analysis

Statistical analyses were performed utilizing SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Power

**Table 1. Baseline characteristics of patients**

| | Control group (n=27) | Non-DR (n=28) | DR (n=30) | *p* |
|---|---|---|---|---|
| Age (years)* | 54.4±5.61 | 52.0±5.81 | 56.9±5.92 | 0.007 |
| | | $^{\Psi}$p=0.246 | $^{\phi}$p=0.252, $^{\delta}$p<0.001 | |
| Male sex (%)* | 11 (40.7%) | 11 (39.3%) | 13 (43.3%) | 0.951 |
| Disease duration (years)** | NA | 8.4±5.23 | 12.8±4.84 | <0.001 |
| Insulin treatment, n (%)*** | NA | 8 (28.6%) | 19 (63.3%) | <0.001 |
| Smoking, n (%)* | 8 (29.6%) | 9 (32.1%) | 8 (26.7%) | 0.900 |
| Hypertension, n (%)* | 9 (33.3%) | 8 (28.6%) | 10 (33.3%) | 0.906 |
| Total cholesterol (mg/dl)* | 185.9±40.81 | 189.3±40.42 | 197.5±45.03 | 0.562 |
| HDL cholesterol (mg/dl)* | 43.9±6.53 | 38.9±10.12 | 47.3±23.21 | 0.123 |
| LDL cholesterol (mg/dl)* | 113.1±32.52 | 116.6±30.61 | 119.0±36.64 | 0.799 |
| Triglycerides (mg/dl)* | 152.9±64.75 | 163.4±62.86 | 162.1±97.27 | 0.861 |
| Body mass index (kg/m$^2$)* | 24.9±1.62 | 26.1±2.41 | 27.5±1.41 | |
| | | $^{\Psi}$p<0.001 | $^{\phi}$p<0.001, $^{\delta}$p=0.022 | <0.001 |
| Hemoglobin A1c (%)* | 5.5±1.21 | 7.5±1.62 | 8.4±1.61 | |
| | | $^{\Psi}$p=0.254 | $^{\phi}$p<0.001, $^{\delta}$p=0.083 | <0.001 |
| Serum creatinine (mg/dl) | 0.7±0.12 | 0.7±0.11 | 0.7±0.21 | 0.735 |

DR: Diabetic retinopathy, NonDR: Diabetic patients without retinopathy; HDL: High density lipoprotein; LDL: Low density lipoprotein.
*One-way ANOVA; **independent samples t-test and ***chi-square tests were used for comparisons. Then post-hoc Tukey's test was performed for the variables which had a p value of <0.05 in the ANOVA test.
$^{\Psi}$Shows the comparisons between the control group and non-DR group; $^{\phi}$Shows the comparisons between the control group and DR group; $^{\delta}$Shows the comparisons between the non-DR group and DR group. P<0.05 was accepted as significant.

analysis was conducted by using analysis of variance with G*power 3.1.9 program (probability of error=0.05) to determine the sample size with a power value of 0.8 (effect size=0.61), and total size of 30 was calculated. The power value of our study was calculated as 0.99. Numerical variables were expressed as mean±SD, and minimum-maximum values were expressed as numbers and percents. Kolmogorov-Smirnov test was used to determine if the numerical values demonstrated a normal distribution. The homogeneity of group variances was examined via Levene's test. One-way analysis of variance test was used to compare groups. Post-hoc comparisons with Tukey's honest significant difference and Conover-Iman's multiple comparison tests were used for parametric and nonparametric variables, respectively. Chi-square and independent samples t-tests were used to compare the 2 experimental groups in cases such as insulin treatment and DM duration where the control group was not available for comparison. Linear regression analysis was used for multivariate analysis. A p value of <0.05 was considered significant.

## RESULTS

Baseline characteristics of the patients are summarized in Table 1. No statistically significant difference was found between the groups in terms of their lipid profiles (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride) and creatinine values. The duration of diabetes was significantly different between patients who had retinopathy (12.6±6.92 years) and those who did not have retinopathy (8.4±5.31 years) (p<0.001). A statistically significant difference was found between the 2 groups in terms of use of insulin dependence (DR: non-DR, 65%:26%, p=0.007) (Table 1).

Mean carotid intima-media value was found to be 0.9±0.17 mm in the DR group, 0.8±0.16 mm in the non-DR group, and 0.7±0.13 mm in the control group. A significant difference was found between the patients with and without retinopathy in terms of CIMT (p<0.001). There was also a statistically significant difference between the DR group and control group

**Table 2. Multivariate analysis including several risk factors of atherosclerosis to predict carotid intima-media thickness**

| | β value | 95 % Confidence interval | | *p* |
|---|---|---|---|---|
| | | Lower bound | Upper bound | |
| Age (Years) | 0.336 | 0.005 | 0.015 | <0.001 |
| Gender (Male) | -0.128 | -0.112 | 0.020 | 0.169 |
| Hemoglobin A1c (%) | -0.061 | -0.018 | 0.027 | 0.616 |
| Total cholesterol (mg/dl) | 0.116 | -0.001 | 0.002 | 0.483 |
| High density lipoprotein cholesterol (mg/dl) | -0.135 | -0.004 | 0.001 | 0.187 |
| Low density lipoprotein cholesterol (mg/dl) | 0.318 | 0.001 | 0.004 | 0.063 |
| Hypertension | 0.018 | -0.059 | 0.073 | 0.834 |
| Cigarette smoking | -0.042 | -0.085 | 0.052 | 0.636 |
| Presence of diabetic retinopathy | 0.416 | 0.021 | 0.160 | 0.011 |
| Disease duration(months) | -0.004 | -0.007 | 0.007 | 0.975 |
| Body mass index (kg/m$^2$) | 0.108 | -0.008 | 0.026 | 0.277 |

$R^2$ is 0.496 for the carotid intima-media thickness model. Linear regression analysis was used for multivariate analysis.

in terms of CIMT (p<0.001). No significant difference was found between the control group and the non-DR group in terms of CIMT (p=0.154).

After multivariate analysis was performed, presence of DR was independently associated with increased CIMT (β=0.416, p=0.011). The results of multivariate analysis are shown in Table 2.

## DISCUSSION

The present study shows that diabetic patients with retinopathy who do not have an overt cardiovascular disease have an increased atherosclerotic burden, which has been demonstrated by increased CIMT values. The association between presence of DR and CIMT was still present after multivariate analysis was performed, including major cardiovascular risk factors.

There is controversy in the literature regarding the association between subclinical atherosclerosis and diabetic retinopathy. Several studies reported findings similar to those of our study. In the CURES 2 study,[7] a strong relationship between retinopathy and CIMT was reported after several cardiovascular risk factors were adjusted. In a study performed by Malecki et al., CIMT was found to be higher in patients with retinopathy compared to patients without retinopathy, and it was concluded that the presence of retinopathy was an independent risk factor for increased CIMT in type 2 DM patients.[8] In the ARIC study, CIMT was found to be significantly increased in patients with retinopathy.[9] Our findings support these studies, and following multivariate analysis, presence of DR was one of the independent factors associated with increased CIMT. In contrast, Hoorn revealed that retinal microvascular disease was not an independent risk factor in terms of increased CIMT.[10] No relationship was found between retinopathy and early atherosclerosis in the CHS study, though a strong relationship was found between coronary arteries with positive clinical findings and retinopathy.[11] The difference between the results of these studies may be explained by the difference of age between the subject groups used in these studies. While the age range of the subjects included in the ARIC study was 51–72 years, the age range in the CHS study was 69–102 years. In our study, we included younger patients, which might explain the significant association between DR and subclinical atherosclerosis.

Many studies have reported that CIMT is an indicator of early atherosclerosis and is related with the presence of coronary artery disease (CAD).[12–16] CIMT shows an increase even at the onset of atherosclerosis and can be used as an early and non-invasive marker of atherosclerosis. In our study, increased CIMT values and presence of carotid plaques were found in patients with DR, and presence of DR is an

independent risk factor for increased CIMT, thus atherosclerosis. Atherosclerosis is known to be a macrovascular complication of DM, but DR is accepted as a microvascular complication. Our finding of significant association between microvascular and macrovascular complications of DM has been confirmed in several studies in the literature. Framingham[17] showed that presence of retinopathy was related with presence of microangiopathy in type 2 DM patients. In younger subgroups, presence of retinopathy increases the risk of cardiovascular events by 15-fold. In the EURODIAB study, it was determined that the frequency of cardiovascular events was higher in type 2 DM patients with retinopathy.[18] de Kreutzenberg et al. demonstrated that retinopathy was significantly and independently related with carotid plaques in type 2 DM patients.[19] Similarly, we found a relationship between the severity of microangiopathy and carotid atherosclerosis. Cheung et al. specified the presence of retinopathy as an independent risk factor for cardiovascular events and mortality related with cardiovascular events.[20] However, in the Valpolicella Heart Diabetes study, this correlation was not confirmed when risk factors including arterial hypertension were adjusted.[21] Nor could Spijkerman et al. find a relationship between retinopathy and early vascular disease markers, and therefore emphasized that retinopathy had limited value in predicting development of CAD.[22]

There are some limitations of our study. First, the size of our study groups was not sufficient to establish rigorous conclusions. Second, direct relationship between retinopathy and macrovascular disease could not be demonstrated, due to the cross-sectional nature of the study. To assess the cardiovascular risk associated with a microvascular complication such as DR in patients with DM, longitudinal studies are warranted.

## Conclusion

We conclude that the presence of retinopathy is an independent risk factor in terms of increased CIMT in type 2 DM patients. It is well known that CIMT is an early marker of atherosclerosis, and it is related with CAD and CAD-related mortality. Therefore, we believe that type 2 DM patients with retinopathy are in an elevated risk group in terms of coronary and peripheral arterial disease, even when in in the asymptomatic atherosclerosis period. In addition, we believe that the results of our study should be examined carefully in terms of emphasizing the importance of close follow-up of type 2 DM patients with retinopathy in terms of cardiovascular events.

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## REFERENCES

1. Making a difference. The World Health Report 1999. Health Millions 1999;25:3–5.
2. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. Clin Sci (Lond) 2005;109:143–59. CrossRef
3. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5. CrossRef
4. Traub O, Berk BC. Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force. Arterioscler Thromb Vasc Biol 1998;18:677–85. CrossRef
5. Mukherjee D, Yadav JS. Carotid artery intimal-medial thickness: indicator of atherosclerotic burden and response to risk factor modification. Am Heart J 2002;144:753–9. CrossRef
6. Mayet J, Stanton AV, Chapman N, Foale RA, Hughes AD, Thom SA. Is carotid artery intima-media thickening a reliable marker of early atherosclerosis? J Cardiovasc Risk 2002;9:77–81. CrossRef
7. 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 2004;27:1962–7. CrossRef
8. Malecki MT, Osmenda G, Walus-Miarka M, Skupien J, Cyganek K, Mirkiewicz-Sieradzka B, et al. Retinopathy in type 2 diabetes mellitus is associated with increased intima-media thickness and endothelial dysfunction. Eur J Clin Invest 2008;38:925–30. CrossRef
9. Klein R, Sharrett AR, Klein BE, Moss SE, Folsom AR, Wong TY, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes : the atherosclerosis risk in communities study. Ophthalmology 2002;109:1225–34. CrossRef
10. van Hecke MV, Dekker JM, Nijpels G, Stolk RP, Henry RM, Heine RJ, et al. Are retinal microvascular abnormalities associated with large artery endothelial dysfunction and intima-media thickness? The Hoorn Study. Clin Sci (Lond) 2006;110:597–604. CrossRef
11. Klein R, Marino EK, Kuller LH, Polak JF, Tracy RP, Gottdiener JS, et al. The relation of atherosclerotic cardiovascular

disease to retinopathy in people with diabetes in the Cardiovascular Health Study. Br J Ophthalmol 2002;86:84–90. CrossRef

12. Jadhav UM, Kadam NN. Carotid intima-media thickness as an independent predictor of coronary artery disease. Indian Heart J 2001;53:458–62.
13. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399–406. CrossRef
14. O'Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. Am J Cardiol 2002;90:18–21. CrossRef
15. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 1997;146:483–94. CrossRef
16. Mayet J, Stanton AV, Chapman N, Foale RA, Hughes AD, Thom SA. Is carotid artery intima-media thickening a reliable marker of early atherosclerosis? J Cardiovasc Risk 2002;9:77–81. CrossRef
17. Hiller R, Sperduto RD, Podgor MJ, Ferris FL 3rd, Wilson PW. Diabetic retinopathy and cardiovascular disease in type II diabetics. The Framingham Heart Study and the Framingham Eye Study. Am J Epidemiol 1988;128:402–9.
18. van Hecke MV, Dekker JM, Stehouwer CD, Polak BC, Fuller JH, Sjolie AK, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. Diabetes Care 2005;28:1383–9. CrossRef
19. de Kreutzenberg SV, Coracina A, Volpi A, Fadini GP, Frigo AC, Guarneri G, et al. Microangiopathy is independently associated with presence, severity and composition of carotid atherosclerosis in type 2 diabetes. Nutr Metab Cardiovasc Dis 2011;21:286–93.
20. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes Care 2007;30:1742–6. CrossRef
21. Targher G, Bertolini L, Tessari R, Zenari L, Arcaro G. Retinopathy predicts future cardiovascular events among type 2 diabetic patients: The Valpolicella Heart Diabetes Study. Diabetes Care 2006;29:1178. CrossRef
22. Spijkerman AM, Gall MA, Tarnow L, Twisk JW, Lauritzen E, Lund-Andersen H, et al. Endothelial dysfunction and low-grade inflammation and the progression of retinopathy in Type 2 diabetes. Diabet Med 2007;24:969–76. CrossRef

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