

Retinal and Cardiovascular Diseases: The “Common Soil” Theory

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Abstract

Retinal and cardiovascular diseases share many risk factors, such as hypertension, hyperlipidaemia and cigarette smoking. The effects of hypertension and diabetes on the retina are well known. In response to elevated blood pressure, the retinal vasculature undergoes a series of changes clinically seen as hypertensive retinopathy. Patients with hypertensive retinopathy signs are more likely to develop stroke, ischaemic heart disease, heart failure and to die from these conditions. In persons with diabetes, retinopathy is a common microvascular complication and the leading cause of blindness in working adults. Hyperglycaemia, hypertension and hyperlipidaemia are risk factors for the development and progression of diabetic retinopathy, and the presence of even early signs of retinopathy is associated with increased cardiovascular morbidity in persons with diabetes. Various cardiovascular diseases have also been associated with the development of other retinal conditions, including retinal vein occlusions, retinal arteriolar emboli and age-related macular degeneration. Ophthalmologists and physicians should therefore recognise the protean effects of cardiovascular diseases on the retina to better manage their patients.

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Introduction

There is increasing evidence that retinal and cardiovascular diseases share a “common soil”. Risk factors for cardiovascular disease, such as hypertension, diabetes, hyperlipidaemia and cigarette smoking, are known to influence the development of a range of retinal diseases, including hypertensive retinopathy, diabetic retinopathy, retinal vein and artery occlusion, retinal arteriolar emboli and age-related macular degeneration (AMD). Concurrently, many of these retinal conditions may be “markers” of underlying subclinical vascular disease and predict the future development of cardiovascular events and mortality. Understanding the inter-relationship between retinal and the cardiovascular diseases will allow both researchers and clinicians to design new preventative strategies and therapies, and to better manage patients with these conditions. This review summarises recent findings on the relationship of cardiovascular disease and common retinal conditions.

Hypertensive Retinopathy

The retinal circulation undergoes a series of pathophysi-

ological changes in response to elevated blood pressure, resulting in a spectrum of clinical signs commonly referred to as hypertensive retinopathy.¹ Hypertensive retinopathy can be classified into 3 grades of increasing severity,² consisting of “mild” retinopathy (retinal arteriolar signs such as generalised retinal arteriolar narrowing, focal arteriolar narrowing, arterio-venous nicking and arteriolar wall opacification or silver wiring), “moderate” retinopathy (blot and dot retinal haemorrhages, cotton wool spots, hard exudates and microaneurysms) and “severe” or “malignant” retinopathy (mild or moderate signs with optic disc swelling).

Recent studies using retinal photography to document hypertensive retinopathy signs show that these signs are common (up to 14% of the general non-diabetic adult population) and are strongly associated with elevated blood pressure.³⁻⁶ Studies have also used computer imaging techniques to measure generalised retinal arteriolar narrowing and have shown this sign predicts the subsequent development of hypertension in individuals initially classified as “normotensive”,⁷⁻⁹ and may thus be an early marker of pre-clinical hypertension.

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Hypertensive retinopathy signs are markers of increased cardiovascular risk. There has been consistent association of hypertensive retinopathy with stroke.^{1,10} In one large population-based study of more than 10,000 participants, patients with hypertensive retinopathy signs were 3 times more likely to develop a clinical stroke over a 3-year period than those without retinopathy.¹¹ In that study, while controlling for age, sex, race, mean arterial blood pressure, diabetes, and other stroke risk factors, retinal microvascular signs were predictive of incident stroke, with adjusted relative risks of 2.58 [95% confidence interval (CI), 1.59-4.20] for any retinopathy, 3.11 (95% CI, 1.71-5.65) for microaneurysms, 3.08 (95% CI, 1.42-6.68) for cotton wool spots, 2.55 (95% CI, 1.27-5.14) for blot haemorrhages, 2.26 (95% CI, 1.00-5.12) for flame-shaped haemorrhages, and 1.60 (95% CI, 1.03-2.47) for arteriovenous nicking. Other studies have now linked hypertensive retinopathy signs with cognitive decline,¹² subclinical cerebral disease,¹³ small artery lacunar infarctions,¹⁴ magnetic resonance imaging (MRI) defined cerebral atrophy,¹⁵ and stroke mortality.^{16,17}

Hypertensive retinopathy has also been linked with coronary artery stenosis as seen on angiography,¹⁸ and with risk of clinical coronary events in both men¹⁹ and women.²⁰ In a prospective study, “moderate” hypertensive retinopathy signs predicted a 3-fold higher incidence of congestive heart failure, even in patients without a previous myocardial infarction (relative risk 2.98; 95% CI, 1.50-5.92).²¹ These associations suggest that microvascular disease may be important in the development of heart failure in the absence of established coronary artery occlusion.

Various international clinical guidelines for the management of hypertension support the value of a retinal assessment for cardiovascular risk stratification.²² Patients with “mild” retinopathy will only require routine care. However, patients with “moderate” retinopathy may benefit from a more careful assessment of blood pressure control, evaluation of other vascular risk factors (e.g., cholesterol levels) and, if indicated, appropriate cardiovascular risk reduction therapy (e.g., cholesterol lowering drugs). Physicians should also examine the retina in the group of patients with “borderline” or “white coat” hypertension, where the presence of hypertensive retinopathy may serve as evidence of target end organ damage, thus providing the basis for initiating anti-hypertensive treatment. Patients with “severe” or “malignant” retinopathy will need urgent cardiovascular assessment and anti-hypertensive management, including possibly intravenous therapy.

There is some evidence that treatment of hypertension could reverse retinopathy changes,²³ but it remains unclear if regression of hypertensive retinopathy signs is accompanied by a reduction in cardiovascular risk. It is also

uncertain if specific medications, such as those suggested to have direct beneficial effects on microvascular structure and function (e.g., angiotension-converting enzyme inhibitors), would reduce retinopathy damage beyond the effects of lowered blood pressure alone. If so, it is possible that such medications in patients with hypertensive retinopathy may have added therapeutic value in preventing and treating cardiovascular diseases.

Diabetic Retinopathy

In patients with either type 1 or type 2 diabetes, retinopathy is the most specific microvascular complication, and one of the leading causes of visual impairment, particularly in middle-aged persons.²⁴ Diabetic retinopathy can be broadly classified into an early stage of non-proliferative retinopathy and a later, more advanced stage of proliferative retinopathy.

The 3 classic risk factors for diabetic retinopathy are hyperglycaemia, hypertension and hyperlipidaemia. These cardiovascular risk factors have been shown to be important for both the initial development of diabetic retinopathy, the subsequent progression to advanced retinopathy.

Landmark clinical trials such as the United Kingdom Prospective Diabetes Study (UKPDS) show that blood pressure control is effective in preventing visual loss from diabetic retinopathy. In the UKPDS, “tight” blood pressure control reduced the rate of progression of diabetic retinopathy by 35%, and deterioration of visual acuity by 50%, and each 10 mm Hg reduction in systolic blood pressure was associated with a 10% reduction in the risk of retinopathy.²⁵ Furthermore, there is good evidence that controlling for multiple cardiovascular risk factors has added benefits. The Steno-2 Study showed that in patients with type 2 diabetes, an intensive, multifactorial approach that targeted hyperglycaemia, hypertension and dyslipidaemia, reduced the risk of retinopathy by 60% compared with conventional treatment alone.²⁶

Diabetic retinopathy has also long been known to signal an increased risk of cardiovascular morbidity in patients. Numerous studies have now shown that patients with retinopathy have higher risk of stroke, coronary artery disease and cardiovascular mortality than patients without retinopathy, irrespective of glycaemic and blood pressure levels.²⁷⁻³³ In a prospective study on more than 1500 patients with type 2 diabetes, even the presence of mild retinopathy signs were associated with a 2-fold higher risk of stroke (relative risk 2.34; 95% CI, 1.13 to 4.86).³⁴ In another long-term follow-up study, the risk of stroke was 6-fold higher and stroke mortality 2-fold higher in diabetic patients with proliferative retinopathy than those without any retinopathy.³⁵ These data suggest that both ophthalmologists and physicians should be aware that patients with diabetic retinopathy may warrant a more careful

cardiovascular assessment and follow-up.

Retinal Vein Occlusion

Retinal vein occlusion (RVO) is a common, sight-threatening retinal vascular condition characterised clinically by dilated and tortuous retinal veins and the presence of retinal haemorrhages, cotton wool spots, and macular and optic disc oedema. RVO and cardiovascular diseases share many similar risk factors.³⁶⁻³⁸ Studies have documented strong and consistent relationships between hypertension and the risk of RVO.³⁶⁻³⁸ One study suggested that patients with hypertension were 5 times as likely to have RVO as those without hypertension.³⁶ RVO is also associated with other cardiovascular risk factors, including diabetes,^{36,37} cigarette smoking,³⁶⁻³⁸ and carotid artery disease,³⁸ and has been linked with stroke and cardiovascular mortality.³⁷

Patients with RVO should be evaluated for cardiovascular disease and risk factors such as blood pressure. It has been suggested that in young people (e.g., <40 years), assessment of possible haematological abnormalities (e.g., hyperhomocysteinaemia, anti-cardiolipin antibodies, protein S and C deficiencies, activated protein C resistance, and Factor V Leiden mutation) may also be indicated. However, the usefulness of these investigations requires further study. Although there is no evidence that treatment of cardiovascular risk factors would reduce the risk of complications associated with RVO, or prevent the development of RVO in the unaffected eye, physicians should consider this retinal condition as an indication to more closely monitor cardiovascular risk and to initiate or modify therapy.

Retinal Arteriolar Emboli and Retinal Artery Occlusion

Retinal arteriolar emboli are discrete plaque-like lesions that may be single or multiple, and are composed of cholesterol crystals or fibrin, platelets, calcium and other materials in the lumen of retinal arterioles. Asymptomatic retinal emboli are fairly common in older persons^{39,40} but are often transient. In one study, 90% of emboli detected initially were not present 5 years later at follow-up.⁴¹ Retinal emboli and cardiovascular disease also share a “common soil” with similar vascular risk factors, including hypertension, diabetes and cigarette smoking.³⁹⁻⁴³ A population-based study in Australia showed that individuals with hypertension had a 2-fold higher risk of a retinal emboli than those without hypertension,^{39,43} and amongst hypertensive persons who were also cigarette smokers, the risk was increased to 6 fold.⁴⁴

It has long been known that patients with retinal arteriolar emboli have a higher risk of developing thrombo-embolic stroke and other cardiovascular events.^{40,41,44,45} In one study, patients with retinal emboli were twice as likely to have

coronary artery disease and 4 times as likely to have carotid artery plaque as those without emboli.³⁸

Retinal artery occlusion is an uncommon consequence of emboli when the distal portions of the arterioles are fully occluded. Retinal artery occlusion is associated with a similar spectrum of cardiovascular risk factors, and may be a risk marker for stroke and cardiovascular mortality.^{46,47} In one 4-year prospective study of patients with retinal artery occlusion, the absolute risk of death was 8% per year.⁴⁸ In another study, patients with retinal artery occlusion with visible emboli had significantly higher mortality than age-gender population controls, although the risk of death was not higher among patients with retinal artery occlusion without visible emboli.⁴⁹ Thus, the presence of emboli is important for prognosis.

Physicians and ophthalmologists should conduct a systemic cardiovascular assessment in patients with retinal emboli and/or retinal artery occlusion. Identifying the source of the emboli (e.g., carotid or cardiac source) is important, although some have questioned the utility of carotid ultrasonography and the benefit of carotid endarterectomy in patients with asymptomatic retinal emboli and significant carotid artery stenosis.⁴² However, patients who have retinal emboli and detected to have atrial fibrillation may need systemic anti-coagulation.

Age-Related Macular Degeneration

AMD is the most common cause of visual impairment in patients aged 65 years and older in the Western world. AMD is characterised by the presence of drusen and pigmentary abnormalities (early AMD) with subsequent visual loss from progression of early to late AMD, involving either the development of new vessels in the choroid (commonly termed “wet” or exudative AMD) or geographic atrophy of the retina.

AMD and cardiovascular disease have also been suggested to share a “common soil”. There is now good evidence that hypertension is a risk factor for AMD, supported by both cross-sectional^{50,51} and prospective data.^{52,53} AMD also shares many other cardiovascular risk factors, notably cigarette smoking,⁵⁴⁻⁵⁶ carotid artery disease,⁵³ and systemic markers of inflammation.⁵⁷ The association of cigarette smoking with AMD is strong and consistent. In the Blue Mountains Eye Study, cigarette smoking was significantly associated with late AMD [odds ratio (OR), 3.92], including neovascular AMD (OR, 3.20) and geographic atrophy (OR, 4.54), and early age-related maculopathy (OR, 1.75).⁵⁶ In the Rotterdam study, an increase in carotid artery wall thickness (OR, 1.15; 95% CI, 1.03-1.28, per standard deviation increase in thickness) increased the risk of AMD.⁵³ In the Age-Related Eye Disease Study (AREDS), a multicentre randomised trial of antioxidant vitamins and

minerals, serum C-reactive protein levels were significantly higher among participants with advanced AMD than among those with no AMD.⁵⁷ In models adjusting for age, sex, smoking and body mass index, the OR for AMD was 1.65, comparing the highest versus the lowest quartile of C-reactive protein levels.

There is now evidence that the presence of AMD may also signify a higher risk for the development of stroke,⁵⁸ coronary artery disease,⁵⁹ and cardiovascular mortality.⁶⁰ This relationship is important as there have been a range of new treatment options for AMD, including the use of vascular endothelial growth factor (VEGF) inhibitors. These anti-VEGF inhibitors, even when administered into the eye (intra-vitreous injection), have been suggested to increase systemic haemorrhage, and may also increase cardiovascular risk.^{61,62}

There is no data that shows if lowering blood pressure or controlling other vascular risk factors has beneficial effects in preventing AMD development or progression. There is some suggestion that statin use may reduce the risk of AMD, but this remains an important aspect of future research.⁶³

Conclusions

This review highlights the close relationship between retinal and cardiovascular diseases, supporting a theory that they share a “common soil”. Cardiovascular risk factors such as hypertension and diabetes have widespread effects on the retina, and retinal diseases in turn appear to be a marker of various subclinical and clinical cardiovascular diseases, including stroke and heart disease. Thus, ophthalmologists should be aware that patients with these retinal conditions may be at increased risk of developing cardiovascular diseases. Concurrently, general physicians should be encouraged to examine the retina in patients with cardiovascular risk factors.

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