Retinopathy Is Related to the Angiographically Detected Severity and Extent of Coronary Artery Disease in Patients With Type 2 Diabetes Mellitus

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SUMMARY

Diabetic retinopathy (DR) is an early and frequent marker of other vascular complications of diabetes and its relation with coronary ischemia is known. The aim of the present study was to evaluate the association between DR and indices of coronary artery disease (CAD) severity and extent determined by coronary angiography.

Sixty-nine diabetic patients undergoing coronary angiography for suspected CAD were evaluated. The severity and extent of CAD were scored from coronary angiograms by using 3 scores. Retinopathy was graded by fundus examination.

There were differences in the severity score, extent score, number of vessels with disease, duration of diabetes, diabetes therapy, history of previous myocardial infarction (MI), and serum creatinine level among patients with and without DR. CAD severity was associated with the presence of DR (r: 0.53, \( P < 0.001 \)), grade of DR (r: 0.52, \( P < 0.001 \)), duration of diabetes (r: 0.28, \( P: 0.019 \)), history of previous MI (r: 0.36, \( P: 0.002 \)); and serum creatinine level (r: 0.24, \( P: 0.049 \)) where the presence of DR was the only independent factor related to the severity score in multivariate analysis (r: 0.48, \( P < 0.001 \)).

The parameters related to the extent score were the presence of DR (r: 0.50, \( P < 0.001 \)); grade of DR (r: 0.48, \( P < 0.001 \)); previous MI (r: 0.37, \( P: 0.002 \)) and age of the patient (r: 0.26, \( P: 0.033 \)). Factors independently related to the extent score in multivariate analysis were the presence of DR (r: 0.37, \( P: 0.001 \)), previous MI (r: 0.30, \( P: 0.006 \)), and age of the patient (r: 0.22, \( P: 0.003 \)).

Among diabetics who are suspected of having CAD, those with retinopathy have more diffuse and severe coronary atherosclerosis, compared with diabetics without retinopathy. This cannot be explained by a longer duration or inferior control of the disease. (Int Heart J 2005; 46: 639-646)

Key words: Coronary artery disease, Diabetes mellitus, Diabetic retinopathy, Coronary angiography

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Diabetic retinopathy (DR) and coronary artery disease (CAD) are two vascular complications of type 2 diabetes mellitus (DM), where DR is an example of microangiopathy and CAD of macroangiopathy. 1) CAD is the leading cause of mortality and morbidity among the complications of diabetes. 2) The presence of DR has been shown to correlate with the risk for macroangiopathies, which includes CAD. 3) DR is an early and frequent sign of vascular complication and its relation to coronary ischemia detected by myocardial perfusion scintigraphy is known. 4) To date, no studies have focused on the relation between DR and the extent and severity of CAD. Therefore, the aim of the present study was to evaluate the relationship between the presence of DR and indices of the extent and severity of CAD detected by coronary angiography.

**Methods**

**Study patients:** Sixty-nine cases were selected from consecutive type 2 DM patients who were referred for coronary angiography because of suspected CAD to the catheterization laboratory of our institution between April 2002 and February 2003. Type 2 DM was diagnosed according to the recommendations of the American Diabetes Association. 5) Exclusion criteria were known duration of DM of less than 1 year, type 1 diabetes mellitus, uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 100 mmHg), previous coronary bypass surgery, and known nondiabetic retinal disease.

**Coronary angiography:** Selective coronary cineangiography was performed from the femoral approach using Judkin's technique. Multiple views were obtained in all patients, with the left anterior descending and left circumflex coronary arteries visualized in at least four views and the right coronary artery in at least two views by using cine-angiographic equipment (Philips Integris H 3000, Holland). The coronary angiograms were recorded on compact discs in DICOM format. Coronary angiograms were scored according to three techniques:

1. **Vessel score.** This was the number of vessels with a significant stenosis (50% or greater reduction in lumen diameter). Degree of stenosis was defined as the greatest percentage reduction of luminal diameter in any view compared with the nearest normal segment and was determined visually. Scores ranged from 0 to 3, depending on the vessels involved. Left main artery stenosis was scored as single vessel disease.

2. **Severity score.** This was the Gensini score, which has been described previously. 6) Briefly, the coronary arterial tree was divided into segments with multiplying factors according to the functional importance of any given segment (5 for the left main trunk to 0.5 for the most distal segments) and the percent reduction in lumen diameter of each narrowing was assigned a score (0, 1, 2, 4, 8, 16,
or 32 according to the degree of stenosis). The sum of the scores of all segments gives the Gensini score, which places emphasis on the severity of the disease.

3. **Extent score.** This score, which was proposed by Sullivan, indicates the proportion of the coronary arterial tree involved by angiographically detectable coronary atheroma. The proportion of each vessel involved by atheroma, identified by lumen irregularity, was multiplied by a factor for each vessel, which was related with the length of that vessel. The scores for each vessel were added to give a total score out of 100, that is the percentage of the coronary intimal surface area containing coronary atheroma.

The scores were determined by one of the investigators (T.N. and G.H.) without any knowledge of the clinical history or retina results. In an examination of random repeated evaluations of angiograms on 20 individuals, the interobserver and intraobserver variations for the three scores were low (interobserver variability: 4.5 ± 3.9%; 5.7 ± 4.5%; 6.5 ± 6.0%; interobserver variability: 5.3 ± 4.0%; 6.0 ± 5.2%; 7.0 ± 6.1% for vessel, severity and extent scores, respectively).

**Detection of DR:** Indirect ophthalmoscopy of all patients was performed by an experienced ophthalmologist using a slit lamp biomicroscope (this is the actual name of the device. More information about it is available at: www.academy.org.uk/lectures/barnard.7.htm) after pupillary dilatation with tropicamid 1% (Tropamide, Bilim ilac sanayi, Turkey) and the presence of retinopathy was evaluated and classified. Fundoscopic findings were classified as normal, nonproliferative DR (mild, moderate or severe), or proliferative DR. According to the presence of DR, patients were categorized into either the DR (+) group (patients with DR) or DR (-) group (patients without DR).

We also evaluated risk factors for CAD, which included patient age, sex, duration of diabetes, hypertension, hypercholesterolemia, smoking status, history of a cerebrovascular accident or peripheral arterial disease, and family history of CAD. Subjects who had quit smoking for over 5 years were considered nonsmokers. The therapeutic modality for DM (oral antidiabetics or insulin) and history of previous myocardial infarction (MI) were also recorded. Biochemical parameters including blood fasting glucose, serum total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, and hemoglobinA1C (HbA1c) levels were noted.

**Statistics:** Results are expressed as the mean ± SD. For univariate analysis, the significance of differences between the two groups for continuous variables was assessed with the unpaired Student’s t test, while the chi-square test was used for nominal variables. Comparisons of the severity and extent scores of CAD between the study groups were performed with 2-way ANOVA using appropriate covariates (with parameters having significant differences in univariate analysis). The correlations between the CAD severity and extent scores with other parameters...
ters were analyzed using simple correlation analysis. Multivariate associations of the CAD severity and extent scores were determined by performing multiple stepwise linear regression analysis with parameters having significant correlations in the simple correlation analysis. A $P < 0.05$ was considered statistically significant. All analyses were performed using an SPSS statistical program (SPSS for Windows 10.0.1, SPSS Inc., Chicago, Illinois).

RESULTS

Diabetic retinopathy: According to the results of the fundus examinations, 31 (45%) of 69 patients had DR (nonproliferative mild in 13, moderate in 5, severe in 2, and proliferative in 11) whereas the remaining 38 (55%) had no retinopathy.

Comparison of clinical characteristics and risk factors: The patients with DR had a significantly longer duration of known diabetes ($P < 0.001$), a higher ratio of being on insulin therapy ($P = 0.012$), higher serum creatinine levels ($P = 0.026$), and a higher ratio of history of previous MI ($P = 0.020$). There were no significant differences with regard to patient age, sex, risk factors for CAD, and other biochemical parameters (Table I). The differences in both the severity and extent scores persisted even after covariate analyses in which the duration of diabetes, therapeutic modality of diabetes, and history of previous MI were taken as covariates ($P < 0.001$ and $P < 0.001$, respectively).

<table>
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<tr>
<th>Table I. Comparison of Clinical Characteristics and Risk Factors Between DR (+) and DR (-) Groups</th>
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<td><strong>DR (+)</strong></td>
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<td>Age (years)</td>
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<td>History of hypertension</td>
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<td>Family history of CAD</td>
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<td>History of CVA</td>
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<td>History of PAD</td>
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<td>History of previous MI</td>
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<td>Creatinine (mg/dL)</td>
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<td>Duration of diabetes (years)</td>
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<td>No. of patients taking insulin</td>
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NS = not significant; CVA = cerebrovascular accident; PAD = peripheral arterial disease.
Coronary angiographic findings: Comparison of coronary angiographic data showed that the patients in the DR (+) group had significantly higher vessel (2.3 ± 0.9 versus 1.3 ± 1.1, \( P < 0.001 \)), severity (63.7 ± 41.0 versus 22.6 ± 14.9, \( P < 0.001 \)) and extent (71.3 ± 23.3 versus 38.6 ± 24.1, \( P < 0.001 \)) scores than patients in the DR (-) group (Table II). Fourteen (36.8%) patients in the DR (-) group had normal coronary angiograms with no detectable coronary atheroma, whereas only 2 (6.5%) patients in the DR (+) group showed normal coronary angiograms. The distribution of the number of vessels having greater than 50% stenosis according to group is shown in the Figure.

Correlations of the CAD severity and extent scores: Univariate analysis of the correlation for the CAD severity score showed that the presence of retinopathy (r: 0.53, \( P < 0.001 \)); grade of retinopathy (r: 0.52, \( P < 0.001 \)); history of previous MI
(r: 0.36, P: 0.002); duration of diabetes (r: 0.28, P: 0.019), and serum creatinine level (r: 0.24, P: 0.049) were related to the severity score. The presence of retinopathy was the only independent factor related to the severity score in multivariate linear regression analyses (r: 0.48, P < 0.001). In a similar fashion, the parameters found to be correlated to the extent score in the univariate correlation analysis were the presence of retinopathy (r: 0.50, P < 0.001); grade of retinopathy (r: 0.48, P < 0.001); history of previous MI (r: 0.37, P: 0.002), and age of the patient (r: 0.26, P: 0.033). Multivariate linear regression analysis revealed that the factors independently related with the extent score were the presence of retinopathy (r: 0.37, P: 0.001), history of previous MI (r: 0.30, P: 0.006), and age of the patient (r: 0.22, P: 0.003).

**DISCUSSION**

The results of the present study demonstrate that there is a relationship between the presence of DR and the extent and severity of CAD detected by coronary angiography. Our findings are in accordance with previous epidemiological studies, which have reported that patients with DR were more likely to have cardiovascular disease, which includes CAD, and have a high risk of death from CAD.\(^3,8,9\) An increased rate of cardiac events in patients with DR was demonstrated in a prospective follow-up study,\(^10\) and a five-year follow-up of the Milan Study on Atherosclerosis and Diabetes (MiSAD) showed DR is an independent predictor of cardiac events.\(^11\) Yoon, *et al* described the relation of DR with coronary ischemia determined by thallium myocardial perfusion scintigraphy.\(^4\) In another study, scores of coronary calcification determined by electron beam computed tomography were found to be closely related to the extent of diabetes complications, including DR.\(^12\) However, none of these studies evaluated the extent and severity of CAD by coronary angiography, which is the gold standard of the diagnosis of CAD.

Since the probability of having DR increases with the duration of diabetes, severity of hyperglycemia, and inadequacy of diabetic control, which are also risk factors for CAD, it could be argued that the observed relation between DR and CAD may actually be dependent on these factors. However, this appears unlikely because multivariate linear regression analysis, including all possible factors in the model, demonstrated DR to be a significant independent risk factor for both the severity and extent scores. In addition, there were no significant differences in fasting blood glucose or HbA1c levels between the two groups and the significant differences between the DR and CAD indices persisted even after correction for duration of diabetes as a confounding factor.
Klein, et al reported an association between DR and carotid artery intima-media wall thickness in a cross-sectional study from a population-based cohort of diabetic adults but they found no association between severity of DR and plasma lipids or other atherosclerotic risk factors. We similarly did not observe any relation between DR and risk factors for CAD.

A recent study has focused on the nonenzymatic glycation reaction under prolonged hyperglycemia, which results in the formation and accumulation of advanced glycation end-products (AGEs). The interaction of AGEs with the receptor for AGEs (RAGEs) has been implicated in the development of the vascular complications. AGEs elicited vascular cell changes typical of diabetes, including angiogenic and thrombogenic responses of endothelial cells, and a decrease in pericytes, the hallmarks of diabetic retinopathy. AGEs play an important role in the accelerated course of atherosclerosis in DM. Wang, et al have demonstrated that the AGEs-RAGEs interaction in vascular smooth muscle cells, in addition to growth factors induced by AGEs, contributes to the stimulatory effect of diabetes on vascular smooth muscle cell proliferation which can accelerate atherosclerosis. Aso, et al measured the serum concentrations of AGEs in type 2 DM patients and proposed that they were associated with the development of CAD as well as diabetic retinopathy and nephropathy. Therefore, it is reasonable to speculate that there is at least one common pathway in the development of diabetic retinopathy and diabetic atherosclerotic lesions.

Limitations of the study: We have evaluated the extent of coronary atherosclerosis by lumen irregularities detected on coronary angiographic images, however, the growth of atherosclerotic plaque that does not protrude into the lumen may result in an underestimation of the CAD extent, which could have been recognized by use of intravascular ultrasound. However, even by using coronary angiography, the relation with CAD extent and DR was significant.

Clinical implications: CAD may accompany atypical or no symptoms in diabetic patients where co-existence with CAD causes a rise in morbidity and mortality in diabetics. Therefore, making the diagnosis of CAD in patients with DM has critical importance. According to the results of the present study, the presence of DR in patients with DM was associated with more diffuse and severe CAD. Meanwhile, a fundus examination is a simple, noninvasive, and routinely employed technique used in the follow-up of diabetic patients. CAD should be investigated once DR is diagnosed in a patient with type 2 DM.

Conclusion: Among diabetics suspected of having CAD, those with retinopathy have more diffuse and severe coronary atherosclerosis, compared with diabetics without retinopathy, which cannot be explained by the longer duration or inferior control of the disease. Further studies focusing on the mechanisms of this situation are needed.
REFERENCES