Hyperviscosity-Related Retinopathy in Waldenström Macroglobulinemia

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Objectives: To determine the earliest retinal changes associated with Waldenström macroglobulinemia (WM) and to ascertain the serum IgM and serum viscosity (SV) levels at which these changes occur.

Methods: Patients with WM were evaluated using indirect ophthalmoscopy with scleral depression, laser Doppler retinal blood flow measurements, and serum IgM and SV determinations. Hemodynamic findings were compared with those of a group of age-matched controls. A retinopathy severity scale was developed, and the associated IgM and SV values were related to particular morphologic changes.

Results: A total of 46 patients with WM and 14 age-matched, healthy controls participated in the study. Patients exhibited far-peripheral hemorrhages and venous dilation with increasing SV and IgM values. Central retinal changes were associated with significantly higher SV values. Retinal vessel diameter increased with increasing serum IgM and SV levels. The mean IgM level of patients with the earliest retinal changes was 5442 mg/dL. The mean SV level was 3.1 cP.

Conclusions: Retinal manifestations of hyperviscosity syndrome occur at lower serum IgM and SV levels than previously reported. Indirect ophthalmoscopy with scleral depression along with retinal vessel diameter measurements are able to detect the earliest hyperviscosity syndrome–related complications and should be considered in the treatment of patients with WM.

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WALDENSTRÖM MACroglobulinemia (WM) is a lymphoproliferative B-cell disorder characterized by overproduction of monoclonal IgM[1] and is the most frequent diagnosis in patients with hyperviscosity syndrome (HVS) caused by paraproteinemias. Approximately 17% of all patients with WM show clinical symptoms related to HVS.[2] IgM is a large molecular compound that is secreted in a pentamer form and weighs approximately 1 million Da. Because of its large size, 70% to 90% of IgM produced is found in the intravascular compartment.[3] IgM may bind water through its carbohydrate component and can also form aggregates. In addition, immunoglobulins are cationic and can therefore lower the repulsive forces among normally anionic erythrocytes.[4] All of these attributes contribute to HVS and rouleaux formation.

Symptoms due to HVS can be categorized into (1) general symptoms, such as tiredness, fatigue, weight loss, and anorexia; (2) neurologic symptoms, such as headaches, nausea, vertigo, dizziness, ataxia, paresthesia, decreased hearing, and, rarely, coma; and (3) vascular disturbances, such as epistaxis, gingival and gastrointestinal hemorrhages or menorrhagia, congestive heart failure, retinopathy (including retinal hemorrhages), papilledema, dilated retinal veins and visual disturbances, and perfusion-related renal problems.[5]

Vascular disturbances play a major role in HVS and can especially be observed in the retina, where microvascular changes are readily observable. The HVS-related retinopathy with central retinal hemorrhages and vascular dilation is commonly seen in patients with WM.[6] We suspected that the earliest changes at lower serum viscosity (SV) levels might be present in the far periphery of the retina, which can be evaluated only with indirect ophthalmoscopy and scleral depression.

Multiple studies[7] have investigated SVs in patients with WM to determine the threshold level of viscosity at which symptoms or clinical findings might occur. Al-

Table 1. Characteristics of Patients With Waldenström Macroglobulinemia (WM)

Characteristics	No. (%) of Patients (N = 46)
Chemotherapy*	19 (41)
Untreated for WM	27 (59)
Hypertension	8 (17)
Diabetes†	4 (9)
Aspirin therapy	6 (13)

*Patients were treated with either monotherapy or combination therapy. Drugs used for treatment included thalidomide; rituximab; cyclophosphamide, doxorubicin, vincristine (Oncovin), prednisone (CHOP) therapy; fludarabine phosphate; bortezomib; alemtuzumab; chlorambucil; oblimersen sodium; and cladribine.

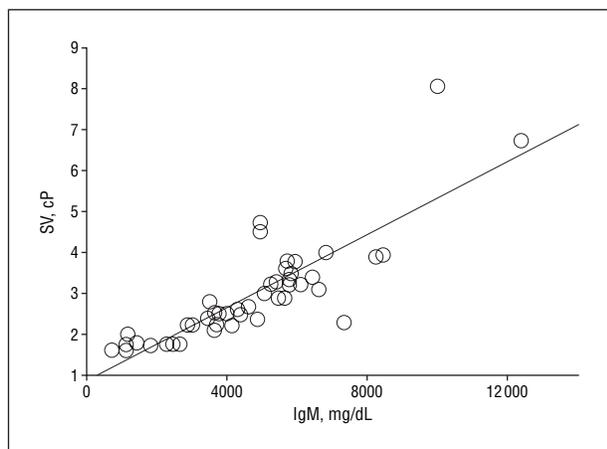†All non–insulin-dependent diabetes.

Figure 1. Regression plot showing the correlation between serum IgM and serum viscosity (SV) levels ($P<.001$; $R^2 = 0.71$).

though acknowledging in these studies that the SV at which symptoms occurred varied among patients, no patient was found to have exhibited symptoms at an SV of less than 4 cP.[5,8] Our study was conducted to investigate whether retinal changes might occur at lower levels of SV by examining patients with WM using indirect ophthalmoscopy with scleral depression. In addition, retinal hemodynamic changes due to HVS were, for the first time to our knowledge, quantitatively assessed using a retinal laser Doppler instrument.[9] Both ophthalmoscopic and retinal hemodynamic findings were used to introduce a new scale for HVS severity in patients with WM.

METHODS

A total of 46 patients (17 women and 29 men; mean age, 61 ± 9 years) with a diagnosis of WM were referred for the study. In addition, 14 age-matched, healthy controls (7 women and 7 men; mean age, 62 ± 5 years) were included. The study was designed as a prospective, consecutive case series. Patients gave written informed consent to participate in the study, and the protocol, approved by the Schepens Eye Research Institute institutional review board, followed the guidelines of the Declaration of Helsinki. Each patient had undergone a complete examination and hematological evaluation, including

determinations of serum IgM and SV levels, at the Dana Farber Cancer Institute before the ophthalmic procedures. The mean disease duration was 36 months, with a range of 1 to 176 months. **Table 1** gives the characteristics of the patients with WM.

Each patient received a dilated fundus examination using slitlamp biomicroscopy and indirect ophthalmoscopy with scleral depression by an experienced retinal specialist. For the ophthalmoscopic examination, patients were in a recumbent position. Digital retinal photographs using a Topcon TRC-50EX system (Topcon Corporation, Tokyo, Japan) were taken to document the ophthalmoscopic findings. Hemorrhages were considered to be central when they appeared within a 40° field of view centered on the macula.

Retinal hemodynamics were assessed using a Canon Laser Doppler Blood Flow Meter (CLBF100; Canon Inc, Tokyo), an instrument that simultaneously measures the centerline red blood cell speed and the blood column diameter in individual retinal vessels.[9] The retinal blood flow rate is automatically calculated at each measurement site. In this study, sites along major temporal retinal arteries and veins were measured in both eyes. The eye with the largest vein diameter was included in the study. For analysis, only one measurement location of the vein and the corresponding artery was used. Ophthalmic examiners were masked to the hematological findings in the patients. Veins were considered dilated if the measured diameters were 180 μm or larger. This value represents the upper 95% confidence limit of retinal vein diameters reported by Jonas et al[10] in a study of 275 eyes of healthy subjects. In addition, retinal arterial diameters, vein diameters, venous blood speed, and flow values were compared with those of a group of healthy, age-matched controls.

Statistical comparisons between patients and controls were made using unpaired t tests. Statistical comparisons among patient groups were made using nonparametric Kruskal-Wallis and Mann-Whitney U tests. Pearson correlation coefficients between measured variables were determined using simple linear regression analysis. $P<.05$ was considered statistically significant. Results are presented as mean ± SD.

RESULTS

In the patients, the mean serum IgM level was 4732 ± 2343 mg/dL, and the mean SV was 3.0 ± 1.2 cP. Serum IgM and SV levels were highly correlated with each other ($P<.001$; $R^2=0.71$) (**Figure 1**). The mean venous diameter was 165 ± 26 μm in the patient group and 146 ± 16 μm in the control group. The difference was statistically significant ($P=.02$). The mean venous blood speed was 26.1 ± 8.7 mm/s in the patient group and 31.2 ± 6.5 mm/s in the control group. This difference was also statistically significant ($P=.04$). The mean venous blood flow was 16.7 ± 8.1 μL/min in the patient group and 16.1 ± 5.0 μL/min in the control group. The difference was not statistically significant ($P=.78$). In addition, we found no statistically significant difference between arterial diameter in the patient group (120 ± 11 μm) compared with controls (115 ± 8 μm) ($P=.28$).

We found statistically significant positive correlations between IgM levels and retinal vein diameters ($P<.001$; $R^2=0.411$) and artery diameters ($P=.01$; $R^2=0.187$) (**Figure 2**). In addition, IgM levels were negatively correlated with venous blood speeds ($P=.02$; $R^2=0.117$). The SV was also positively correlated with venous diameter ($P<.001$; $R^2=0.268$) and negatively correlated with venous blood speed ($P=.007$; $R^2=0.159$).

Twenty-two patients (48%) showed signs of HVS, such as peripheral dot and blotlike hemorrhages, dilated retinal veins, central hemorrhages, tortuous blood vessels with venous sausaging, and optic disc edema, during ophthalmoscopic examination. A severity scale was applied to the patients based on retinal findings and retinal blood flow measurements. Group 1 included patients with no indication of retinal changes due to HVS (24 patients); group 2, patients with dilated retinal veins and/or peripheral retinal hemorrhages (18 patients); and group 3, patients with peripheral and central retinal hemorrhages accompanied by dilated veins, optic nerve head edema, or venous sausaging (4 patients). **Figure 3**A is a fundus image of a patient with WM with no signs of HVS (group 1). Figure 3B is a fundus image of a patient in group 2. No retinal hemorrhages were visible, but the retinal veins appeared dilated. Figure 3C is a fundus image of a different patient with WM in group 2. Peripheral retinal hemorrhages were seen as indicated in the figure. Figure 3D shows central retinal changes in a patient in group 3. Central retinal hemorrhages, optic disc edema, and venous sausaging are indicated in the figure.

Table 2 gives the serum IgM and SV values, arterial and venous diameters, venous blood speeds, and venous blood flows in the 3 patient groups and in the controls. **Figure 4** shows the corresponding box plots of group comparisons for arterial diameter, venous diameter, blood speed, and blood flow. Arterial blood speed and flow values could not be obtained in all of the patients and therefore were not used in the analysis. The mean serum IgM level of patients in group 2 was 5442 mg/dL. The range of serum IgM levels associated with group 2 was 2950 to 8440 mg/dL. Patients in group 3 had a mean serum IgM level of 8515 mg/dL. The range of IgM levels associated with group 3 was 5700 to 12 400 mg/dL. The mean SV level of patients in group 2 was 3.1 cP. The range of SV levels associated with group 2 was 2.1 to 4.7 cP. Patients in group 3 had a mean SV level of 5.6 cP. The range of SV levels associated with group 3 was 3.8 to 8.0 cP.

No significant differences were found between untreated patients (n=27, 58.7%) and patients who were receiving chemotherapy (n=19, 41.3%) at the time of our study in IgM and SV levels, vessel diameter, venous blood speed, and flow. None of our study patients were using vasodilatory agents. Six patients were taking aspirin at the time of their examination. Aspirin showed no effect on any of the parameters tested. In addition, results in patients with systemic hypertension (n=8) or type 2 diabetes mellitus (n=4) were not different from those without these conditions.

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COMMENT

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Our results indicate that the most severe HVS-related retinopathy involves both the central and peripheral retina. As indicated in Table 2, these changes occur at the highest IgM and SV levels. Previous studies[6,11,12] have described only these central or midperipheral abnormalities associated with HVS. We have shown that milder HVS-
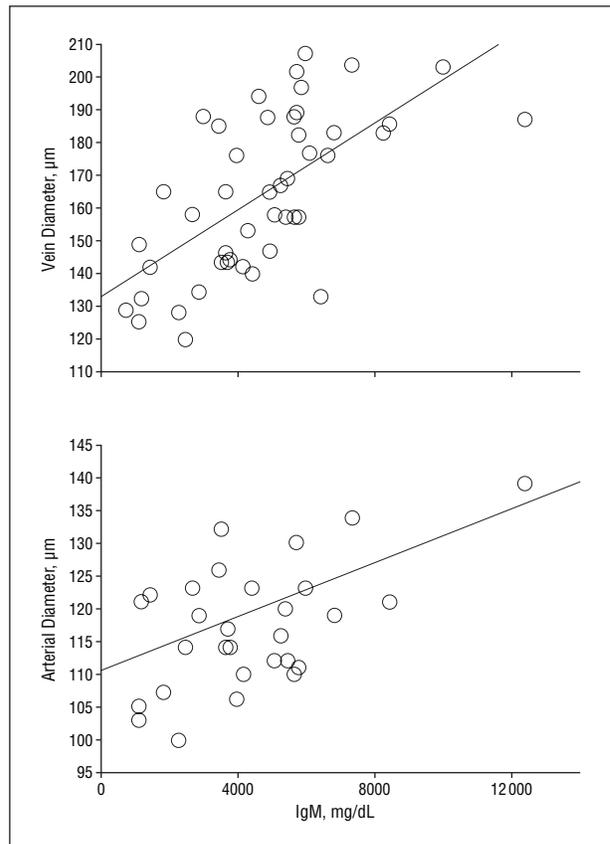

Figure 2. Regression plots showing the correlations between retinal venous (top; $P<.001$; $R^2 = 0.411$) and arterial (bottom; $P=.01$; $R^2 = 0.187$) diameters and serum IgM levels.

related retinopathy at intermediate SV levels involves only peripheral hemorrhages and/or dilated veins. What this study has found is that HVS-related retinopathy (albeit mild) occurs at lower SV levels than previously thought. Crucial in this determination is the identification of hemorrhages in the far periphery.

In addition, the major retinal arteries and veins showed increasing dilation with increasing serum IgM levels (Figure 2), and the correlation between increasing retinal vein diameter and increasing SV levels was also significant. A quantitative relationship between retinal vessel diameter and SV levels in HVS had been previously reported only in a patient with multiple myeloma followed for a period of 1 year.[13] The fact that patients in group 1 had completely normal retinal blood flow parameters with no significant differences compared with age-matched, healthy controls indicates that retinal hemodynamic analysis is useful in identifying the first signs of HVS.

Other investigators[14,15] used video fluorescein angiography to investigate the retinal circulation in patients with HVS. They found increases in the arteriovenous passage time of the dye tracer in the patients compared with reference values in healthy individuals. This finding suggested a slowing of the retinal circulation and perpetuated the supposition[16] that HVS is a type of venous stasis retinopathy that is also found in central retinal vein occlusion. In fact, our laser Doppler measurements found this not to be the case. As indicated in Table 2 and
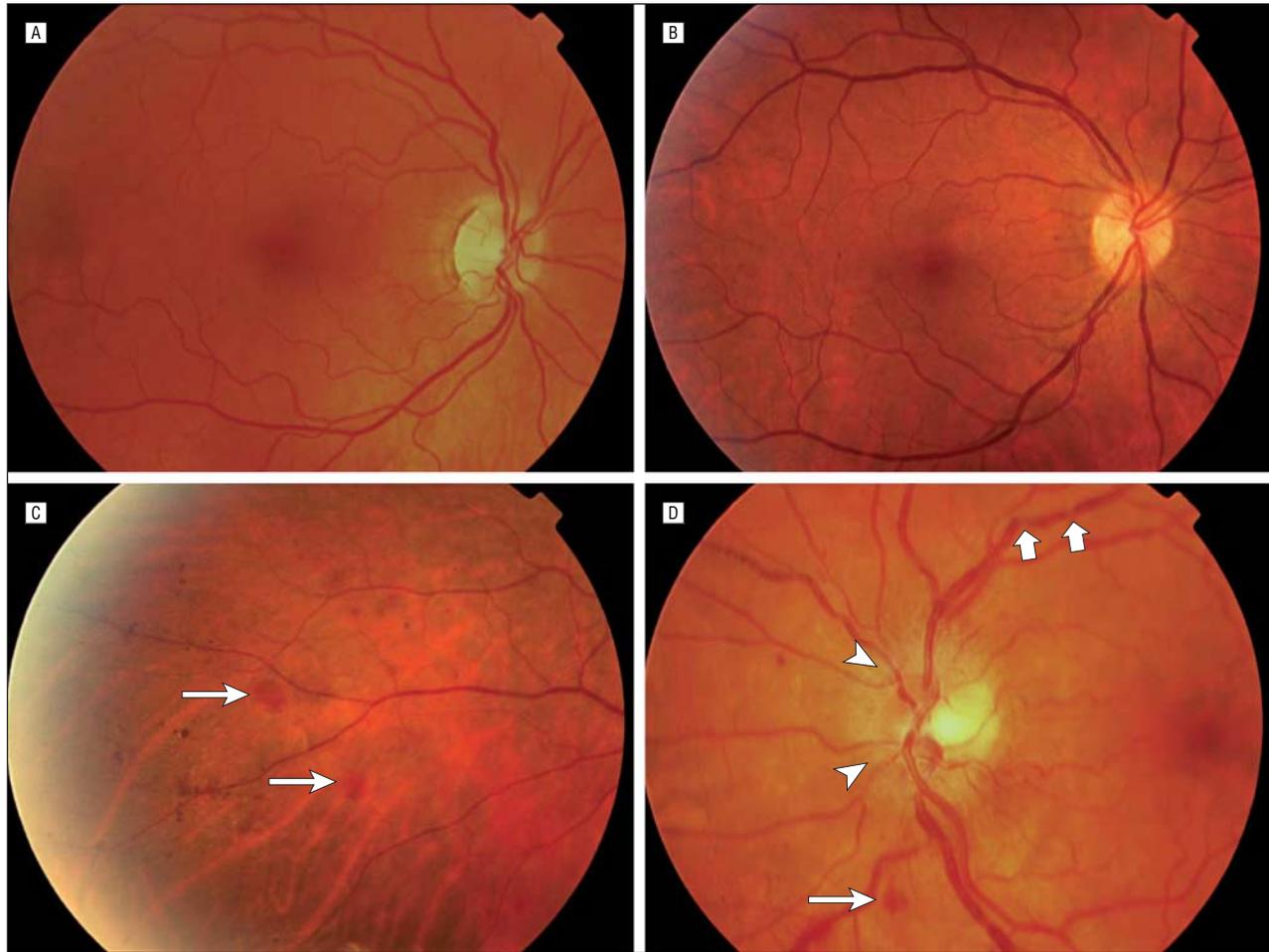
Figure 3. Fundus images of patients with Waldenström macroglobulinemia. A, No retinopathy (group 1); B, dilated veins (group 2); C, peripheral retinal hemorrhages in a group 2 patient (arrows); and D, central retinal hemorrhage (thin arrow), optic disc edema (arrowheads), and venous sausaging (thick arrows) in a group 3 patient.

Table 2. Serum Viscosity (SV), IgM, and Retinal Hemodynamic Values According to the Severity of Retinal Hyperviscosity Syndrome

	SV, cP	Serum IgM, mg/dL	Arterial Diameter, μm	Venous Diameter, μm	Venous Speed, mm/s	Venous Flow, μL/min
Laboratory values*						
Controls (n = 14)	NA	NA	115 ± 8	146 ± 16	31.2 ± 6.5	16.1 ± 5.0
Group 1 (n = 24)	2.5 ± 0.7	3569 ± 1767	114 ± 7	146 ± 15	28.1 ± 8.1	14.1 ± 4.1
Group 2 (n = 18)	3.1 ± 0.7	5442 ± 1625	127 ± 12	181 ± 15	20.7 ± 5.3	15.8 ± 5.9
Group 3 (n = 4)	5.6 ± 0.7	8515 ± 3241	131 ± 11	200 ± 9	22.0 ± 9.9	20.8 ± 11.1
P values for differences†						
Controls and group 1	NA	NA	.85	.82	.17	.25
Controls and group 2	NA	NA	**.04**	**<.001**	**.004**	.66
Controls and group 3	NA	NA	.06	**.003**	.10	.71
Groups 1 and 2	**.02**	**.001**	**.01**	**<.001**	.05	.08
Groups 1 and 3	**.003**	**.002**	**.04**	**.002**	.14	.22
Groups 2 and 3	**.01**	.06	.83	.06	.55	.92

Abbreviation: NA, not applicable.
*Data are presented as mean ± SD.
†Statistically significant *P* values are shown in boldface type.

Figure 4, we found that in HVS the retina maintains a constant blood flow despite an increased level of SV.

The phenomenon of blood flow autoregulation in a healthy retinal vasculature is well known.[17] In the case of HVS, the autoregulatory mechanism results in retinal vascular dilation with an accompanying decrease in blood speed, yielding an essentially constant blood flow rate. **Figure 5** illustrates the autoregulatory response of a healthy retina to elevated SV levels and explains our observations. Only the major retinal arteries and veins can
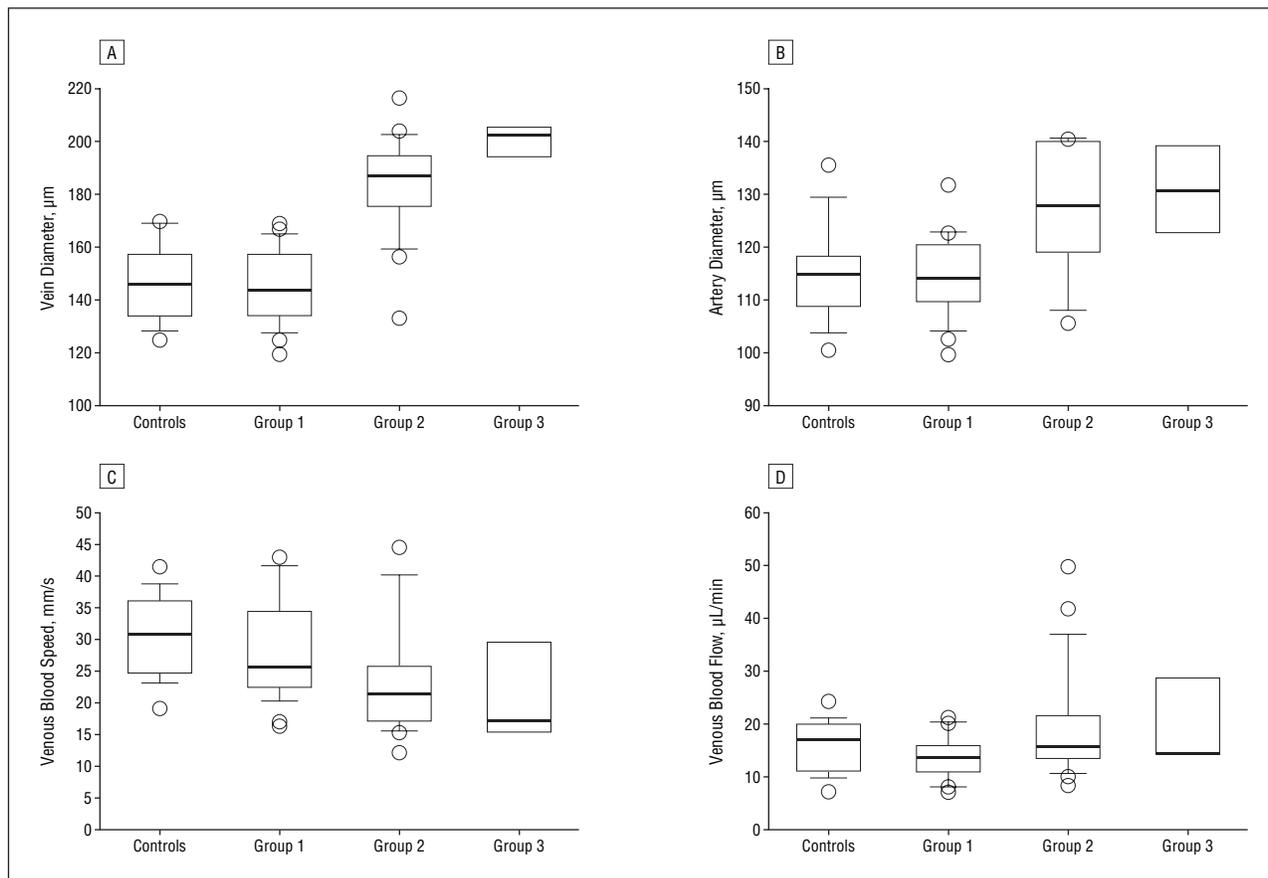
Figure 4. Box plot representation of the differences between the 3 patient groups and controls in vein diameter (A), artery diameter (B), venous blood speed (C), and venous blood flow (D). The corresponding *P* values are given in Table 2. Lines within each box indicate the median value (50th percentile); upper and lower lines, 75th and 25th percentiles, respectively; and upper and lower error bars, 90th and 10th percentiles, respectively. Values outside these limits are shown as separate circles.

be measured with the laser Doppler technique. However, most autoregulatory vasoactivity occurs in the smaller retinal arterioles, which respond to elevated values of blood viscosity by active dilation. Instead of the normal pattern of decreased intravascular blood pressure progressing from the arterial to the venous side of the vascular system, the pressure decreases more gradually when there is arterial and arteriolar dilation. The higher local intravasculature pressures throughout the capillary network lead to retinal hemorrhages. In addition, the elevated intravascular pressure carries over to the venous side of the system and explains the observed venous dilation due to an elevated transmural pressure. The finding that HVS, at least in its early stages, affects only the blood components and not the vessels themselves is consistent with the presence of an intact retinal autoregulatory mechanism.

The results of this study show that clinical findings such as retinal vessel dilation and hemorrhages might occur at a wide range of SV and IgM levels. Retinal changes were found in patients with SV levels as low as 2.1 cP. These values are lower than the previously reported value of 4 cP.[5,8] Although the presence of retinal hemorrhages clearly indicates structural damage due to HVS, their location in the peripheral retina renders them asymptomatic and unnoticed by the patient. The HVS-related changes in the eye become symptomatic only when the
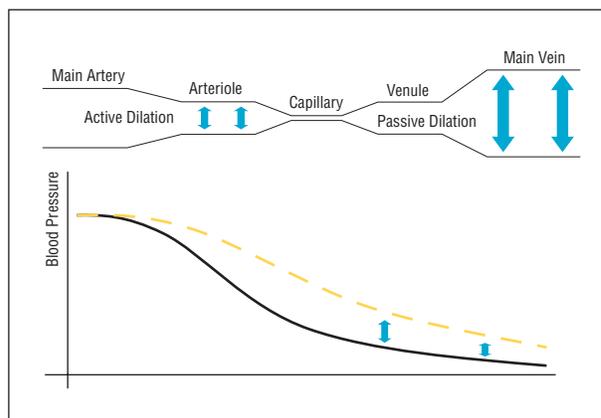

Figure 5. Response of the retinal vasculature to elevated blood viscosity. Solid curve indicates the normal blood pressure decrease through the vasculature. Dashed curve indicates a more gradual blood pressure decrease with autoregulatory vasodilation accompanying elevated blood viscosity. Arrows in upper part of figure indicate active arteriolar dilation and passive venous dilation; arrows in lower part of figure, elevation in intravascular pressure on the venous side of the circulation (difference between the dashed and solid curves) responsible for the observed venous dilation.

central retina is involved. We found that such involvement (group 3) occurs only at high serum IgM and SV levels. In our group 3 patients, the mean IgM level was 8515 mg/dL and the mean SV level was 5.6 cP.

In conclusion, for the first time to our knowledge, indirect ophthalmoscopy with scleral depression was combined with laser Doppler retinal blood flow measurements to assess HVS in patients with WM. Based on these findings, a new severity scale was developed. The earliest retinal changes can occur at SV and IgM levels that are lower than previously reported in other studies. Clinically, indirect ophthalmoscopy with scleral depression provides a straightforward means of evaluating the earliest structural damage due to HVS.

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