Defective Myogenic Response to Posture Change in Retinal Vessels of Well-Controlled Type 1 Diabetic Patients with No Retinopathy

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Purpose. The current approach to the prevention of diabetic retinopathy relies on intensive anti-diabetes treatment and is only partially successful. A marker of retinopathy risk would enable strategies of surveillance, screening of adjunct drugs, and targeted drug interventions. The authors sought to identify early abnormalities of retinal vessels that are not prevented by the current therapeutic approach.

Methods. Retinal thickness (an informer of vascular permeability) and hemodynamic parameters at baseline and longitudinally were measured in 27 subjects (age, 32 ± 9 years [mean ± SD]) with well-controlled type 1 diabetes of 12.4 ± 6.4 years' duration and no retinopathy, and in 27 control subjects. In a subset of 17 patients and 11 controls, the hemodynamic response to reclining, a postural change that increases retinal perfusion pressure, was measured.

Results. Baseline foveal thickness and hemodynamic parameters were similar in the diabetic and control subjects. Foveal thickness increased over 12 months in the diabetic subjects, from 217 ± 22 μm to 222 ± 20 μm ($P = 0.0036$), remaining however within the normal range. Reclining uncovered in 47% of diabetic subjects ($P = 0.016$ compared with controls) an absent myogenic response (i.e., unchanged or increased arterial diameter instead of the normal decrease). The patterns were repeatable. Only the diabetic group with defective vasoconstriction showed widening arterial diameter over 12 months, a change presaging vascular dilatation in diabetic retinopathy.

Conclusions. Defective myogenic response to pressure was the first detectable abnormality of retinal vessels in subjects with well-controlled type 1 diabetes. Because of its selective occurrence, interpretability in individual patients, and pathogenic potential, the abnormality deserves evaluation as a risk marker for retinopathy. (*Invest Ophthalmol Vis Sci.* 2010;51:6770–6775) DOI:10.1167/iovs.10-5785

Retinopathy has historically been the most frequent complication of diabetes. Until the early 1990s, its prevalence approached 90% after 15 to 19 years of type 1 diabetes,[1] and it was categorized as an "inevitable" complication of diabetes.[2] Today, the implementation of intensive insulin treatment has substantially reduced the incidence of retinopathy[3,4] and the development of proliferative retinopathy.[5] However, the very same studies documenting the reduced incidence warn that retinopathy still develops, despite intensive treatment. This likely reflects the facts that the current means of controlling diabetes do not ensure sustained normoglycemia, and even mild residual hyperglycemia may damage the vessels of susceptible individuals.

For patients who are making their best effort to achieve good glycemic control, the addition of safe drugs that preempt or limit the tissue effects of residual hyperglycemia would enhance the likelihood of prevention. The search for adjunct drugs continues, but promising results obtained in experimental animals[6] will require tools to "preview" effects in humans. This is necessary to select for clinical trials of retinopathy prevention drugs that justify the large investment of time and resources required when the measured outcome is clinical retinopathy. The same tools usable to screen drugs would be usable to identify those patients likely to benefit from a given drug, so that preventive treatment could be initiated in selected patients at specific times rather than in every patient from the time of diabetes diagnosis. This approach would make the use of adjunct drugs safe and cost-effective.

The tools needed are markers of retinopathy risk that have critical characteristics: detectable before any clinical sign of retinopathy, causally linked to retinopathy development, informative in the individual patient, and reversible for at least some time. Currently, we do not have markers with these characteristics. A larger caliber of retinal arterioles predicts retinopathy development in young patients with type 1 diabetes,[7] but measurements are not interpretable in the individual patient because of the wide range of calibers of retinal vessels in healthy subjects[8] and the overlap in persons with retinopathy and those without.[7] Measurements of retinal hemodynamics at steady state have shown variable direction of the abnormalities identified in diabetic patients,[9] in part attributable to the influence of elevated blood glucose levels at the time of testing.[10] Measurements of retinal hemodynamics in response to stimuli have tested the autoregulation of retinal blood flow (i.e., the capability of retinal blood vessels, which are devoid of autonomic innervation, to adjust blood flow in response to stimuli to serve the functional needs of the retina or maintain retinal homeostasis). The autoregulatory abnormalities detected to date in patients with type 1 diabetes but no retinopathy may or may not be markers of developing retinal microangiopathy. The decreased dilatation of retinal arteries in response to flickering light[11] cannot be definitively attributed to a vascular defect because the light stimulus affects retinal vessels by way of the neural retina, and decreased retinal neural activity occurs in diabetes.[12] A similar caveat applies to the abnormal

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response to 100% oxygen breathing.[13,14] Multiple mechanisms govern the response to hyperoxia, and the impaired constriction of retinal vessels in diabetic patients may reflect defective vascular reactivity but also some degree of hypoxia or other metabolic imbalances in the diabetic retina.[13,14] Additionally, it is unknown whether an abnormal response to hyperoxia is detectable in patients with relatively well-controlled diabetes or represents solely the blunting effect of high blood glucose levels on the retinal autoregulatory response.[15]

In an initial study searching for markers of retinopathy risk applicable to today's patients with well-controlled type 1 diabetes and free of retinopathy, we observed that after a median diabetes duration of 8 years, such patients showed uniformly normal retinal hemodynamics at steady state.[8] Thus, in the follow-up study presented here, we examined a cohort with longer diabetes duration, introduced measurements (foveal thickness) informative of capillary permeability, obtained longitudinal data, and tested the autoregulatory response of retinal vessels to a physiological perturbation. The perturbation was a change in posture from sitting to reclining,[16] which, like isometric exercise,[17] increases retinal perfusion pressure and thus transmural pressure, to which retinal arteries respond by constricting through a myogenic mechanism to maintain a constant blood flow. We chose increased perfusion pressure as a stimulus because it works in isolated retinal vessels,[18] and thus by purely vascular mechanisms, without contributions from the neural retina.

Methods

Subjects

The studies were approved by the institutional review board of the Schepens Eye Research Institute and were performed in accordance with the tenets of the Declaration of Helsinki. All study subjects provided written informed consent after receiving explanation of the nature and possible consequences of the studies. Inclusion criteria for the diabetic subjects were age 18 to 50 years, type 1 diabetes of 5 to 25 years' duration, and absent or minimal retinopathy (up to two microaneurysms) as detected by dilated fundus examination and documented with retinal photographs. Exclusion criteria were retinal diseases, systemic diseases other than diabetes, hypertension, anemia, renal insufficiency, pregnancy, smoking or use of nicotine patches in the previous 6 months, and use of angiotensin antagonists, nonsteroidal anti-inflammatory drugs, or high doses of vitamin E. The inclusion criterion for the control subjects was age 18 to 50 years; the exclusion criteria were presence of diabetes and those listed for the diabetic subjects.

Study Design and Procedures

The diabetic subjects ($n = 27$) were studied at baseline and 6 and 12 months later. The baseline visit included a complete eye examination with measurement of intraocular pressure (IOP) using an applanation tonometer (Tono-Pen XL; Medtronic, Jacksonville, FL) and digital retinal photography (TRC-50EX; Topcon Corporation, Tokyo, Japan). At each visit the subjects underwent measurement of HbA1c, retinal hemodynamics, and retinal thickness. At the 12-month visit, a subgroup of the diabetic subjects ($n = 17$) was tested for retinal vessel autoregulation and again received a complete eye examination. The control subjects ($n = 27$) were studied at baseline and 12 months later. At the 12-month visit, a subgroup of the control subjects ($n = 11$) was also tested for retinal vessel autoregulation. In all subjects, the eye with the thicker fovea at baseline was designated as the study eye and was used in all follow-up studies except autoregulation. Factors such as sex,[19] diurnal changes,[20] and blood glucose levels,[10] known to influence the results of the tests used, were taken into account as follows: the groups of diabetic and control subjects were matched for age and sex precisely, and all retinal tests were performed at the same time of day (3–5 PM) and when capillary blood glucose in the diabetic subjects was between 70 and 200 mg/dL.

Measurements were acquired through a dilated pupil using noninvasive techniques. Foveal thickness, representing the average thickness within the central 1-mm diameter area of the macula, was measured by optical coherence tomography (OCT) using a macular thickness map scan protocol (OCT3; StratusOCT, software version 4.0.4; Carl Zeiss Meditec Inc., Dublin, CA).[21] Retinal hemodynamic parameters were measured by laser Doppler using a laser Doppler blood flowmeter (CLBF 100; Canon, Tokyo, Japan).[22] 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.

The superior temporal retinal artery was chosen for the measurements because the lesions of diabetic retinopathy are more prevalent in the superior temporal quadrant of the retina than in the other quadrants.[23] Measurements are reproducible and can be repeated at the same vessel site.[22] In 22 of the diabetic subjects and in 14 of the control subjects, the measurement sites were along the main superior temporal artery proximal to any bifurcations; in the remaining five diabetic subjects and 13 control subjects, the measurement sites were distal to the first bifurcation. Only the measurements from sites along the main superior temporal artery proximal to any bifurcations were used for the cross-sectional comparisons of arterial diameter, blood speed, and blood flow between the diabetic and control subjects. This was done to ensure that the measured hemodynamic parameters were representative of the blood supply to the entire superior temporal quadrant of the retina in each subject.

The response of retinal hemodynamics to a change in posture from sitting to reclining was measured as described.[16] First, baseline measurements of systolic, diastolic, and mean brachial artery blood pressure and heart rate (Keller Vital Signs Monitor; Keller Medical Specialties, Antioch, IL) and of retinal hemodynamic parameters (CLBF 100; Canon) in the left eye were obtained in the sitting position. Subjects were then asked to recline on their right side, and retinal arterial diameter and blood speed—at the same arterial site used at baseline—were measured after 30 minutes of reclining. Brachial blood pressure and heart rate were automatically measured and recorded every 5 minutes. The last set of retinal hemodynamic measurements was obtained 20 minutes after the subjects had resumed the sitting position.

In a previous application of this experimental arrangement to study the effect of postural changes on retinal arterial diameter,[24] the authors used ophthalmodynamometry to measure the increase in ophthalmic artery pressure induced by the change from sitting to reclining in order be able to estimate ocular perfusion pressure. They found that the perfusion pressure while reclining was approximately $MAP_{reclining} - IOP$, where $MAP_{reclining}$ is the mean brachial artery blood pressure measured in the left arm with the subject reclining on the right side. IOP and venous pressure also increase while reclining, but venous pressure does not exceed the IOP.[25–27] This information was used to estimate the change in ocular perfusion pressure in our subjects. HbA1c was measured at the Massachusetts General Hospital HbA1c laboratory.

Statistical Analysis

Subjects' characteristics and results of retinal measurements are summarized using the mean ± SD. Continuous data from diabetic and control subjects were compared using the nonpaired *t*-test or ANOVA followed by Fisher's PLSD when comparing three groups. The Fisher's exact test was used for analysis of categorical variables. Longitudinal data in the diabetic patients were compared using the paired *t*-test or repeated-measures ANOVA when comparing three time points. The percentage changes in arterial diameter, blood speed, and blood flow in response to reclining showed unequal variances in the diabetic and control groups; hence, those data are summarized using the median and range, and comparisons were performed with the Mann-Whitney *U* test. All tests were two-tailed.

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Table 1. Characteristics of the Type 1 Diabetic Subjects at Baseline

Variable	Patients with Diabetes (n = 27)	Control Subjects (n = 27)	P
Age, y	31.6 ± 9.2	31.7 ± 8.0	0.96
Females, %	60	60	
Diabetes duration, y	12.4 ± 6.4	n/a	
HbA1c, %	7.6 ± 1.0	5.4 ± 0.3	<0.0001
Blood glucose, mg/dL*	148.2 ± 49.1	106.4 ± 19.7	0.0001
Systolic blood pressure, mm Hg	105.0 ± 9.6	104.1 ± 11.6	0.76
Diastolic blood pressure, mm Hg	70.8 ± 7.6	68.0 ± 8.2	0.20
Retinopathy, n†	3	n/a	

n/a, not applicable. Values are expressed as mean ± SD.

* Measured immediately before the baseline retinal studies; primarily postprandial levels.

† Two patients had one microaneurysm, and one patient had two microaneurysms.

Results

Characteristics of the study subjects at baseline are summarized in Table 1. Diabetic subjects received insulin through multiple daily injections or an external pump; their HbA1c declined progressively from the baseline values (7.6% ± 1.0%) during the longitudinal follow-up (7.3% ± 1.0% at 6 months and 7.0% ± 0.7% at 12 months; P = 0.0007).

Retinal Vascular Measurements at Steady State and Longitudinal Changes

Foveal thickness at baseline was 217 ± 22 μm in the diabetic subjects and 209 ± 19 μm in the controls (P = 0.15). In the diabetic subjects, thickness did not change at the 6-month measurement (216 ± 23 μm), but it increased at 12 months to 222 ± 20 μm (P = 0.0036), remaining, however, within the normal range of values obtained with the OCT3.[21] In contrast, foveal thickness did not change in the control subjects (n = 10) retested at 12 months (211 ± 13 μm, compared with 211 ± 14 μm at baseline). The steady state measurements of hemodynamic parameters—retinal arterial diameter, blood speed, and blood flow in the superior temporal quadrant of the retina—did not differ between the diabetic and control subjects at baseline or at 12 months. In particular, arterial diameter in the diabetic subjects was 122 ± 11 μm at baseline compared with 120 ± 13 μm in the control subjects (P = 0.65) and did not show significant changes after 6 months (122 ± 10 μm) or 12 months (123 ± 10 μm).

Retinal Vascular Measurements in Response to a Postural Change

Given that the steady state hemodynamic measurements were similar in the diabetic and control subjects, we asked whether a stimulus would uncover differences. Figure 1 shows the results of the retinal hemodynamic responses to reclining in the 17 diabetic subjects without retinopathy and 11 control subjects tested for retinal vessel autoregulation. In response to reclining, the retinal arterial diameter decreased in each of the control subjects (median change, −6.2% of baseline values; range, −2.8% to −9.9%; P = 0.018 vs. baseline). In contrast, 8 of 17 diabetic subjects failed to show vasoconstriction. In 4 of these 8 subjects, the median change from baseline was −0.4% (range, −0.8% to +0.8%), and in the other four subjects paradoxical vasodilation occurred. The arterial diameter response of the diabetic group was significantly different from that of the control group (P = 0.016). Retinal blood speed increased in each of the control subjects (median change, +13.9%; range, +2.8% to +33.1%; P = 0.0008 vs. baseline), and blood flow remained relatively constant (median change, −3.0%; range, −8.1% to +25.3%; P = 0.61 vs. baseline). Blood speed and flow responses in diabetic subjects were highly variable, showing exaggerated changes in some subjects and a tendency for the blood flow responses to differ from those of control subjects (P = 0.053). The largest increase in blood flow (87%) in response to reclining occurred in one of the diabetic subjects with paradoxical increase (+5.9%) in arterial diameter. Three patients were retested several months apart and showed repeatable diameter responses (Fig. 2) but not speed or flow responses.

Because defective arterial constriction was the most prevalent and reproducible abnormality in the diabetic subjects, we looked for associations that may point to mechanisms and consequences. Table 2 shows that the diabetic subjects with abnormal arterial diameter responses to reclining had clinical and hemodynamic characteristics similar to those of diabetic subjects with normal responses and control subjects. Only the levels of HbA1c differed from those in control subjects. When compared with diabetic subjects with normal responses, the diabetic subjects with defective responses showed a trend toward lower HbA1c, lower blood glucose levels, and longer diabetes duration, but the differences were not significant.

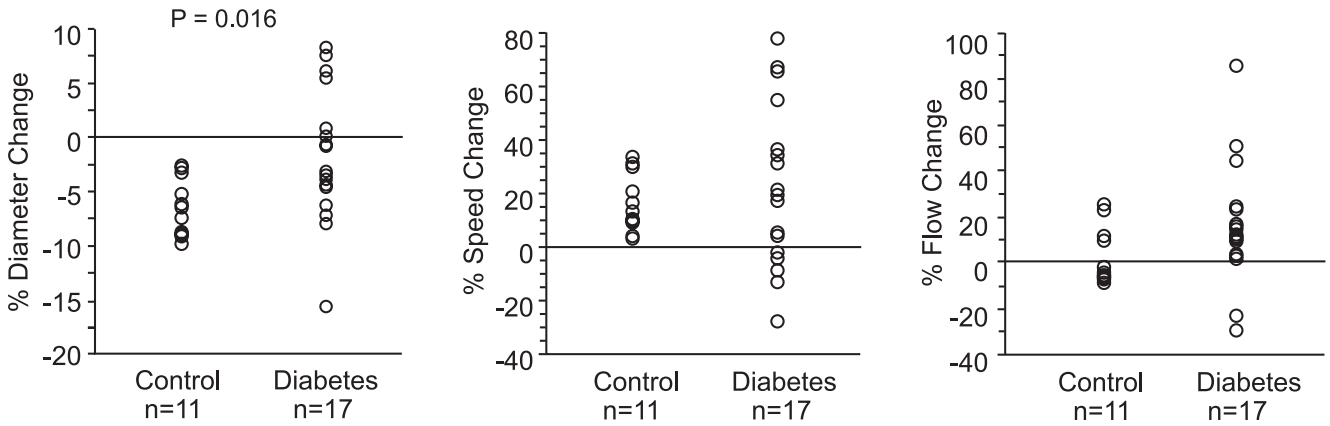

Figure 1. Retinal hemodynamic responses to postural change in subjects with type 1 diabetes and no retinopathy. Shown are the percentages of change in arterial diameter, blood speed, and blood flow recorded in subjects 30 minutes after changing position from sitting to reclining. Change in arterial diameter differed between diabetic and control subjects.

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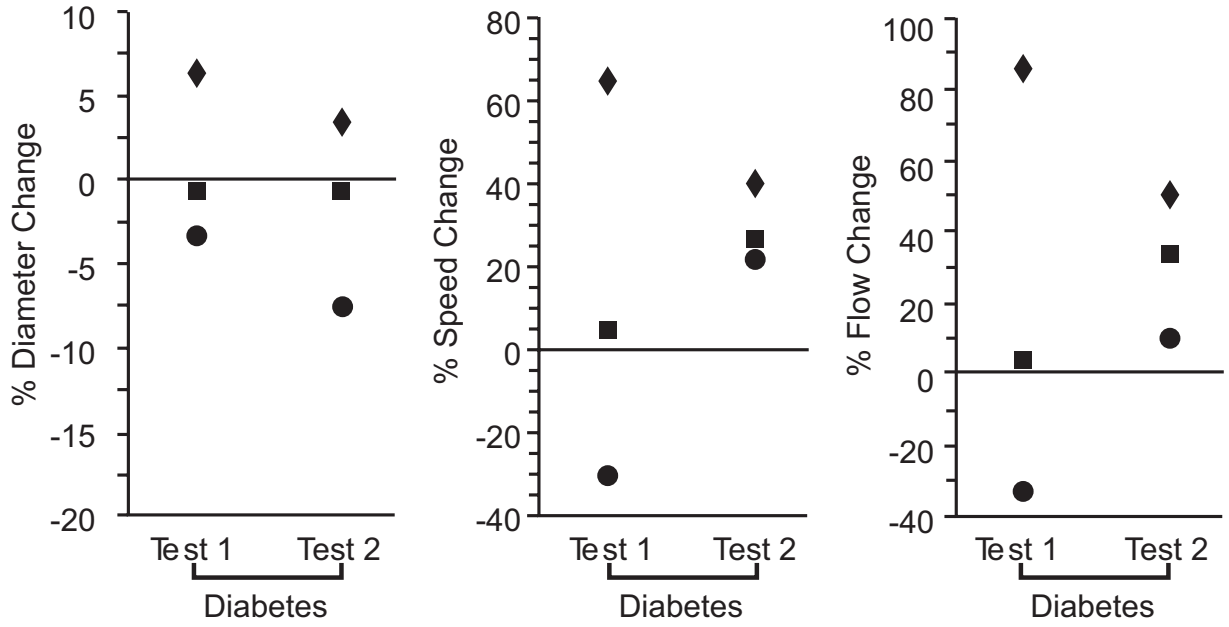

FIGURE 2. Retinal hemodynamic responses to postural change in subjects with type 1 diabetes but no retinopathy measured on two occasions. Shown is the test-retest repeatability of the arterial diameter responses in three diabetic subjects. In both test 1 and test 2, the subject identified by the *circles* showed normal diameter decrease, the subject identified by the *squares* showed absent response, and the subject identified by the *diamonds* showed paradoxical increase. The patterns of blood speed and blood flow responses were not as repeatable.

Response to a Postural Change and Longitudinal Retinal Vascular Measurements

We used the longitudinal measurements to assess whether defective arterial constriction was associated with the development of vascular changes presaging diabetic retinal microangiopathy. Over the 12 months of observation (Table 3), the group of patients with absent arterial constriction in response to reclining experienced a significant increase in retinal arterial diameter ($P = 0.03$ compared with baseline) and a tendency toward increased foveal thickness ($P = 0.06$ compared with baseline). No such changes were observed in the group of diabetic subjects with normal arterial constriction in response to reclining (Table 3).

DISCUSSION

We found that patients with relatively well-controlled type 1 diabetes and no clinical retinopathy are also free of most subclinical abnormalities of retinal vessels detectable by noninvasive means, even after a median diabetes duration of 12 years. This new status quo differs greatly from that prevailing until the mid-1990s, before the DCCT-triggered emphasis on tight blood glucose control, when teenagers or young adults with just 4 to 7 years' duration of type 1 diabetes, if still free of retinopathy, showed abnormal retinal blood flow at steady state[10,28] and already increased vascular diameters.[28]

TABLE 2. Characteristics of the Type 1 Diabetic Subjects with Abnormal Response of Retinal Arterial Diameter to a Change in Posture

Variable	Response of Patients with Diabetes: Abnormal Response ($n = 8$)	Response of Patients with Diabetes: Normal Response ($n = 9$)	Control Subjects ($n = 11$)	P
Age, y	31.6 ± 8.6	32.4 ± 9.4	30.5 ± 8.3	0.87
Females, %	62	55	54	>0.99
Diabetes duration, y	14.6 ± 6.4	11.6 ± 5.2	n/a	0.29
HbA1c, %	7.0 ± 0.6	7.4 ± 0.6	5.4 ± 0.2	<0.0001*
Blood glucose, mg/dL†	128.5 ± 47.4	143.0 ± 46.8	110.6 ± 7.5	0.39
MAP, mm Hg	92.8 ± 6.9	92.7 ± 7.4	93.9 ± 8.4	0.92
IOP, mm Hg	15.5 ± 2.0	14.8 ± 3.0	13.5 ± 1.9	0.18
OPP at baseline (sitting), mm Hg‡	46.4 ± 5.6	47.0 ± 5.0	49.1 ± 6.5	0.56
OPP reclining, % increase§	19.2 ± 13.6	16.0 ± 10.0	14.9 ± 10.0	0.70

MAP, mean arterial pressure; OPP, ocular perfusion pressure. Values are expressed as mean ± SD.

* P for difference between the control group and each of the diabetes groups. The two diabetes groups did not differ from each other ($P = 0.85$).

† Measured immediately before the autoregulation test; primarily postprandial levels.

‡ Calculated using the standard formula OPP = ⅔MAP − IOP.

§ Estimated from $MAP_{reclining}$ − IOP.

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TABLE 3. Longitudinal Changes in Retinal Arterial Diameter and Foveal Thickness in the Type 1 Diabetic Subjects with Abnormal Response of Retinal Arterial Diameter to a Change in Posture

	Response of Patients with Diabetes	
Variable (μm)	Abnormal Response (n = 8)	Normal Response (n = 9)
Arterial diameter		
At baseline	122 ± 8	121 ± 15
12 months later	126 ± 9*	122 ± 13
Foveal thickness		
At baseline	216 ± 28	220 ± 19
12 months later	224 ± 28†	222 ± 17

Values are expressed as mean ± SD.
* $P = 0.03$ vs. baseline values.
† $P = 0.06$ vs. baseline values.

Among our well-controlled patients, the first abnormality to become detectable was the absence of retinal arterial constriction in response to a pressure stimulus (i.e., a defect in the myogenic response). The passage of blood exerts two types of physical force, pressure and shear stress, on the wall of blood vessels.[29] As transmural pressure is increased or decreased, resistance vessels reciprocally decrease or increase their diameters by myogenic reactivity, a highly regulated process based on the contractile properties of the smooth muscle cells.[29,30] Impaired myogenic reactivity to pressure stimuli appears to be a distinct signature of diabetes. It is more prevalent in diabetes than in other ocular pathologic conditions with disturbed hemodynamics, such as glaucoma[16]; in diabetes, it is not confined to the retinal vessels.[31]

The mechanisms for the defect are likely to originate within the vascular cells because the pressure-induced myogenic response can be elicited in isolated retinal arteries,[18] indicating that the sensing and transduction of the pressure signal, which eventually culminates in Ca^{2+} entry into smooth muscle cells and contraction, are fully contained within the vessels. Different duration and severity of diabetes may contribute different mechanisms. In the presence of established microangiopathy, the defective myogenic response of retinal arteries may carry an important contribution from loss of contractile cells.[32,33] However, the myogenic response to pressure can be defective in diabetes when the effector cells are alive and functional. For example, arterioles isolated from biopsy samples of fat from patients with type 2 diabetes fail to constrict in response to pressure but constrict normally in response to norepinephrine.[31] Additionally, the myogenic response of retinal vessels to isometric exercise in patients with type 1 diabetes does increase when glycemic control improves,[34] suggesting that at early stages the impairment is functional. In the latter study, lack of a control group of nondiabetic subjects and lack of information on the individual responses of the diabetic subjects to improved glycemic control preclude definitive conclusions on the frequency and reversibility of the abnormality. At its initial stages, the myogenic defect induced by diabetes may be upstream of smooth muscle contraction, perhaps inherent to events and structures involved in generating the pressure stimulus (e.g., ion channels that sense stretch[35]) or at steps that modulate the intensity of contraction.[30] Endothelial products may be important among the modulators. In humans, the blockade of endothelin-1 blunts retinal arterial constriction in response to isometric exercise,[36] and similar blunting was reported after an acute rise in blood glucose level.[37] In the rat, the blunting effects of very high glucose levels on the in vitro responses of the ophthalmic[38] and cerebral[39] arteries to increased transmural pressure are dependent on the presence of the endothelium and appear to be mediated by endothelial vasodilators. These observations may or may not be relevant to the mechanisms operative in our diabetic patients, in whom hyperglycemia is chronic but of modest degree.

Multiple features of the defective myogenic response of retinal arteries observed in our patients match features desirable in a marker of disease risk.[40,41] First, the defective response provided information not available from a careful clinical assessment, and the information was specific for microangiopathy because both the stimulus and the response are contained within the vessel. Second, the myogenic response was defective in approximately half the patients studied, separating responders and nonresponders in the absence of metabolic and drug confounders, and was reproducible. This indicates that the defective response uncovers a new state of the retinal vessels and potentially identifies persons with a heightened sensitivity to an even mild, if protracted, degree of hyperglycemia. Third, the myogenic response was either normal or absent, rather than blunted. The dichotomous outcome makes the marker interpretable in the individual patient, a highly desirable feature unmatched, to our knowledge, by any other marker of retinopathy proposed to date. Fourth, the consequences of a defective myogenic response are such that the defect becomes an unequivocal risk factor for the development of retinopathy. In vessels larger than 80 μm in diameter, the blood flow is directly proportional to the fourth power of the vessel radius.[42] Hence, effective constriction of resistance arteries in response to increased pressure is a critical mechanism for the control of blood flow rate and the protection of the smaller vessels and the parenchyma downstream.

Repetitive daily episodes of inappropriately high flow could contribute to the small hemorrhages and microaneurysms that mark the onset of clinical diabetic retinopathy. This possibility finds support in the observation made in diabetic animals that the drugs that correct defective retinal autoregulation do prevent the histopathology of retinal vessels[43] and is consistent with our longitudinal data. Several of our patients with defective myogenic response still had a relatively normal blood flow response to reclining, indicating that defective constriction was the earliest event compensated for, at least some of the time, by other still functional mechanisms of autoregulation. However, patients with absent myogenic response showed an increase in arterial diameter and foveal thickness over 12 months not evident in patients with normal myogenic response. Insofar as larger retinal arteriolar diameter is a predictor of diabetic retinopathy[7] and foveal thickness reflects fluid balance in the retina and capillary permeability,[44] the patients with defective myogenic response appeared to be on the path to retinopathy.

Finally, there is a suggestion that a defective myogenic response in patients without retinopathy is amenable to correction.[34] This would add to the candidate marker the highly desirable characteristic of being a potential surrogate end point for drug studies and a target for early interventions to abort clinical retinopathy. However, we have noted above that the study providing this important suggestion does not permit definitive conclusions.

Our study, conducted in a small cohort of patients, yielded a candidate biomarker of retinopathy risk. An appropriately powered larger study is now required to probe whether the abnormality has predictive value for the development of clinical retinopathy and, thus, clinical usefulness. While validation studies are being planned, it also appears urgent to begin learning whether the defective myogenic response of retinal vessels found in our patients can be restored by some drug. In view of the hemodynamic consequences of the abnormality, leaving it uncorrected appears as a missed opportunity to help prevent retinopathy.

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References

1. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes.* 1990;39:1116–1124.
2. Krolewski AS, Warram JH, Rand LI, Kahn CR. Epidemiologic approach to the etiology of type I diabetes mellitus and its complications. *N Engl J Med.* 1987;317:1390–1397.
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986.
4. Mohsin F, Craig ME, Cusumano J, et al. Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002. *Diabetes Care.* 2005;28:1974–1980.
5. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience. *Arch Intern Med*. 2009;169:1307–1313.
6. Lorenzi M. Mechanisms and strategies for prevention of diabetic retinopathy. *Curr Diabetes Rep.* 2006;6:102–107.
7. Cheung N, Rogers SL, Donaghue KC, Jenkins AJ, Tikellis G, Wong TY. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. *Diabetes Care.* 2008;31:1842–1846.
8. Lorenzi M, Feke GT, Cagliero E, et al. Retinal haemodynamics in individuals with well-controlled type 1 diabetes. *Diabetologia.* 2008;51:361–364.
9. Pournaras Cj, Rungger-Brandle E, Riva CE, Hardarsonn SH, Stefansson E. Regulation of retinal blood flow in health and disease. *Prog Retin Eye Res.* 2008;27:284–330.
10. Bursell SE, Clermont AC, Kinsley BT, Simonson DC, Aiello LM, Wolpert HA. Retinal blood flow changes in patients with insulin-dependent diabetes mellitus and no diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1996;37:886–897.
11. Garhöfer G, Zawinka C, Resch H, Kothy P, Schmetterer L, Dorner GT. Reduced response of retinal vessel diameters to flicker stimulation in patients with diabetes. *Br J Ophthalmol.* 2004;88:887–891.
12. Holopigian K, Seiple W, Lorenzo M, Carr R. A comparison of photopic and scotopic electroretinographic changes in early diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 1992;33:2773–2780.
13. Grunwald JE, Riva CE, Brucker AJ, Sinclair SH, Petrig BL. Altered retinal vascular response to 100% oxygen breathing in diabetes mellitus. *Ophthalmology.* 1984;91:1447–1452.
14. Trick GL, Edwards P, Desai U, Berkowitz BA. Early supernormal retinal oxygenation response in patients with diabetes. *Invest Ophthalmol Vis Sci.* 2006;47:1612–1619.
15. Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. *Diabetes.* 1995;44:603–607.
16. Feke GT, Pasquale LR. Retinal blood flow response to posture change in glaucoma patients compared with healthy subjects. *Ophthalmology.* 2008;115:246–252.
17. Dumskyj MJ, Eriksen JE, Dore' CJ, Kohner EM. Autoregulation in the human retinal circulation: assessment using isometric exercise, laser Doppler velocimetry, and computer-assisted image analysis. *Microvasc Res.* 1996;51:378–392.
18. Delaey C, Van de Voorde J. Pressure-induced myogenic responses in isolated bovine retinal arteries. *Invest Ophthalmol Vis Sci.* 2000;41:1871–1875.
19. Bressler NM, Edwards AR, Antoszyk AN, et al. Retinal thickness on Stratus optical coherence tomography in people with diabetes and minimal or no diabetic retinopathy. *Am J Ophthalmol.* 2008;145:894–901.
20. Frank RN, Schulz L, Abe K, Iezzi R. Temporal variation in diabetic macular edema measured by optical coherence tomography. *Ophthalmology.* 2004;111:211–217.
21. Chan A, Duker JS, Ko TH, Fujimoto JG, Schuman JS. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. *Arch Ophthalmol.* 2006;124:193–198.
22. Yoshida A, Feke GT, Mori F, et al. Reproducibility and clinical application of a newly developed stabilized retinal laser Doppler instrument. *Am J Ophthalmol.* 2003;135:356–361.
23. Tang J, Mohr S, Du J-P, Kern TS. Non-uniform distribution of lesions and biochemical abnormalities within the retina of diabetic humans. *Curr Eye Res.* 2003;27:7–13.
24. Hague S, Hill DW. Postural changes in perfusion pressure and retinal arteriolar caliber. *Br J Ophthalmol.* 1988;72:253–257.
25. Caprioli J, Coleman AL. Blood pressure, perfusion pressure, and glaucoma. *Am J Ophthalmol.* 2010;149:704–712.
26. Selvadurai D, Hodge D, Sit AJ. Aqueous humor outflow facility by tonography does not change with body position. *Invest Ophthalmol Vis Sci.* 2010;51:1453–1457.
27. Wise GN, Dollery CT, Henkind P. Physiologic principles. *The Retinal Circulation*. 1st ed. New York: Harper & Row; 1971:94–95.
28. Grunwald JE, DuPont J, Riva CE. Retinal haemodynamics in patients with early diabetes mellitus. *Br J Ophthalmol.* 1996;80:327–331.
29. Bevan JA, Laher I. Pressure and flow-dependent vascular tone. *FASEB J.* 1991;5:2267–2273.
30. Scholfield CN, McGeown JG, Curtis TM. Cellular physiology of retinal and choroidal arteriolar smooth muscle cells. *Microcirculation.* 2007;14:11–24.
31. Schofield I, Malik R, Izzard A, Austin C, Heagerty A. Vascular structural and functional changes in type 2 diabetes mellitus: evidence for the roles of abnormal myogenic responsiveness and dyslipidemia. *Circulation.* 2002;106:3037–3043.
32. Mizutani M, Kern TS, Lorenzi M. Accelerated death of retinal microvascular cells in human and experimental diabetic retinopathy. *J Clin Invest.* 1996;97:2883–2890.
33. Gardiner TA, Archer DB, Curtis TM, Stitt AW. Arteriolar involvement in the microvascular lesions of diabetic retinopathy: implications for pathogenesis. *Microcirculation.* 2007;14:25–38.
34. Blum M, Kloos C, Günther S, Hunger-Dathe W, Müller UA. Improved metabolic control results in better myogenic response of retinal arterioles in patients with diabetes mellitus type 1. *Ophthalmologica.* 2008;222:373–377.
35. Brayden JE, Earley S, Nelson MT, Reading S. Transient receptor potential (TRP) channels, vascular tone and autoregulation of cerebral blood flow. *Clin Exp Pharmacol Physiol.* 2008;35:1116–1120.
36. Luksch A, Wimpissinger B, Polak K, Jandrasits K, Schmetterer L. ETa-receptor blockade, but not ACE inhibition, blunts retinal vessel response during isometric exercise. *Am J Physiol Heart Circ Physiol.* 2006;290:H1693–H1698.
37. Blum M, Brändel C, Müller UA. Myogenic response reduction by high blood glucose levels in human retinal arterioles. *Eur J Ophthalmol.* 2005;15:56–61.
38. Ito I, Jarajapu YP, Guberski DL, Grant MB, Knot HJ. Myogenic tone and reactivity of rat ophthalmic artery in acute exposure to high glucose and in a type II diabetic model. *Invest Ophthalmol Vis Sci.* 2006;47:683–692.
39. Cipolla MJ, Porter JM, Osol G. High glucose concentrations dilate cerebral arteries and diminish myogenic tone through an endothelial mechanism. *Stroke.* 1997;28:405–411.
40. Manolio T. Novel risk markers and clinical practice. *N Engl J Med.* 2003;349:1587–1589.
41. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation.* 2007;115:949–952.
42. Goldsmith HL. The microrheology of red blood cell suspensions. *J Gen Physiol.* 1968;52:5s–28s.
43. Berkowitz BA, Roberts R. Prognostic MRI biomarkers of treatment efficacy for retinopathy. *NMR Biomed.* 2008;21:957–967.
44. Knudsen ST, Bek T, Poulsen PL, Hove MN, Rehling M, Mogensen CE. Macular edema reflects generalized vascular hyperpermeability in type 2 diabetic patients with retinopathy. *Diabetes Care.* 2002;25:2328–2334.

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