Defective Myogenic Response of Retinal Vessels Is Associated With Accelerated Onset of Retinopathy in Type 1 Diabetic Individuals

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PURPOSE. We seek to identify pathogenic mechanisms for diabetic retinopathy that can become therapeutic targets beyond hyperglycemia and hypertension. We investigated if a defective myogenic response of retinal arteries to increased perfusion pressure, which exposes capillaries to increased pressure and flow, is associated with the onset of clinical retinopathy.

RESULTS. Five of seven participants who 4 years prior had a defective myogenic response had now developed clinical retinopathy; as compared with only one of six participants who 4 years prior had a normal response (P = 0.10). In the cross-sectional study, all participants had normal retinal hemodynamics at steady state. In response to the postural change, only the E-DR group showed defective myogenic response (P = 0.005 versus controls, P = 0.02 versus L-DR) and abnormally high retinal blood flow (P = 0.016 versus controls).

CONCLUSIONS. In type 1 diabetic patients, a defective myogenic response of retinal arteries to pressure is not required for the development of clinical retinopathy, but is prominently associated with an accelerated onset of retinopathy.

Keywords: type 1 diabetes, retinopathy, myogenic response, retinal blood flow, retinal circulation, laser Doppler, accelerator, biomarker

After implementation of the lessons learned from the Diabetes Control and Complications Trial1 and the UK Prospective Diabetes Study Group,2 the onset and progression of diabetic retinopathy have been delayed substantially, but predictable prevention remains beyond reach. The main reason is that the glycemic levels that can cause retinopathy are lower than the levels that patients can safely maintain with today’s treatment modalities. Data from ethnically diverse populations reveal that diabetic retinopathy begins to appear at HbA1c levels of 6.5%, just above the upper limit of normal.3 So consistent is this apparent threshold, that HbA1c of 6.5% or higher has become a diagnostic criterion for diabetes.4 However, HbA1c less than 6.5% is an elusive target even for patients committed to tight glycemic control, and may be unsafe.5 An additional reason for the difficulty to prevent retinopathy is the likely pathogenic contribution of factors that we do not know and/or we do not routinely assess.

In practical terms, once we have intervened to control blood glucose and blood pressure (BP) levels as well as it is safely possible, we have nothing more to offer toward predictable prevention or arrest of retinopathy. If, instead, we knew about mechanisms that accelerate development or progression in the context of even mild hyperglycemia and normal systemic BP, and if such mechanisms were amenable to measurements interpretable in the individual patient, we could become more proactive. We would survey patients systematically for the pathogenic abnormality, attempt to develop adjunct interventions against such an abnormality, and use the interventions in a timely and selective manner in the patients expected to benefit from them.

Retinal hemodynamic measurements are an attractive approach to identify abnormalities that precede clinical retinopathy because they relate directly to the vessels, and can be performed noninvasively in humans. We reported that contemporary type 1 diabetic individuals, relatively well-controlled and with no or minimal retinopathy, do not show abnormalities of the retinal circulation at steady state.6 However, when we imposed a challenge, a simple change in position from sitting to reclining, a fraction of such patients without clinical retinopathy showed a functional abnormality, manifested as lack of arterial constriction in response to the increased perfusion pressure induced by the postural change.7 The constriction of arteries to pressure is termed “myogenic response” because it is intrinsic to the arterial smooth muscle
cells; in the retina as in other organs it dampens the transmission of pressure to capillaries and parenchyma, thereby protecting against microvascular and organ damage.\textsuperscript{8} Thus, the absence of constriction or paradoxical dilation of retinal arteries that we had observed in approximately half of our patients still free of clinical retinopathy reflects a defective myogenic response, and could be a mechanism for accelerating the development of retinopathy. To gain insight into the relationship between a defective myogenic response of retinal blood vessels and the development of retinopathy, we asked two questions: whether a defective myogenic response (1) predicted the appearance of retinopathy (prospective arm of the study), and (2) was present in all cases of clinical retinopathy of recent onset (cross-sectional arm of the study).

\section*{Methods}

\subsection*{Design and Participants}

The procedures followed the Declaration of Helsinki, and the institutional review boards of the Massachusetts Eye and Ear Infirmary (MEEI) and of the Massachusetts General Hospital (MGH) approved the study. The participants gave written informed consent.

The study had two arms. One was a prospective-longitudinal cohort study, based on the type 1 diabetic individuals in whom we had measured the myogenic response of retinal vessels to pressure 4 years earlier, when they had no retinopathy.\textsuperscript{6} There were no criteria of exclusion. We attempted to contact all 17 patients, but only 13 could be reached or responded. The second arm consisted of a cross-sectional study of type 1 diabetic individuals age 18 to 50 years who had developed retinopathy within approximately 2 years and age- and sex-matched nondiabetic individuals. The 2 years maximal known duration of retinopathy was intended to permit us to study early retinopathy, before long-standing or severe structural abnormalities of vessels might impose their own changes on retinal hemodynamics. To capture a potential accelerator role of the defective myogenic response, we recruited individuals who had developed diabetic retinopathy early in the course of the disease. We chose as threshold 18 or fewer years of diabetes, because at such duration fewer than 20\% of contemporary type 1 diabetic patients have any retinopathy.\textsuperscript{9} We also recruited individuals with late onset of retinopathy, to compare and contrast with the early-onset group. The nondiabetic participants, matched for age and sex, had no history of diabetes and had HbA1c levels lower than 6\%. The exclusion criteria were the same as in our previous studies of retinal hemodynamics\textsuperscript{6,7}: smoking; pregnancy; systemic diseases other than type 1 diabetes, in particular hypertension and renal disease; retinal diseases other than diabetic retinopathy; and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs including low-dose aspirin, and high doses of vitamin E. Nine of the 12 diabetic participants were taking medications: contraceptives, antidepressants, lipid-lowering medications, inhalers for asthma, and thyroid replacement medications.

\subsection*{Procedures and Hemodynamic Measurements}

In both the prospective and the cross-sectional studies, after giving informed consent, the participants underwent an eye examination inclusive of measurement of the IOP using Goldmann applanation tonometry, pupil dilation with 1\% tropicamide, and seven-field stereo fundus photography. A blood sample was obtained to measure HbA1c. The cross-sectional study included also the hemodynamic measurements, performed in all participants at the same time of day, between 5:00 PM and 5:00 PM. In the diabetic participants, the hemodynamic studies were performed only if the capillary blood glucose was between 70 and 220 mg/dL to prevent confounding influences of hypoglycemia or severe hyperglycemia.

The retinal hemodynamic measurements were acquired noninvasively through a dilated pupil using a laser Doppler flowmeter (CIBF 100; Canon, Tokyo, Japan). The instrument measures arterial blood column diameter and centerline blood speed in individual retinal vessels; the blood flow rate in microliters per minute is calculated automatically as the product of the cross-sectional area of the artery at the measurement site and the average blood speed, assuming a circular arterial cross-section. Measurements are reproducible, and can be repeated at the same vessel site.\textsuperscript{10} As in all our previous studies,\textsuperscript{6,7} the measurements were performed at the superior temporal artery because the lesions of diabetic retinopathy are more prevalent in the superior temporal than in the inferior retinal quadrants.\textsuperscript{11} Baseline measurements were acquired after a 20-minute equilibration period in the sitting position. The measurements included systolic, diastolic, and mean brachial artery BP and heart rate (Keller Vital Signs Monitor; Keller Medical Specialties, Antioch, IL, USA); ocular perfusion pressure (OPP), calculated using the formula OPP = 2/3 mean arterial pressure - IOP; and superior temporal artery diameter, blood speed, and blood flow in the left eye. The retinal circulatory parameters were then measured after a postural change from sitting to reclining, as in our previous work.\textsuperscript{7} Briefly, the participants were asked to recline on their right side, with their head supported by a foam wedge making an angle of 24\% from the horizontal, for 30 minutes while brachial BP and heart rate were automatically measured from the left arm and recorded every 5 minutes. At the end of the 30 minutes of reclining, the hemodynamic measurements were repeated in the left eye at the same arterial site used at baseline. While reclining, there is an elevation of the OPP; the change in OPP was calculated following the formula validated by direct measurements of the OPP using ophthalmodynamometry.\textsuperscript{12,13} The final set of measurements was taken after the participants had returned to the sitting position for 20 minutes.

Recruitment of study participants was through the MGH Diabetes Center. All procedures were performed at the MEEI; the HbA1c was measured by the Clinical Laboratory, and the retinal photographs were taken in the Retina Photography Service. Retinopathy was diagnosed and graded on the photographs on the basis of the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale: level 10, absent retinopathy; level 20, microaneurysms only; level 35, microaneurysms and hard exudates. The grader (LS) was masked to all hemodynamic results. In statistical comparisons we analyzed the ETDRS levels both for the worst eye (as per convention in grading diabetic retinopathy) and for the left eye, on which the hemodynamic studies were performed.

\section*{Statistical Analysis}

Data were analyzed for normality using the Shapiro-Wilk and the Shapiro-Francia tests; normally distributed data were summarized with the mean ± SD, nonnormally distributed data with the median and interquartile range. All statistical analyses were performed using the Stata 12 software (Stata Statistical Software: Release 12, StataCorp LP, College Station, TX, USA) and 2-tailed tests. Continuous data normally distributed were analyzed using ANOVA followed by the Bonferroni adjustment for multiple comparisons; except for
Table 1: Prospective Study: Development of Clinical Retinopathy in the Cohort of Type 1 Diabetic Participants Tested for the Myogenic Response 4 Years Earlier When Still Free of Retinopathy

<table>
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<th>Participants</th>
<th>Change in Arterial Diameter on Reclining, %</th>
<th>Current Age, y</th>
<th>Sex, F/M</th>
<th>Current Diabetes Duration, y</th>
<th>HbA1C, %</th>
<th>Retinopathy</th>
<th>ETDRS Level†‡</th>
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Data are Mean ± SD or median and interquartile range (except for categorical variables).

* As measured 3.9 ± 0.2 years earlier, when all diabetic subjects were free of retinopathy, and as reported in Ref. 7. The change in retinal arterial diameter, representing the myogenic response, was measured upon the postural change from sitting to reclining described in Methods. Patients 1 to 7 failed to show the decrease in arterial diameter that represents the normal myogenic response to pressure. Patients 8 to 13 showed a normal myogenic response. All participants were Caucasian.

† ETDRS retinopathy level graded on fundus photographs: 10, no retinopathy; 20, microaneurysms only; 35, microaneurysms and hard exudates.
‡ P = 0.0026 versus the normal arterial constriction shown by subjects 8 to 13.
§ P = 0.06 versus subjects with normal arterial constriction.
‖ P = 0.10 by Fisher’s exact test versus incidence among the subjects with normal arterial constriction.

Results

Prospective Study

Among the 17 type 1 diabetic individuals who had their retinal circulation tested in response to the postural change 4 years earlier while still free of clinical retinopathy, approximately half had manifested a defective myogenic response; that is, a failure to constrict (or even paradoxical dilation of) the retinal arteries in response to the postural change. We sought to uncover whether the abnormality would predict the development of retinopathy. Table 1 shows the results in the 15 participants who responded to our recall. Of the participants who 4 years prior had manifested a defective myogenic response, five of seven had developed clinical retinopathy. In contrast, of the participants who 4 years prior had shown a normal vasoconstrictor response only one of six had developed retinopathy (P = 0.10). The current age and HbA1C were similar in the two groups; the current diabetes duration tended to be longer, albeit not significantly (P = 0.06), in the patients who had manifested 4 years earlier a defective myogenic response. When we compared the patients who did and those who did not develop retinopathy, we observed that the pattern of diameter change measured 4 years earlier was significantly different in the two groups. Those who did develop retinopathy had shown no change or an increase in retinal diameter in response to reclining (3.3% [0.0%–7.4%]), whereas the patients who did not develop retinopathy had shown mostly diameter constriction (−4.0% [−6.1%–0.0%]) (P = 0.010).

Cross-Sectional Study

We investigated the prevalence of a defective myogenic response in individuals who had already developed clinical retinopathy. Based on the duration of diabetes at onset of retinopathy, we defined two groups: early-onset diabetic retinopathy (E-DR) and late-onset diabetic retinopathy (L-DR). Table 2 shows the characteristics of the groups compared. The E-DR participants were younger, had developed diabetes at the same age as the L-DR participants, and at the time of study had a duration of diabetes of 15 ± 2 years. Taking into account that they had retinopathy of up to a 2-year duration, the onset of retinopathy had been as early as after 11 to 15 years of diabetes. The L-DR participants had a duration of diabetes of 26 ± 3 years (P = 0.0001 versus E-DR group), and had thus developed retinopathy after 21 to 27 years of diabetes. The E-DR participants had higher HbA1C levels. One E-DR participant in particular had a very high HbA1C value (11%). We thus tested how the data would be affected by the exclusion of this individual. The HbA1C of the E-DR group would become 7.6% ± 0.5%, not statistically different from the 7.1% ± 0.6% of the L-DR group; while all hemodynamic findings would remain the same and maintain the statistically significant differences recorded when including the individual with 11% HbA1C. The individual was thus included in all computations.

Both the E-DR and the L-DR participants had normal retinal hemodynamic measurements at steady state (Table 3). In contrast, in response to the challenge imposed by the postural change from sitting to reclining, the E-DR group showed abnormalities not shown by the L-DR group (see Fig.). The E-DR group failed to constrict the diameter of the retinal artery in...
response to pressure: among the five participants, four showed paradoxical dilation and one normal constriction; and this pattern was different from both the control group (P = 0.005) and the L-DR group (P = 0.020). The L-DR group was not significantly different from the control group, with six of the seven L-DR participants constricting normally and one showing dilation. The E-DR participants manifested a defective myogenic response despite the fact that the changes in systemic BP and OPP while reclining were similar to those in the other groups. The reclining systolic and diastolic BP were, respectively (in mm Hg), 99 ± 6 in the E-DR participants, and 94 ± 10 and 57 ± 6 in the L-DR participants. The OPP while reclining, estimated from mean arterial pressure (MAP) – IOP, was (in mm Hg) 55 ± 9 in controls, 51 ± 5 in the E-DR participants, and 49 ± 5 in the L-DR participants. Consequently, the increase in OPP induced by reclining, which represents the driving stimulus for the myogenic arterial constriction, was similar in all groups: 15% (11%–20%) in the controls, 15% (9%–26%) in the E-DR group, and 21% (10%–30%) in the L-DR group (P = NS). The blood speed response to reclining was especially variable among the L-DR participants, but did not differ among the groups. In agreement with the fact that blood flow is the product of the arterial diameter and blood speed, the lack of diameter constriction in the E-DR group resulted in an abnormally increased retinal blood flow (P = 0.016 versus controls). In contrast, in the L-DR group, the blood flow changes were not different from controls (P = 0.60).

**DISCUSSION**

This report provides four new insights toward reconstructing the pathogenesis of retinal microangiopathy in contemporary type 1 diabetic patients. First, at steady state, the retinal circulation of these relatively well-controlled individuals does not show abnormalities of vessel diameter or blood speed and flow, even in the presence of established retinopathy up to ETDRS level 35. This is a substantial departure from the many abnormalities reported at steady state in the retinal circulation of diabetic patients with and without retinopathy in the early 1990s.\(^1\)\(^4\)\(^5\) Second, the need for an adaptation of the retinal circulation, as physiological as that required by an increased perfusion pressure due to a postural change, uncovers in some patients a defective myogenic response of retinal arteries that tends to predict the onset of clinical retinopathy. Third, many patients who developed retinopathy after prolonged diabetes duration show a normal myogenic response. Fourth, and operationally most important, when the onset of retinopathy occurs after short diabetes duration, the myogenic response is prominently defective.

The observations in the participants with late-onset retinopathy make clear that a defective myogenic response to pressure is not a requirement for the development of clinical retinopathy. In those patients, in excellent glycemic control and normotensive, retinopathy is likely the consequence of total glycemic exposure. This best-documented risk factor for retinopathy in type 1 diabetes\(^6\) predicts that, when of long duration, even minimal hyperglycemia becomes an effector of vascular damage. If a defective myogenic response is not required for the development of retinopathy, then it cannot be an unqualified biomarker of retinopathy risk, insofar as the absence of the marker would not exclude the development of retinopathy at some point in time.

The defective myogenic response to pressure may instead realistically claim a role as “accelerator” of retinopathy development. The prospective study showed that it was mostly the individuals with a defective myogenic response who went on to develop clinical retinopathy within 4 years.
FIGURE. Cross-Sectional study: retinal hemodynamic parameters in response to the change in posture from sitting to reclining in the type 1 diabetic participants with clinical retinopathy and nondiabetic participants. The box plots present the data for the 15 controls, 5 type 1 diabetic participants with E-DR, and 7 type 1 diabetic participants with L-DR. Each box plot shows the 10th, 25th, 50th (median), 75th, and 90th percentile of the indicated parameters. Values above the 90th percentile are plotted as points. *\( P = 0.005 \) and **\( P = 0.020 \) for indicated comparisons.
Myogenic Response in Diabetic Retinopathy

Despite having HbA1c levels similar to, and diabetes duration not statistically different from, the participants who had a normal myogenic response. In complementary fashion, the cross-sectional study showed that the participants who had already developed clinical retinopathy after a remarkably short diabetes duration were those with a defective myogenic response and an abnormally increased retinal blood flow response to pressure. We cannot exclude that a defective myogenic response to pressure could be an epiphenomenon in a process that leads to accelerated retinopathy via mechanisms that we do not yet know. However, concepts that are known indicate that a defective myogenic response could have a pathogenic role for diabetic retinopathy. According to Pous-elle’s law, blood flow is related to the fourth power of the vessel radius. Retinal arteries that do not constrict normally to increased perfusion pressure allow a larger fraction of such pressure to reach the capillaries, where it can facilitate the dilations that cause microaneurysms, the leakage that causes edema, and the ruptures that cause hemorrhages.17 Of note, these hemodynamic mechanisms, when working in the opposite direction, can be protective against diabetic retinopath-athy. For example, the protection exerted by high myopia17,18 has been attributed to the attenuation of the perfusion pressure along the longer arterioles of the elongated myopic eye, with resultant protection of the capillary bed.17,19

The original hemodynamic hypothesis of diabetic retinop-athy was formulated before the era of tight glycemic control, and was based on the evidence of increased retinal blood flow at steady state in diabetes. The hypothesis was thus centered on hyperglycemia as the direct inducer of increased flow, with the effects eventually compounded by loss of autoregulation and systemic hypertension.14 Given that contemporary, well-controlled type 1 patients show normal retinal blood flow at steady state, the hemodynamic hypothesis requires an update. The update could be centered on the defective myogenic response, because this abnormality (1) is detected in the absence of clinical retinopathy and may predict its onset, (2) is associated with increased retinal blood flow, and (3) is present when retinopathy has an accelerated onset. In this new formulation, the hemodynamic hypothesis incorporates a functionally better defined mechanism (defective myogenic response), with a more specific role (accelerator), and a more selective epidemiology (early-onset retinopathy rather than retinopathy in general). The added facts that the pattern of the myogenic response is repeatable when the individual patient is retested months apart, and readily interpretable being a qualitative outcome, make the defective myogenic response of retinal vessels a reasonable target of potential adjunct drugs.

The main limitation of this study is the small number of patients tested. Additionally, the study addressed solely patients with type 1 diabetes who did not take vasoactive drugs, thus, it is unknown whether the findings can be extended to the much more common setting of patients with type 2 diabetes, often taking drugs for systemic hypertension. This is, however, not unlikely, because a defective myogenic response of retinal vessels to a pressure stimulus (increased systemic BP induced by isometric exercise) has been noted also in type 2 diabetic patients, some treated with vasoactive drugs, who had retinopathy with or without macular edema.20 Observations in type 2 diabetic patients have revealed that a loss of myogenic constriction to pressure occurs also in arteries other than the retinal arteries, and is selective for the pressure stimulus insofar as the response to noradrenergic agonists is intact.21 When addressing mechanisms, it must be noted that, in addition to pressure, the retinal vessels of diabetic patients show abnormal responses also to light flickering22 and oxygen inhalation.23 Whether these abnormalities coexist in the same individual and stem from the same mechanism, is currently unknown. Given that the myogenic response to pressure is a well-defined mechanism of vascular homeostasis that is already actively investigated as a pharma-cologic target,8 its early defect could profitably become the focus of investigations to disable an accelerator of diabetic retinopathy.

Our new observations that a defective myogenic response to pressure of retinal vessels can be an accelerator of retinopathy, together with the observations that a defective myogenic response to pressure is prevalent in type 2 diabetes, and is present in sight-threatening retinopathy, call for a definitive longitudinal cohort study. If a fully powered study confirmed that a defective myogenic response predicts an accelerated onset and/or course of diabetic retinopathy, there will be rationale and impetus to developing targeted drugs. In the meantime, our findings renew the emphasis on monitoring and treating aggressively in our patients any increase in systemic BP, because a defective vascular constriction magnifies widely the effects of any increment in BP on retinal vessels.14

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References


