

The Role of Systemic Risk Factors in Diabetic Retinopathy

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Abstract Diabetic retinopathy is an increasingly common medical issue in the United States. The risk of developing the disease or having the disease progress is caused by many systemic health factors. This article examines the existing literature on the links between glycemic control, arterial hypertension, high cholesterol and hyperlipidemia, obesity, inflammatory markers, sleep-disordered breathing, and exercise with risk of diabetic retinopathy development and prevention. The literature shows benefit for good glycemic and blood pressure control. The effects of cholesterol, and lipid control, inflammatory markers, sleep-disordered breathing, obesity, and exercise are less well established.

Keywords Diabetic retinopathy · Hypertension · Obesity · Cholesterol · Exercise · Sleep-disordered breathing

Introduction

Diabetes mellitus (diabetes) is a group of conditions in which elevation and dysregulation of blood glucose levels result from either decreased production of insulin or systemic resistance to insulin's effects. It is a large health burden in the United States with over 22 million Americans

(7 %) carrying the diagnosis of diabetes mellitus [1]. The prevalence of diabetes is expected to increase so that a quarter to a third of all Americans will be diabetic by 2050 [2]. The economic cost of treating diabetes is over 176 billion dollars a year in the United States, over 20 % of which is spent on the ophthalmic complications [1]. In 2005, there were an estimated 5.5 million people over the age of 40 with diabetic retinopathy, and this number is predicted to rise to 16 million by 2050. The corresponding numbers for vision-threatening diabetic retinopathy were 1.2 million in 2005, and would be 3.4 million by 2050 [3].

Although there are an increasing number of treatments for diabetic retinopathy, the best method of minimizing its impact is prevention of ocular complications. Insulin resistance, which often precedes type 2 diabetes, is a component of the metabolic syndrome. Those with diabetes are more likely to have other components of the metabolic syndrome including abdominal obesity, dyslipidemia, hypertension, prothrombotic state, and a proinflammatory state [4]. Having one or more of these components of the metabolic syndrome has been associated with a higher risk of diabetic complications, including retinopathy [5].

Diabetes is a chronic condition and managing the disease can be a substantial burden to patients. Although primary care physicians and endocrinologists are at the forefront of managing the disease, ophthalmologists are in a unique position to help motivate patients to control their disease. The time of diagnosis of diabetic eye disease can be a pivotal moment in the patients' lives. A threat of vision loss can be a critical wake-up call for patients to invest in habits that will maintain their overall health and the health of their eyes. Familiarity with how systemic health conditions impact diabetic eye disease can help the ophthalmologist educate patients on these habits. Such education at a critical moment can be the catalyst a patient

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needs to pursue lifelong healthier habits. This article examines the effects that these additional systemic health conditions and management have on diabetic eye disease.

Glycemic control

The effects of blood glucose control on the clinical course of diabetes have been well documented and those with well-controlled blood sugars are at significantly lower risk for microvascular complications [6]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, patients who were randomized to an intensive blood sugar control regimen with a target hemoglobin a1c (HbA1c) level of <6.0 % had a significantly lower rate of progression for their diabetic retinopathy compared to those with a target level of 7.0–7.9 % (7.3 vs 10.4 % progression) [7]. This level of risk reduction was also found in a Cochrane Review on intensive glucose control in type 2 diabetics [8]. For every 10 % reduction in HbA1c, there is an associated 42 % decrease in the risk of retinopathy progression. For every 10 % increase in HbA1c, the risk of retinopathy progression increased by 64 % [9]. This study echoed previous studies, which also found a decreased retinopathy risk with tighter blood glucose control [10, 11]. The beneficial effects of tight blood glucose control appear to last for years as similarly managed patients in the Epidemiology of Diabetes Interventions and Complications Trial (EDIC) extension to the Diabetes Control and Complications Trial (DCCT) had a significantly lower risk of retinopathy progression if they were previously randomized to intensive insulin therapy vs. conventional therapy (39 vs 56 % progression over 3 years) [12•].

Pancreas transplantation is a relatively new therapy for diabetes. It can have dramatic effects on blood sugars, with many patients achieving a euglycemic state. There have been case reports of stabilization and even regression of diabetic retinopathy after pancreas transplantation [13, 14].

Controversy has surrounded the potential ocular effects of thiazolidinediones, a class of medications used to control blood sugar. Systemically, they have been associated with peripheral edema refractory to diuretics and ophthalmologic case series have suggested that they may also contribute to diabetic macular edema [15, 16]. The ACCORD trial, however, included a pre-specified analysis comparing rates of macular edema with or without exposure to these drugs and saw no effect [17].

In summary, there is strong evidence that better glycemic control leads to a large reduction in the risk of development and progression of diabetic retinopathy. Controversy remains regarding the ideal HbA1c target for diabetics. The ACCORD trial used a HbA1c goal <6.0 %, whereas the ADVANCE trial used a goal of <6.5 % [7]. The American Diabetes Association recommends a goal <7.0 %.

Arterial Hypertension

Hypertension is the most common modifiable risk factor for cardiovascular disease in the United States. About 20 % of adults under age 60 and 65 % of adults over 60 in the United States meet the criteria for diagnosis which is systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg [18]. Diabetics are particularly susceptible to the effects of hypertension with respect to their risk for developing cardiovascular disease. There are multiple hypotheses for why this may be, with a combination of several being, most likely to represent the full picture. One mechanism implicates interactions between hormonal control of blood sugar levels and the renin-angiotensin-aldosterone system (RAS) at multiple levels and in both directions; those with diabetes have elevation of the RAS leading to hypertension, and those with hypertension have increased rates of developing diabetes. Pharmacologic blockade of the RAS both reduces the risk of diabetes development in hypertensive patients and decreases the risk of hypertension in previously normotensive diabetics [19]. A meta-analysis showed that those on RAS inhibitors had about 7 % decreased risk of retinopathy, a 5 % decreased risk of progression of diabetic retinopathy, and an increased probability of regression of their diabetic retinopathy. The same meta-analysis showed that diabetics on angiotensin-converting enzyme (ACE) inhibitors had a statistically significant decreased risk of diabetic retinopathy and retinopathy progression, and an increased probability of regression. Interestingly, angiotensin receptor blockers (ARBs) were only associated with a decreased incidence of retinopathy [20].

The combination of diabetes and hypertension is associated with an increased mortality rate, largely due to cardiovascular disease. Diabetics with adequate blood pressure control have only 70 % risk of mortality and those with poorly controlled hypertension have almost double the risk of death from cardiovascular disease as those diabetics with good blood pressure control [21]. Not surprisingly, having both hypertension and diabetes increases a patient's risk of retinal disease. Studies have shown that the relative risk of diabetic retinopathy for diabetics also having hypertension is 1.7 [21–23]. One study found that for every 10 mmHg increase in systolic blood pressure, there was a 1.23 times increased risk of diabetic retinopathy and 1.19 times increased risk of vision-threatening retinopathy [24]. Interestingly, the same study identified a decreased risk profile with increasing diastolic blood pressure. For every 10 mmHg increase in diastolic blood pressure, there was a 0.71 relative risk of diabetic retinopathy and 0.65 relative risk of vision-threatening retinopathy [24]. Effective treatment of hypertension (goal blood pressure less than 150/85) has been shown to reduce the rate of worsening of diabetic

retinopathy by 34 % over 7.5 years [22, 25]. Additionally, such efforts at decreasing blood pressure in hypertensive diabetics lowered the risk of vision loss of three lines or more by 47 %. A Cochrane Review found that there was a beneficial effect on treatment of elevated blood pressure to prevent diabetic retinopathy but not for slowing its progression [26]. Notably, the ACCORD trial did not find a significant difference in the rates of diabetic retinopathy progression between those undergoing intensive blood pressure control (goal systolic blood pressure <120 mmHg) and standard management (goal <140 mmHg).

Control of blood pressure to a level of <140/90 is recommended under the Joint National Committee 8 regulations [27]. Best current evidence from the ophthalmology literature does not suggest any benefit to altering this recommendation for patients with confirmed diabetic retinopathy.

High Cholesterol and Hyperlipidemia

Elevated serum cholesterol and lipid levels are a known component of the metabolic syndrome. Their well-documented link to cardiovascular events and cardiovascular deaths, as well as the beneficial effects of intervention on these risk factors, has led to regular primary care dyslipidemia screening for diabetic patients. Studies have linked elevated serum cholesterol and lipid levels to an increased risk of long-term vision loss in diabetic retinopathy. One study found an average baseline cholesterol level of 244 in those who had a persistent drop in vision to 5/200 or worse compared to 228 in those who did not develop such loss [28].

In a large meta-analysis, diabetics with macular edema have been found to have higher levels of total cholesterol, low-density lipoproteins, and serum triglycerides [29••]. Elevated cholesterol and lipid levels have also been linked to higher rates of hard retinal exudates. Compared to those with a cholesterol level <200 mg/dL, those with a cholesterol level \geq 240 mg/dL were twice as likely to have hard retinal exudates. A similar doubling of risk was seen for those with low-density lipoprotein cholesterol \geq 160 mg/dL compared to those with <130 mg/dL. There was a slightly more modest effect in those with very-low-density lipoprotein cholesterol of >61 mg/dL—1.84 times in terms of the risk compared to those with <18 mg/dL [28]. The effects of high-density lipoprotein cholesterol and triglycerides in this study were modest and not statistically significant. Other studies have not found an effect of cholesterol on risk of diabetic eye disease [24, 30].

Statins (HMG-CoA reductase inhibitors) are a common treatment for high cholesterol. Interestingly, their use prior to diabetes diagnosis has been associated with a

significantly decreased rate of development of diabetic retinopathy [31] and its use in patients with existing retinopathy has been linked to better average visual acuity improvement [32]. Fibrates are another class of medications used to treat hyperlipidemia. In the ACCORD trial, those placed on a fenofibrate had a lower rate of progression of diabetic retinopathy (6.5 vs 10.2 %) [7]. Another study also found that those on a fenofibrate had a lower rate of chance of needing laser treatment for diabetic retinopathy than those on a placebo [33].

Control of serum cholesterol and lipids is associated with a lower rate of complications from diabetic eye disease. Monitoring and treatment of serum lipids to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines of low-density lipoprotein cholesterol <100 mg/dL is a reasonable goal [34]. Fibrate medications may offer additional retinal benefits for diabetic patients and further investigation is warranted regarding the ideal role for these drugs in managing patients with diabetic retinopathy.

Obesity

There is a strong link between obesity and diabetes. Those with class 3 obesity (body mass index >40) have a 5 times higher chance of developing diabetes than normal weight individuals [35].

Increased body mass index has been linked to an increased risk of diabetic retinopathy [36]. However, not all studies have confirmed an increased risk of diabetic retinopathy in obese diabetics or those with a higher body mass index. Some studies have even found the reverse to be true, that body mass index and obesity have a protective effect [37–39]. There has been suggestion that the link between body mass index and diabetic retinopathy may be clouded by inclusion of those with type 1 or juvenile diabetes, who likely have a different metabolic risk profile [37].

The waist-to-hip ratio has been identified as a marker for abdominal obesity and has been linked to significantly higher rates of diabetic retinopathy [40, 41]. In one study, those in the highest tertile of waist-to-hip ratio had 40 times the risk of developing diabetic retinopathy. Interestingly, even increased neck and waist circumference have been linked to both increased risk of and higher severity of diabetic retinopathy [41].

Obesity is an integral part of the metabolic syndrome and weight management should be encouraged in diabetics. The effect of bariatric surgery on diabetic retinopathy is not yet fully defined but appears to be unpredictable and may even be associated with worsening of existing diabetic retinopathy after surgery [42, 43].

Inflammatory markers

Inflammatory markers have been associated with elevated risk of cardiovascular disease and cancer. They have also been associated with diabetic retinopathy. Those with both mild and severe diabetic retinopathy were shown to have significantly higher levels of CRP than their diabetic counterparts without diabetic retinopathy [36, 44]. Elevated CRP has been associated with elevated risk of clinically significant macular edema and retinal hard exudates [39, 44]. Although currently there are no recommendations for monitoring systemic inflammatory markers in diabetics, this represents an interesting area for future research.

Sleep-disordered breathing

Sleep-disordered breathing or obstructive sleep apnea (OSA) is characterized by repeated upper airway obstructions leading to blood oxygen desaturation and sleep disruption. It is highly related to obesity and is an increasingly recognized source of morbidity. In one study, 86 % of obese diabetic patients qualified for diagnosis of obstructive sleep apnea on overnight oximetry monitoring [45]. The intermittent hypoxia associated with OSA has been linked to oxidative stress at the endothelial level leading to vascular dysfunction and angiogenesis [46]. It is not surprising then that OSA has been associated with a higher rate of diabetic retinopathy [47, 48]. Makers of more severe OSA have also been linked to higher rates of neovascularization of the angle in those with diabetic retinopathy [49]. Studies have not found a link between sleep-disordered breathing and macular edema [50]; however, it has been linked to poor response to anti-vascular endothelial growth factor agents [51••].

Exercise

There are known metabolic advantages to physical activity. It is not surprising then that an increase of 10 min a day in moderate to vigorous activity was associated with a 75 % reduction in risk of developing diabetic retinopathy and an increase of 20 min is associated with a 94 % reduction for women [52]. This study did not find a statistically significant effect for men. A study of how people used their leisure time found an effect of both the intensity of leisure time activity and how often physical activity leisure time occurred. Low intensity leisure time physical activity was associated with a 1.49 times higher risk of diabetic retinopathy. Low-frequency leisure time physical activity is associated with a 2.58 increased rate of diabetic retinopathy [53]. Current physical activity recommendations for adult Americans are 150 min of at least moderate physical activity every week.

Conclusion

In conclusion, patients' risks of diabetic retinopathy and retinopathy progression are dramatically affected by his or her overall systemic health. This underscores the importance of open communication with primary care providers to ensure that these health issues are being addressed. It also highlights the opportunity ophthalmologists and other eye care providers have to educate patients about the importance of overall good health and potentially provide additional motivation to strive for better management of other systemic health concerns.

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Compliance with Ethics Guidelines

Disclosure Elizabeth Atchison and Andrew Barkmeier declare that they have no conflict of interest.

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