Prediction of Proliferative Diabetic Retinopathy With Hemoglobin Level

Baqiyah N. Conway, PhD; Rachel G. Miller, MS; Ronald Klein, MD; Trevor J. Orchard, MD

Objective: To investigate the role of hemoglobin (HGB) level in predicting proliferative diabetic retinopathy (PDR).

Methods: We assessed 426 individuals without PDR at baseline (213 men; 213 women) from the Pittsburgh Epidemiology of Diabetes Complications Study, an 18-year prospective cohort study of childhood-onset type 1 diabetes. Presence of PDR was determined by stereo fundus photography. Cox proportional hazards modeling with stepwise regression was used to determine the independent association of HGB level with PDR. Analyses were sex specific.

Results: There were 206 events. Although the incidence of PDR did not vary by sex (48% in both men and women), in men, HGB exhibited a positive linear relationship with 18-year incidence of PDR (hazard ratio, 1.33; 95% confidence interval, 1.10-1.60; P = .003), while in women, HGB level exhibited a quadratic relationship with PDR (P < .001). After multivariable adjustment for univariately significant covariates, HGB level remained significantly predictive of PDR in both men (P = .004) and women (P = .04).

Conclusion: Higher HGB level predicts the incidence of PDR in type 1 diabetes mellitus, though the association varies by sex, being linear and positive in men and quadratic in women.


Proliferative diabetic retinopathy (PDR) is a leading cause of blindness in the United States and has been linked to retinal hypoxia and characterized by small blood vessel proliferation, retinal microaneurysms, and vitreous hemorrhaging. Lower hematocrit (HCT) levels have been associated with the progression of diabetic kidney disease and with the incidence of PDR, suggesting that anemia may increase complication risk. In contrast, however, stabilization of retinopathy has also been reported in those with end-stage renal disease, a condition associated with anemia. The association between hemoglobin (HGB) and retinopathy is likely, therefore, to be complex, particularly given the recent observation of unusually high HGB levels, reaching 18.8 g/dL, in study participants with nephropathic type 1 diabetes mellitus.

Hemorheological factors are altered in diabetes, and there is some evidence that these disturbances may also be associated with diabetic retinopathy. Increased HCT and blood viscosity have been observed cross-sectionally in those with diabetic retinopathy. Elevated erythropoietin has also been observed in the vitreous fluid of those with diabetic retinopathy and found to be an angiogenic promoter of PDR.

Given these observations, we decided to investigate the association of HGB with the incidence of PDR in type 1 diabetes mellitus.

Methods

The Pittsburgh Epidemiology of Diabetes Complications (EDC) study is an 18-year prospective study based on a well-defined cohort with childhood-onset (age < 17 years) type 1 diabetes living within 100 miles of the University of Pittsburgh at study baseline. The 658 participants (325 female, 333 male; 67% of all those eligible) were diagnosed between January 1, 1950, and May 30, 1980, at Children’s Hospital of Pittsburgh, and first seen in EDC between 1986 and 1988, when the mean age and diabetes duration were 28 and 19 years, respectively. They were then seen biennially for 10 years, after which they were followed up by survey with examinations limited to certain subgroups. Between 2004 and 2007, however, an 18-year follow-up was conducted for all participants. The design and methods of the study have been previously described.

Before attending each cycle of examinations, information was collected by questionnaire concerning demographic characteris-
tics, medical history, and health care behaviors, as previously described. At each cycle, both a standardized medical history and clinical examination were performed by a trained internist to document complications of diabetes.

Fasting blood samples were assayed for lipids, lipoproteins, glycosylated hemoglobin (HbA1c), and HGB. Hemoglobin was measured using the Coulter Counter Model S-Plus IV (Coulter Electronics, Hialeah, Florida) automated blood cell counter. High-density lipoprotein cholesterol level was determined by a heparin and manganese procedure, a modification of the Lipid Research Clinics method. Cholesterol was measured enzymatically. Glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease formula.

Stable HbA1c was originally measured in saline-incubated samples by microcolumn cation exchange chromatography (Isolab, Akron, Ohio). On October 26, 1987, the method was changed to high-performance liquid chromatography (Diamat, Bio-Rad Laboratories, Hercules, California). The 2 methods were highly correlated (r = 0.95; Diamat HbA1c = 0.18 + 1.00 Isolab HbA1c). After the 10-year follow-up, glycosylated hemoglobin A1 (HbA1c) was measured with the DCA 2000 analyzer (Bayer, Tarrytown, New York). The Diamat and DCA were also highly correlated (r = 0.95; DCA HbA1c = −0.18 + 1.00 Diamat HbA1c).

The HbA1c and HbA1c values were converted to Diabetes Control and Complications Trial (DCCT)-aligned HbA1c values using regression formulas derived from duplicate analyses (DCCT HbA1c = [0.83 × EDC HbA1c] + 0.14; DCCT HbA1c = [EDC HbA1c − 1.13]/0.81).

Blood pressure was measured by a random-zero sphygmomanometer according to a standardized protocol after a 5-minute rest period. Blood pressure levels were analyzed using the mean of the second and third readings.

Retinopathy was assessed in 3 standardized visual fields. Stereoscopic fundus photographs were taken in fields 1, 2, and 4 with a Zeiss camera (Carl Zeiss, Oberkochen, Germany), and were read by the Fundus Photography Reading Center, University of Wisconsin, Madison. Gradients were classified by the modified Arlie House System, with PDR defined as a grade of 60 or higher in at least 1 eye. Individuals without gradable fundus photographs were graded according to their medical history data, with confirmation by their ophthalmologist if required. Those with panretinal photocoagulation scars and a grade of less than 60 were recorded as having PDR without gradable fundus photographs. Those with PDR if the medical history indicated that the laser therapy was required by the ophthalmologist if required. Those with panretinal photocoagulation scars and a grade of less than 60 were recorded as having PDR without gradable fundus photographs. Those with PDR if the medical history indicated that the laser therapy was required by the ophthalmologist if required. Those with panretinal photocoagulation scars and a grade of less than 60 were recorded as having PDR without gradable fundus photographs.

Nephropathy status was determined based on consistent results from at least 2 of 3 timed urine collections (24-hour, overnight, and timed samples during examination) and urine albumin excretion rate. The adequacy of urine collection was determined by whether the total amount of creatinine excreted was appropriate for an individual’s age, based on body size and sex. Urinary albumin was determined immunonephelometrically. All procedures were approved by the institutional review board of the University of Pittsburgh.

Continuous data were compared between groups by the t test, with serum creatinine, triglycerides, high-density lipoprotein cholesterol, and non–high-density lipoprotein cholesterol being log transformed prior to testing. Categorical data were compared between groups by χ² tests. Cox proportional hazards modeling with forward selection was used to determine the association of baseline HGB with the 18-year incidence of PDR. The functional form of HGB was assessed by plotting a restricted cubic spline transformation for HGB against the log hazard ratio separately for men and women using Harrell’s SAS macro, %PSPLINET. A Wald test was used to test the assumption of a linear relationship between HGB and the log hazard ratio. Owing to the sex differences in HGB distribution, analyses were conducted sex specifically. Censoring occurred at the time of event or at last follow-up.

Hemoglobin data was available for 652 study participants; the HGB levels ranged from 9.2 to 20.0 g/dL (to convert to grams per liter, multiply by 10), with a median (interquartile range) of 16.2 (15.4-16.9) g/dL in men and 14.1 (13.5-15.0) g/dL in women. Two hundred two participants had PDR at baseline and were excluded from further analyses. Of the remaining 450, 24 provided no further PDR information and complete follow-up to 18 years was available for 78% of those still alive, follow-up being censored at last observation for the remainder. Baseline characteristics of the 426 study participants free of PDR at baseline are described in Table 1 and Table 2 for men and women, respectively.

The cumulative incidence of PDR was 48% after 18 years. The median time to follow-up was 14.6 years. In men, there was no suggestion of any deviation from a linear relationship between HGB and the log hazard ratio (Wald test of linearity P = .15); therefore, HGB was entered into Cox models as a continuous linear covariate. In women, however, the Wald test showed a significant deviation from linearity (P = .02) and a graph of the restricted cubic spline suggested a quadratic relationship between HGB and the log hazard ratio (Figure); therefore, HGB was entered into Cox models as a quadratic term. Univariately, HGB showed a significant linear association with the risk of developing PDR in men (P = .003) and a significant nonlinear association in women (P = .008, quadratic term).

In multivariable analyses allowing for univariately significant covariates, HGB remained significantly predictive of PDR in men (hazard ratio 1.29; 95% confidence interval, 1.08-1.54; P = .004) (Table 3). In women, HGB as a quadratic term also remained significantly predictive of PDR (P = .04). Other significant multivariable predictors included HbA1c and diastolic blood pressure in both sexes, albumin excretion rate in men, and systolic blood pressure and fibrinogen in women. Finally, the association of HGB with other components (markers) of retinopathy was also explored. A significant prediction of both macular edema (P < .001 and P = .03 for men and women, respectively) and 2-step progression (P = .03 and P < .001 for men and women, respectively) was observed.
of diabetes duration\textsuperscript{11}) and the Wisconsin Epidemiological Study of Diabetic Retinopathy population (37% at approximately 26.6 years of diabetes duration\textsuperscript{18}). Although much attention has been given in recent years to anemia and low levels of HGB in diabetes, particularly as it relates to kidney disease,\textsuperscript{22,28} this is the first study, to our knowledge, to show high HGB levels to be predictive of the long-term incidence of PDR. We have also shown that the relationship of HGB with PDR varies by sex, with HGB demonstrating a linear relationship in men, but a nonlinear quadratic (P = .008) relationship in women. These results, if confirmed, may have important clinical relevance, as they may both identify new pathogenetic pathways to PDR and influence clinical treatment. There are several potential explanations for these findings.

First, the HGB levels in this population were relatively high, ranging from 9.2 to 20.0 g/dL. We have observed that HGB levels in our population, including the 120 participants with PDR and 228 with overt nephropathy at baseline, were approximately 1 g/dL higher in both men and women compared with the National Health and Nutrition Examination Survey III white population limited to the same age range.\textsuperscript{29} Higher HGB levels in type 1 diabetes were also noted by Pichler et al,\textsuperscript{30} who observed a higher (0.8 g/dL) difference in HGB levels between children and adolescents with type 1 diabetes compared with controls. Factors related to increased HGB such as testosterone, hypoxia, growth factors, and viscosity may be responsible for the PDR associated with increased HGB in this population.

Androgens, in particular testosterone, are a known stimulant of erythropoiesis,\textsuperscript{31} and testosterone has been fairly consistently shown to be elevated in type 1 diabetes.\textsuperscript{32} Haffner et al\textsuperscript{32} found higher testosterone levels and lower sex hormone-binding globulin\textsuperscript{33} in male participants with type 1 diabetes and PDR compared with those without PDR. Chaurasia et al\textsuperscript{34} also found higher testosterone levels in diabetic retinopathy patients with type 1 diabetes compared with controls. Factors related to increased HGB such as increased testosterone levels may be responsible for the PDR associated with increased HGB in this population.

Table 1. Baseline Characteristics of Men by Subsequent Proliferative Diabetic Retinopathy Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PDR (n=110)</th>
<th>No PDR (n=110)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25.1 (6.4)</td>
<td>24.2 (7.8)</td>
<td>.35</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>16.8 (5.7)</td>
<td>16.1 (6.7)</td>
<td>.43</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>16.5 (1.2)</td>
<td>16.1 (1.2)</td>
<td>.009</td>
</tr>
<tr>
<td>White blood cells, ×10\textsuperscript{11}/mm\textsuperscript{2}</td>
<td>6.2 (1.6)</td>
<td>6.2 (1.8)</td>
<td>.92</td>
</tr>
<tr>
<td>Body mass index\textsuperscript{a}</td>
<td>23.7 (2.9)</td>
<td>22.9 (3.4)</td>
<td>.05</td>
</tr>
<tr>
<td>Overt nephropathy, No. (%)</td>
<td>36 (39.1)</td>
<td>14 (12.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR) estimated GFR (MDRD), ml/min/1.73 m\textsuperscript{2}</td>
<td>107.1 (92.2-146.2)</td>
<td>107.1 (88.7-139.1)</td>
<td>.70</td>
</tr>
<tr>
<td>Median (IQR) albumin excretion rate, µg/min\textsuperscript{b}</td>
<td>14.8 (9.0-65.2)</td>
<td>6.5 (5.7-21.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL\textsuperscript{b}</td>
<td>186.1 (37.7)</td>
<td>174.4 (33.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL\textsuperscript{b}</td>
<td>136.9 (37.0)</td>
<td>124.1 (33.6)</td>
<td>.009</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49.2 (9.0)</td>
<td>50.2 (10.0)</td>
<td>.42</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>262.8 (80.2)</td>
<td>266.2 (81.6)</td>
<td>.76</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114.8 (13.6)</td>
<td>111.3 (12.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74.4 (9.5)</td>
<td>71.0 (9.9)</td>
<td>.01</td>
</tr>
<tr>
<td>HbA\textsubscript{1c}, %</td>
<td>9.0 (1.5)</td>
<td>8.5 (1.5)</td>
<td>.009</td>
</tr>
<tr>
<td>Total insulin, injections/d</td>
<td>2 (1-2)</td>
<td>2 (1-2)</td>
<td>.15</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>22 (21.8)</td>
<td>19 (19.0)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviations: GFR (MDRD), estimated glomerular filtration rate (Modification of Diet in Renal Disease formula); HbA\textsubscript{1c}, glycosylated hemoglobin A\textsubscript{1c}; HDL, high-density lipoprotein; IQR, interquartile range; PDR, proliferative diabetic retinopathy.

\textsuperscript{a}SI conversion factors: To convert mean hemoglobin concentration to grams per liter, multiply by 10; cholesterol to millimoles per liter, 0.0259; fibrinogen to micromoles per liter, 0.0294; HbA\textsubscript{1c} to proportion of total hemoglobin, 0.01.

\textsuperscript{b}Calculated as weight in kilograms divided by height in meters squared. Natural logarithmically transformed before analysis.

Table 2. Baseline Characteristics of Women by Subsequent Proliferative Diabetic Retinopathy Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PDR (n=110)</th>
<th>No PDR (n=110)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26.0 (7.1)</td>
<td>25.7 (8.5)</td>
<td>.76</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>17.0 (6.8)</td>
<td>17.1 (7.5)</td>
<td>.97</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.4 (1.2)</td>
<td>14.2 (1.0)</td>
<td>.24</td>
</tr>
<tr>
<td>White blood cells, No. (×10\textsuperscript{11}/mm\textsuperscript{2})</td>
<td>6.8 (1.9)</td>
<td>6.2 (1.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Body mass index\textsuperscript{a}</td>
<td>23.3 (3.1)</td>
<td>23.2 (3.5)</td>
<td>.70</td>
</tr>
<tr>
<td>Overt nephropathy, No. (%)</td>
<td>33 (35.5)</td>
<td>15 (14.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR) estimated GFR (MDRD), ml/min/1.73 m\textsuperscript{2}</td>
<td>105.2 (86.0-134.3)</td>
<td>104.2 (87.6-129.4)</td>
<td>.92</td>
</tr>
<tr>
<td>Median (IQR) albumin excretion rate, µg/min\textsuperscript{b}</td>
<td>12.9 (7.7-71.6)</td>
<td>9.0 (5.6-19.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL\textsuperscript{b}</td>
<td>195.6 (41.1)</td>
<td>178.6 (32.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL\textsuperscript{b}</td>
<td>136.1 (41.3)</td>
<td>117.8 (30.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>59.5 (13.7)</td>
<td>60.8 (11.8)</td>
<td>.48</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>310.7 (90.5)</td>
<td>270.6 (60.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>109.0 (13.2)</td>
<td>105.3 (10.1)</td>
<td>.004</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70.3 (10.7)</td>
<td>67.7 (7.9)</td>
<td>.05</td>
</tr>
<tr>
<td>HbA\textsubscript{1c}, %</td>
<td>9.2 (1.7)</td>
<td>8.4 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total insulin, injections/d</td>
<td>2 (1-2)</td>
<td>2 (1-2)</td>
<td>.17</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>18 (18.4)</td>
<td>19 (17.4)</td>
<td>.86</td>
</tr>
</tbody>
</table>

Abbreviations: GFR (MDRD), estimated glomerular filtration rate (Modification of Diet in Renal Disease formula); HbA\textsubscript{1c}, glycosylated hemoglobin A\textsubscript{1c}; HDL, high-density lipoprotein; IQR, interquartile range; PDR, proliferative diabetic retinopathy.

\textsuperscript{a}SI conversion factors: To convert mean hemoglobin concentration to grams per liter, multiply by 10; cholesterol to millimoles per liter, 0.0259; fibrinogen to micromoles per liter, 0.0294; HbA\textsubscript{1c} to proportion of total hemoglobin, 0.01.

\textsuperscript{b}Calculated as weight in kilograms divided by height in meters squared. Natural logarithmically transformed before analysis.
angiogenesis and has been found to be associated with an increased risk of retinopathy of prematurity, with poietin to reduce the need for blood transfusions were that infants treated with recombinant human erythro-

nabe et al found both erythropoietin and vascular disease and more cardiovascular events and mortality, an increase in adverse events, ie, a deterioration of kidney function.35 In diabetes, Wata-

normative pathway operating at each end of the spectrum.36 Another potential related mechanism is that the HGB association with PDR reflects increased erythropoietin production stimulated by general hypoxia,11 which may contribute to the microvascular disease seen in both the retina and the kidneys in type 1 diabetes mellitus. Some recent studies have shown increased levels of anemia in type 1 diabetes to be associated with complications of diabetes, including retinopathy, renal impairment, and macrovascular disease. However, these patients were from tertiary care clinics and were older23,28 than our participants. In contrast, other literature suggests increased blood viscosity in diabetes,10,42-44 which may lead to tissue ischemia.8 Vekasi et al found higher levels of HCT, plasma fibrino-

Table 3. Multivariable Prediction of the 18-Year Incidence of Proliferative Diabetic Retinopathy in Type 1 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=213, 103 events)</th>
<th>Women (n=213, 103 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB, g/dL</td>
<td>1.29 (1.08-1.54)</td>
<td>NA</td>
</tr>
<tr>
<td>HGB quadratic, g/dL</td>
<td>NA</td>
<td>1.10 (1.00-1.20)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>1.30 (1.14-1.49)</td>
<td>1.32 (1.16-1.50)</td>
</tr>
<tr>
<td>Albumin excretion rate, µ/mint</td>
<td>1.34 (1.20-1.50)</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>1.03 (1.00-1.05)</td>
<td>2.28 (1.02-5.07)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>NA</td>
<td>1.03 (1.01-1.05)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>NA</td>
<td>1.00 (1.00-1.01)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HGB, hemoglobin; HR, hazard ratio; NA, not applicable; NS, not selected; SBP, systolic blood pressure. SI conversion factors: To convert hemoglobin concentration to grams per liter, multiply by 10; fibrinogen to micromoles per liter, 0.0294; HbA1c, to proportion of total hemoglobin, 0.01.

Another potential related mechanism is that the HGB association with PDR reflects increased erythropoietin production stimulated by general hypoxia,11 which may contribute to the microvascular disease seen in both the retina and the kidneys in type 1 diabetes mellitus. Some recent studies have shown increased levels of anemia in type 1 diabetes to be associated with complications of diabetes, including retinopathy, renal impairment, and macrovascular disease. However, these patients were from tertiary care clinics and were older23,28 than our participants. In contrast, other literature suggests increased blood viscosity in diabetes,10,42-44 which may lead to tissue ischemia.8 Vekasi et al found higher levels of HCT, plasma fibrino-

B Natural logarithmically transformed before analysis.
other limitation of our study was that we could not adequately stratify by renal disease status, a complication associated with both HGB levels and diabetic retinopathy, as only 14% (n=56) of those free of PDR at baseline had overt nephropathy. However, we did try to account for kidney disease by controlling for albumin excretion rate, which, while predictive of PDR, did not account for HGB's association with PDR incidence.

In conclusion, these data suggest that high HGB levels may be associated with increased risk of PDR. Furthermore, these PDR findings are complimented by observations that HGB also predicts 2-step progression and macula edema. Increased testosterone in type 1 diabetics, growth factors, viscosity, and/or compensation for generalized ischemia/hypoxia may account for the association of high HGB levels with PDR. Taken as a whole, these results suggest that further evaluation of the potential adverse role of high HGB in those with type 1 diabetes is warranted.

Submitted for Publication: July 17, 2008; final revision received January 15, 2009; accepted March 10, 2009.
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Author Contributions: Drs Conway and Orchard and Ms Miller had full access to the data and take full responsibility of the data and the accuracy of the data analyses.
Financial Disclosure: None reported.

Funding/Support: This work was funded by National Institutes of Health grant DK34818.

Previous Presentation: Findings of this study were presented in part at the 67th American Diabetes Association Scientific Session, June 25-27, 2007; Chicago, Illinois.

Additional Contributions: We are indebted to the participants of the Pittsburgh Epidemiology of Diabetes Complications Study for their dedication and cooperation to the advancement of knowledge in the scientific community.

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Archives Web Quiz Winner

Congratulations to the winner of our June quiz, Sachindra Laishram, MD, Consultant Cornea & Glaucoma
Services, Shija Eye Care Foundation, Langol, Manipur, India. The correct answer to our June challenge was
congenital melanocytoma. For a complete discussion of this case, see the Letters: Research Letters section in the July
Archives (Bajaj MS, Khuraijam N, Sen S, Pushker N. Congenital melanocytoma manifesting as proptosis with mul-

Be sure to visit the Archives of Ophthalmology Web site (http://www.archophthalmol.com) and try your hand
at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information
from a case report or other feature scheduled to be published in the following month’s print edition of the
Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print jour-
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Clinical Eye Atlas, Clinical Retina, or Users’ Guides to the Medical Literature.