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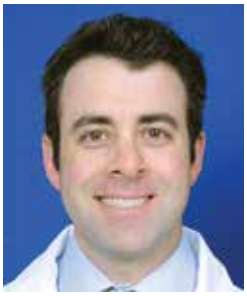

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Diabetic retinopathy: The risk of vision loss and beyond

Introduction

AB*, a 62-year-old male Pacific Islander with a long-standing history of poor diabetic control was referred to our retina clinic for treatment, in both eyes, of proliferative diabetic retinopathy (PDR). He was concurrently treated for hyperlipidemia and hypertension, which was also poorly controlled. His typical in-office blood pressure measurement was ~145/85 mmHg. After receiving prompt pan-retinal-photocoagulation (PRP) OU, AB's visual acuity stabilized at 20/30 OU. Several follow-up visits later, he moved away from the United States to continue his career as a writer. Prior to moving, AB was encouraged and educated about the importance of better control of his diabetes to prevent worsening of his vision and other co-morbidities such as cerebrovascular accidents. In addition, he was also advised to continue getting regular eye evaluations in order to monitor for any additional development of retinopathy. Unfortunately, two years later when AB returned, his diabetes continued to be under poor control, his retinopathy had worsened (Fig 1) and his best-corrected visual acuity had become light-perception OD and 20/60 OS. Fortunately, although there was significant risk, no other comorbidities occurred.

> Studies show that 4.4% of those with diabetes have advanced retinopathy and are at significant risk for blindness — a risk that appears to be increased if the patient also has uncontrolled hypertension and hyperlipidemia.

While the worsening of AB's clinical situation could possibly be attributed to difficulty in access to medical care in a foreign country, in speaking with him, it was apparent that he lacked a clear understanding of the seriousness of his condition, despite extensive discussion regarding the importance of proper care. This is just one of many challenging diabetic cases that prompt a fundamental question: **How can we, as primary eye care providers, effectively manage our patients with diabetes to minimize the risk of blindness and systemic comorbidities?**

*To protect the privacy of the patient, his name has been changed.

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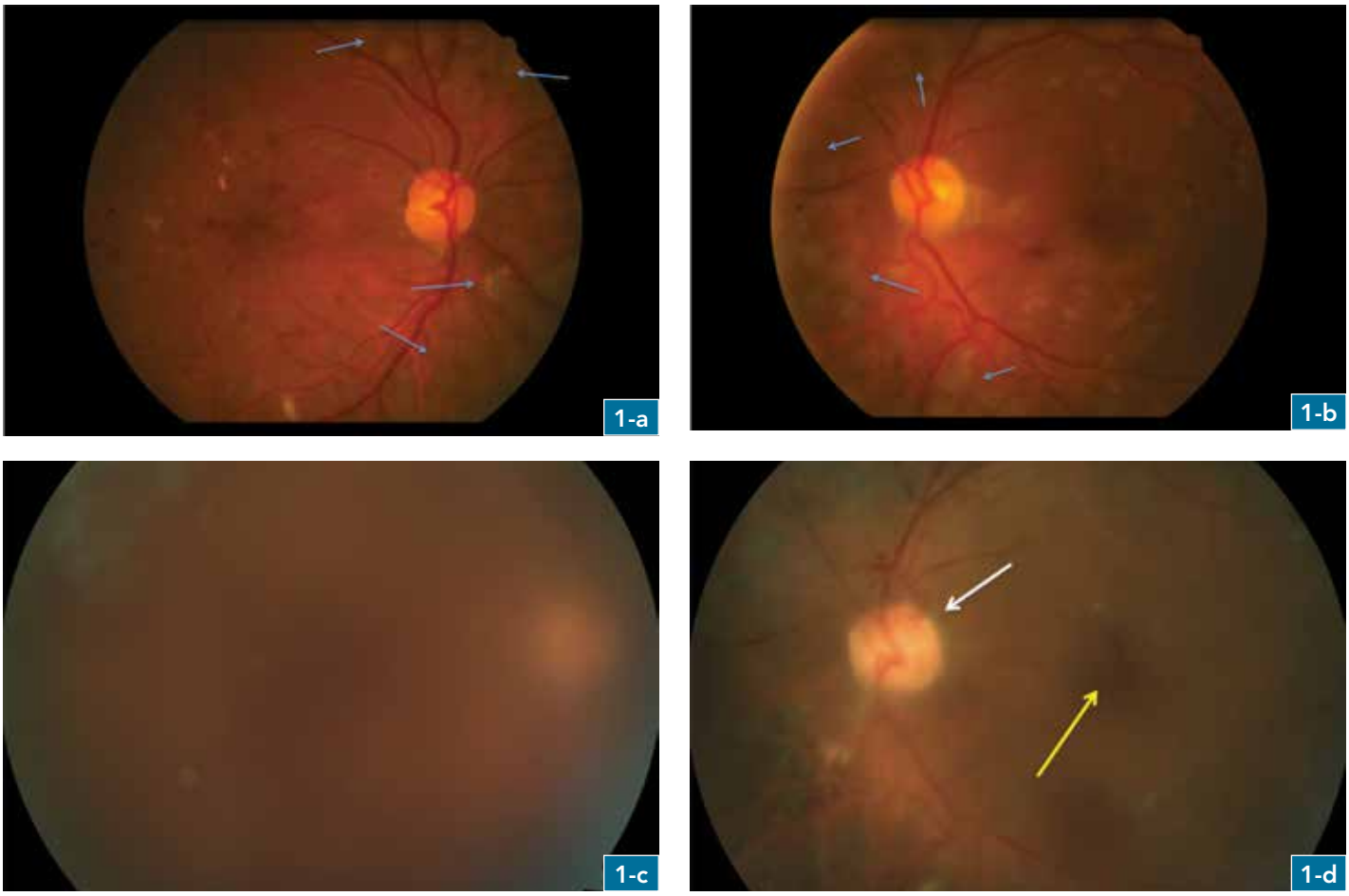

Figure 1: 62-year-old patient received initial PRP treatment (blue arrow: 1-a and 1-b). After two years of poor diabetic control, the patient develops a vitreous hemorrhage, which obscures visualization of the OD retina (1-c). In addition, in the OS (1-d) there is neovascularization of the disc (white arrow) and clinically significant macular edema (yellow arrow).

Background

Diabetes is characterized by loss of capillary endothelial integrity, capillary non-perfusion, abnormally increased vascular permeability, resultant ischemia in affected tissue, and organ failure. While most optometrists recognize that diabetic retinopathy is a major complication of diabetes, it is also important to realize that this disease is a leading cause of blindness among adults in the United States.[4] Studies show that 4.4% of those with diabetes have advanced retinopathy and are at significant risk for blindness[5] — a risk that appears to be increased if the patient also has uncontrolled hypertension and hyperlipidemia.[6,7] Beyond retinopathy, there is an increased risk of other comorbidities such as a cerebrovascular accident (stroke). Someone with diabetes has a 2-4 times increased risk of a cerebrovascular accident and the risk is even higher when advanced retinopathy is present,[3] a point that was also discussed with our patient, AB.

While diabetes can have a devastating effect on quality and longevity of life for individuals like our patient, from a national health perspective, diabetes is a major public health problem that has significant financial implications. The rate of diabetes is increasing worldwide and experts indicate that between 2000 and 2030, the prevalence of diabetes is expected to double. Unfortunately, this is especially relevant in California as it has one of the highest rates of diabetes in the nation, with 1 in 7 adults being diabetic.[2] In addition to threatening vision and quality of life, diabetes has significant financial impact. In 2012, diabetes cost $245 billion due to health care-related costs and loss of work productivity.[3] Because of the significant financial and health costs, a question for optometrists to ask is: **How should we effectively manage patients with diabetes in order to minimize the risk of blindness and other systemic morbidities?**

1) TELEMEDICINE: INCREASING ACCESS TO PREVENTIVE CARE

As many know, severe vision loss due to diabetic retinopathy can usually be averted with timely diagnosis and treatment. Improved effort towards increased screening opportunities could be one answer to address patients' lack of access to care. As seen in Assembly Bill 175 in 2009, the State of California is making continuous effort toward early detection of diabetic retinopathy by expanding opportunities for remote

diabetic retinal screening. Such opportunities could be telemedicine programs, like EyePACS (Eye Picture Archive Communication System: www.eyepacs.org). Although screening by digital fundus photography does not replace the important elements of actual eye examinations, studies show that telemedicine can be sensitive enough to detect significant retinal findings that indicate prompt referral and timely treatment. Litvin, et al.[8] reports 94% sensitivity of detecting clinically significant macula edema via proper digital imaging by using the location of hard exudate as a surrogate marker.

Besides detecting retinopathy in a timely manner, there also is a significant cost advantage with telemedicine for patients, the community and the government. Based on the Medicare reimbursement rate, Li, *et al*.[9] estimates lower cost-per-exam when compared to standard eye exams ($49.95 vs. $77.80). Over one diabetic patient's lifetime, telemedicine could potentially save a median of $2,500 for the government by preventing blindness and necessary welfare service for those who have lost sight.[10] Considering the very low rate of eye examinations in underserved diabetic populations such as rural or low-income areas, experts predict the role of telemedicine is expected to rise.

2) GLYCEMIC CONTROL AS A RISK FACTOR FOR DIABETIC RETINOPATHY

Many studies have looked at ways to increase diabetic patient compliance to treatment. Examples included group education, encouraging home self-monitoring with low-pain lancing devices[11] and Internet-based tools. To this day, one very effective method is still face-to-face education,[12] especially in patients with poor glycemic control. Because roughly 50% of patients with diabetes continue to seek annual retinal exams through eye care providers,[13] optometric consultations with each patient could make a significant impact on the patient's future quality of life.

Previous observational studies have given doctors of optometry an idea of a patient's risk of blindness from diabetic retinopathy (see Table 1). In addition, there are a number of additional risk factors identified for the development and progression of retinopathy. These include glycemic control,[14] duration of diabetes,[15] male gender,[5] insulin use[5] and other cardiovascular markers. Of all the risk factors, glycemic control has consistently been identified as the principal risk factor of retinopathy.[14, 16, 17] Because of this, addressing the importance of glycemic control is crucial in patient education and helping patients realize that poor glycemic control increases his or her risk for blindness.

Currently, the American Diabetes Association[18] recommends that patients with diabetes keep their HbA1c to 7.0% or below in order to prevent microvascular complications. Several studies have supported a positive effect of good glycemic control on progression of retinopathy. The United Kingdom Prospective Diabetic Study[15] (UKPDS) showed a significant reduction in retinopathy with intense glycemic control with median HbA1c of 7.0% in newly diagnosed type 2 diabetic patients. Reichard[17] reported, in a small sample study with type 1 patients, that there was no major progression of retinopathy observed in patients who maintained their HbA1c below 7.0%. In the Diabetes Control and Complication Trial[14] (DCCT) with type 1 diabetes, a 10% reduction in HbA1c (ex: 8.0% to 7.2%) decreased retinopathy progression risk by 35 to 40%. It is notable that some patients in this study showed worsening in retinopathy soon after initiating strict intervention. Its mechanism remains unclear; however, the same phenomenon was observed in the intense glycemic control group in several other studies.[19, 20, 21, 22] Despite this finding, the consensus amongst experts is that long-term benefits of glycemic control outweigh risks from initial worsening.[16] For this reason, it is advisable to closely monitor patients who already have an advanced level of retinopathy and who are just beginning strict glycemic control.

While good glycemic control is helpful, it is important to be aware that attempting to achieve intense control may not always be favorable. A more recent clinical trial with type 2 diabetes, the ACCORD[23] (Action to Control Cardiovascular Risks in Diabetes), confirmed the positive effect of glycemic control. It also looked to confirm if even more strict glycemic control was beneficial. Patients who received intense glycemic control (target HbA1c <6.0%) favored against standard therapy (target 7.0~7.9%). However, intense glycemic control and resultant hypoglycemia had significant association with increased mortality — enough so that the group with intense glycemic control treatment was discontinued early in the trial. Thus, while good glycemic control is advised, it may not be the only answer for blindness prevention.

Table 1: Level of diabetic retinopathy and its risk of progression and blindness, derived from the Early Treatment Diabetic Retinopathy Study[24] and the Diabetic Retinopathy Study[25]

Stage of retinopathy		Progression risk to PDR or vision loss
Non-proliferative	Mild	5% progress to PDR in 1 year
	Moderate	12 ~ 27% progress to PDR in 1 year
	Severe	52% progress to PDR in 1 year
	Very Severe	75% progress to PDR in 1 year
Proliferative	Early	75% progress to High Risk in 5 years
	High Risk	25%~37% risk of Severe Vision Loss in 2 years

3) OTHER CARDIOVASCULAR RISK FACTOR CONSIDERATIONS: BLOOD PRESSURE AND CHOLESTEROL

Blood pressure has long been believed to be a significant risk factor of diabetic retinopathy. Considering that both diabetes and hypertension damage blood vessel integrity, its synergistic effect is not surprising. Patients with diabetes and hypertension are more likely to develop diabetic retinopathy than those without hypertension. The UKPDS[15] provided evidence that blood pressure control of <150/85mmHg has a more protective effect against progression of retinopathy and loss of visual acuity than less strict control of <180/105mmHg. While it may be tempting to think that "lower is better" for blood pressure, experts believe that the protective benefit of blood pressure control may "bottom-out'' in some patients.[29] For example, the ACCORD study did not show any additional benefit with intense blood pressure control (target systolic BP <120mmHg) when compared to standard control (target SBP <140mmHg).[28] It is because of these studies that the American Diabetes Association now recommends target blood pressure of <140mmHg systolic (< 130 mmHg for younger patients) and <80mmHg diastolic for patients with diabetes.

Experimental and epidemiological data suggest that the Renin-Angiotensin-System (RAS) may play some role in diabetic retinopathy control. RAS is a regulatory renal system that balances fluid retention and blood pressure. Examples of RAS blocking medications include enalapril, candesartan and losartan. It is common practice for physicians to prescribe RAS blocking agents to patients with diabetes who are also hypertensive. Patients who received those agents benefitted from a protective effect on other organs compared to conventional hypotensive therapies.[26] Interestingly, even normotensive patients have shown a benefit from RAS blocking treatment. In the Renin Angiotensin System Study,[27] type 1 DM patients with normal blood pressure were given enalapril and losartan. This study was able to show an observed benefit from treatment that was statistically independent from the blood pressure lowering effect.

In addition to good glycemic and blood pressure control, studies also show that patients who control triglyceride and total cholesterol level are less likely to develop or show progression of diabetic retinopathy.[30] Fenofibrate (trade name *Tricor*®) is used to treat hyperlipidemia and it has recently attracted attention on its potential beneficial role in retinopathy management. It reduces LDL (low density lipoprotein), VLDL (very low density lipoprotein) and triglycerides while improving the HDL (high-density lipoprotein) level. Two large clinical trials suggested a benefit for patients with diabetes who were put on fenofibrate therapy.[23, 31] Interestingly, neither study showed great lipid-lowering efficacy by fenofibrate; however, its protective effect against retinopathy progression was significant. At this time, it is unclear if the positive effect of fenofibrate was simply due to the marginal lipid-lowering effect alone or to other unknown therapeutic features.

In summary, to minimize occurrence and progression of diabetic retinopathy, it is important to have a balanced control of cardiovascular risks. (Table 2 summarizes current recommendations for cardiovascular risk factors.)

Table 2: Recommended guidelines of cardiovascular risk factors by the American Diabetes Association[18]

Glycaemia	HbA1c < 7.0%
Blood Pressure	Systolic < 140 mmHg (< 130 mmHg for younger patients) Diastolic <80 mmHg
Lipid	LDL <100 mg/dl
	HDL: >40 mg/dl for men, >50 mg/dl for women
	Triglycerides <150mg/dl

Diabetic retinopathy's association with other end organ damage

Are the eyes a window to the rest of the body?

Retinopathy is just one of the many microvascular complications facing the body's organs in diabetes. It is therefore natural to ask if retinopathy provides any perspective on the risk of damage to any other organ systems. More specifically, is there a link with the severity of diabetic retinopathy and other microvascular complications or even macrovascular complications, i.e., cerebrovascular accident and kidney failure? Since the fundus is the only organ that allows direct inspection without invasive or costly diagnostic tests, researchers have looked at this linkage with a hope of finding the fundus as a biologic marker of systemic status.

Diabetic microvascular complications consist of a triad of retinopathy, peripheral neuropathy and nephropathy. Peripheral neuropathy leads to amputation of extremities and nephropathy to kidney failure. In one study consisting of 645 patients with diabetes, El-Asrar, *et al*.[32] identified that patients with retinopathy are 4 times more likely to have nephropathy than those without. In the same study, the presence of retinopathy also increased the risk of peripheral neuropathy by 2 times. A similar predictive relationship was seen in Coppini's study with 985 patients.[33] Patients with retinopathy at baseline were more likely to later develop peripheral neuropathy. The presence of retinopathy may also provide a forecast on future macrovascular complications and mortality. Patients with proliferative diabetic retinopathy have a significantly high risk of cerebrovascular accident and ischemic heart attack. Those individuals are more likely to carry other significant systemic risks and co-morbidities such as hypertension, impaired renal function and peripheral neuropathies.[34] They may have up to 11 times increased risk of death than those without retinopathy.[34]

> Patients with proliferative diabetic retinopathy have a significantly high risk of cerebrovascular accident and ischemic heart attack.

Although the above studies show a clear relationship between diabetic retinopathy and microvascular and macrovascular complications, caution should be made when consulting with patients regarding retinopathy and its association with other organ damage. The association is not always direct and linear, for example normal kidney function can co-exist with proliferative diabetic retinopathy.[35] The presence and severity of retinopathy does imply other organ damage; however, it does not always accurately predict its diagnosis.

Conclusion

In 2004, the World Health Organization (WHO) estimated that the total number of patients with diabetes worldwide would grow from 171 million in 2000 to 366 million in 2030.[1] Presently, WHO announced that the number has already grown to 344 million.[36] Its exponential growth is imminent, and associated morbidity and mortality are likely to increase. WHO projects that diabetes-related mortality would double from 2005 to 2030.

As primary eye care providers, the utmost concern is our patients' vision. Blindness from diabetic retinopathy is preventable through proper screening and patient education. While glycemic control should be the primary focus, blood pressure control and lipid-lowering therapy also play a significant role — with a balanced control of all three being ideal. As more studies will look to determine the association of diabetic retinopathy with other comorbidities, doctors of optometry will play an even greater role in effectively managing and educating our patients.

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