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A Clinical Review on the Holism of Ophthalmology – The Associations Between Systemic Diseases and Ocular Conditions

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ABSTRACT

This is an up-to-date review on the holism of ophthalmology, covering the associations between eyes and systemic diseases.

Ophthalmology teaching in the undergraduate medical curriculum is often very brief, which seems reasonable in view of other specialties such as internal medicine which have many life-and-death issues and numerous diseases across a wide spectrum of subspecialties. By contrast, ophthalmology gives the impression of being more specialized. However, the value which vision holds in people's hearts is usually underestimated when compared to life or limb. Moreover, the severity of visual impairment in relation to its impact on daily life is also often not proportional; in other words, mild visual impairment may have a detrimental effect on daily life, functionally and emotionally.

This review aims to provide an overview of ocular pathologies that are associated with systemic diseases with emphasis on cardiovascular and autoimmune conditions. In addition, we discuss the potential role of retinal microvascular analysis in the prevention and management of cardiovascular diseases, which has been gaining attention in recent years.

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Introduction

A survey of 11,000 people in 11 countries, conducted by Bausch & Lomb (one of the eye-care giants), demonstrated that rather than losing sight, 67% of people would rather lose 10 years of life, 68% would rather sacrifice a limb, 78% would rather lose their ability to hear and 79% would rather lose their sense of taste.[1] However, while facing numerous life-and-death issues in the medical field, we often forget that there are things that a patient may weigh even more importantly than life – such as vision.

Vision is the dominant sensory modality that the majority of human beings use to interpret the world. The ability to see provides us with a sense of security. We often only appreciate this after it's gone, which may occur even following minor issues, such as the changes in refractive error and the need for new glasses. Nevertheless, the "minor issue" of uncorrected refractive error is the commonest global cause of moderate-to-severe visual impairment according to World Health Organization,[2] even though refractive-error correction is neither difficult nor expensive.

There is also relatively less emphasis in our undergraduate curriculum on the active detection and timely referral of ocular presentations in systemic diseases and the correlation of ocular features with systemic diseases. Therefore, this review seeks to provide a non-exhaustive overview of the holism of ophthalmology to attempt to, at least in part, redress this balance.

Methods

The studies that are cited in this clinical review were retrieved from PubMed and Ovid (Embase). Titles and abstracts retrieved from search strategies were screened based on the sequence of "sort by relevance", then full texts were accessed for selected studies. Three main search methods were applied:

1) Usage of "all fields" of keywords pertaining to particular anatomical structures of the eye (e.g. retina) and "systemic diseases" or the specific name of known associated systemic diseases (e.g. "diabetes mellitus"), with or without the use of filters such as "review", "meta analysis", "published in the last 5 years" and "published in the last 10 years". Relevant studies with higher evidence levels such as meta-analyses and reviews, which can portray the holism of ophthalmology through the association with systemic diseases, were given highest priority during selection of references.

2) Single search terms, e.g. "Vogt Koyanagi Harada disease", "drug-induced uveitis" and "peripheral ulcerative keratitis", applied to "all fields" were used only once a specific system disease was confirmed to have ophthalmological associations and further information was desired.

3) To provide evidence of specific facts such as ten anatomic layers of retina, more specific keywords like "ten layers of retina" under "all fields" with filters such as "review" were used.

Some references were manually searched from the studies that were selected in the first round of abstract screening and some from the "similar articles" and "find similar" sections on PubMed and Ovid (Embase) respectively. Relevant websites, mainly http://emedicine.medscape.com and http://www.uptodate.com, with contents strongly evidence-based, were cited.

Emphasis has been placed on cardiovascular and autoimmune diseases, as these two groups can be commonly encountered in all specialties due to the high prevalence of cardiovascular diseases and the multi-systemic involvement of autoimmune diseases.

Holism of Ophthalmology (from posterior to anterior segment)

A. CARDIOVASCULAR DISEASES

1. Retina

The ocular component that is best known to have associations with cardiovascular disease is the retina. The retina, the innermost layer of the globe, is divided into outer retinal pigment epithelium (RPE) and inner neurosensory layer.[3] It is associated with diabetes mellitus, hypertension, arteriosclerosis, coronary heart disease and cerebrovascular diseases. The uniqueness of being able to view the retinal microvasculature in vivo easily, directly, and non-invasively has greatly contributed to the study of cardiovascular diseases and the potential role of retinal microvasculature properties in predicting their development[4] and progression.[5-6]

(i) Diabetic Retinopathy

Diabetic retinopathy (DR), the most important ocular manifestation of diabetes mellitus, is classified into non-proliferative retinopathy, proliferative retinopathy and maculopathy.[7] Patients are usually asymptomatic until advanced stages where blurring of vision, metamorphopsia, floaters and sudden visual loss may occur.[8] The severity of retinopathy is related to the duration of diabetes, a younger age at diagnosis, higher glycosylated hemoglobin levels, higher systolic blood pressure, use of insulin, presence of proteinuria, and low body mass.[9] Therefore, the signs of diabetic retinopathy (Table 1), of which most are easily detected on direct fundoscopy, should be actively sought, especially in those with the aforementioned risk factors.[7, 8, 10]

Table 1 – Signs of Different Types of Diabetic Retinopathy [7, 8, 10]

Types of DR	Signs
Non-proliferative	• Microaneurysms (earliest clinical sign). • Dot and blot hemorrhages. • Hard exudates. • Soft exudates. • Venous beading. • Intraretinal microvascular abnormalities (IRMA).
Proliferative	• Neovascularization (hallmark). • Preretinal hemorrhage. • Vitreous hemorrhage. • Fibrovascular tissue proliferation. • Tractional retinal detachment. • Macular oedema.
Diabetic Maculopathy/ Diabetic macular oedema (DME)	Clinically significant if any of the below occurs: • Retinal thickening occurs at or within 500 microns of the center of macula. • Hard exudates at or within 500 microns of the center of macula, if associated with thickening of adjacent retina but not residual hard exudates remaining after disappearance of retinal thickening. • Zone(s) of retinal thickening at least 1 disc area, any part of which is within 1 disc diameter of the center of macula.

Visual impairment and blindness are still major concerns in type I diabetes (DM1), despite strict glycemic control and use of laser photocoagulation[4]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) showed that wider retinal arterioles were associated with 10-fold increase in the incidence of DR in patients with type 2 diabetes (DM2) [odds ratio, OR=1.78].[11] This was further supported by a prospective cohort study (OR=4.79).[12] A cross-sectional study demonstrated that lower retinal fractals (a self-similarity characteristic of retinal vasculature where the overall shape and structure will persist regardless of changes in magnification)[13] were associated with proliferative retinopathy (OR=1.45), neuropathy (OR=1.42), nephropathy (OR=1.39), but not macrovascular disease.[14] Therefore, retinal arteriolar caliber and fractals might be useful in predicting the microvascular damage caused by diabetes, without being limited to intrinsic retinal changes.

(ii) Retinal Venous Occlusion

Retinal venous occlusion (RVO) is the second most common retinal venous disease after DR and an important cause of visual morbidity and blindness.[15] Branch RVO can be asymptomatic or produce metamorphopsia or relative scotoma, and on occasion may only be detected incidentally on fundoscopy.[16] Central RVO classically presents as sudden painless monocular visual loss or dense central scotoma, although non-ischemic type may be more subtle and present as intermittent episodes of blurred vision.[16] Retinal signs of RVO are easily detected on direct ophthalmoscopy (Table 2) and hence can be diagnosed clinically.[15, 17]

Table 2 – Clinical Signs and Systemic Risk Factors of Retinal Venous Occlusion[15, 17]

Clinical Signs	• Flame-shaped hemorrhages. • Dot and blot hemorrhages. • Cotton wool spots. • Venous tortuosity. • Macular oedema. • Optic disc swelling in the affected perfusion region.
Systemic Risk factors	• Metabolic syndrome (e.g. diabetes mellitus, hypertension, hyperlipidemia). • Arteriosclerosis. • Vascular cerebral stroke. • Blood hyperviscosity. • Thrombophilia. • Smoking. • Systemic inflammatory diseases (e.g. vasculitis and Behcet's syndrome).

A 2014 meta-analysis evidenced that, apart from the immutable risk factor of advancing age, the other risk factors for RVO are all systemic (Table 2). [15,17] Metabolic syndrome greatly increases the risk of RVO, especially if end-organ damage due to diabetes or hypertension has occurred.[15] The role of thrombophilic risk factors remains controversial, although congenital thrombophilic diseases, hyperhomocysteinemia and anticardiolipin antibodies can all increase the risk of RVO.[15] Therefore, in elderly patients with cardiovascular risk factors that present with sudden painless visual loss, RVO should be among the top differential diagnoses.

(iii) Hypertensive Retinopathy (HR)

In individuals with elevated BP, visual loss can occur due to hypertensive retinopathy (HR).[18] Hence, ophthalmoscopy has long been adopted as part of the evaluation of hypertensive patients.[18, 19] HR can be classified into mild, moderate and malignant according to population-based data (Table 3).[18] Associations with clinical CVA, subclinical CVA, cognitive decline, coronary heart disease, congestive heart failure, and cardiovascular mortality may exist once patients develop mild HR and increase proportionally with severity.[18, 20] An algorithm has been designed to provide specific management plan according HR severity.[18]

Table 3 – Classification of Hypertensive Retinopathy[18]

Severity	Retinal Signs
None	No detectable signs.
Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity ("copper wiring") of arteriolar wall, or a combination of these signs
Moderate	Hemorrhage (blot, dot, or flame-shaped), microaneurysm, cotton-wool spot, hard exudate, or a combination of these signs.
Malignant	Signs of moderate retinopathy plus swelling of the optic disk *.

* = Anterior ischemic optic neuropathy, characterized by unilateral swelling of the optic disk, visual loss, and sectorial visual- field loss, should be ruled out.

(iv) Transient monocular visual field loss (TMVL)

Transient monocular visual field loss (TMVL), typically sudden and painless,[21] is divided into embolic (eTMVL) and non-embolic (neTMVL).[22] Visual field loss can be sectorial (''curtain effect'') or altitudinal, which strongly suggests vascular etiology.[23,24] This may follow the horizontal meridian in a branch retinal arterial occlusion or follow the vertical meridian in a posterior ciliary arterial occlusion, which will also require investigation to exclude a possible occipital stroke [22].

eTMVL is associated with increased stroke risk and hence requires urgent assessment.[22] The source of emboli can be the heart, carotid artery or aorta.[22] There might be co-existing atrial fibrillation, past or recent cardiac ischemia, metabolic syndrome and hypercoagulability.[22]

For central retinal arterial occlusion (CRAO), fundoscopy can be carried out to detect a fibrin-platelet thrombus or cholesterol embolus (a Hollenhorst plaque) within the lumen of the central retinal artery (15-29% detection rate on direct ophthalmoscopy) and retinal infarction with a cherry red spot (during acute phase, 90% of all cases with permanent visual loss and 59% of transient cases).[22,25] Other acute phase signs of CRAO include retinal opacities (59%), visible emboli (15%), disc oedema (11%), disc pallor (11%), attenuated retinal arteries (11%), cotton-wool spots (7%), and attenuated veins (7%).[22]

neTMVL is thought to be associated with retinal vasospasm, which, if observed during direct fundoscopy, is diagnostic.[22] Hence, a broader differential diagnoses of secondary vasospasm should be considered when suspecting neTMVL – including autoimmune diseases (e.g. giant cell arteritis, systemic lupus erythematosus and rheumatoid arthritis); infectious diseases (e.g. bacterial meningitis); vascular diseases (e.g. subarachnoid hemorrhage and intracerebral hemorrhage); and other causes (e.g. malignancy and beta blocker usage).[22]

(v) Cardiovascular Diseases

According to the World Health Organization, cardiovascular disease, particularly ischemic heart disease, cerebrovascular diseases and diabetes mellitus are within the top 10 causes of mortality since 2000 and will continue as such at least till 2030, irrespective of the income levels.[26, 27]

A 2009 review summarized the relationship between retinal vascular caliber with various systemic factors,

such as age, hypertension, obesity, coronary artery disease, smoking, and systemic inflammation.[28] Recent data also demonstrated a potential genetic contribution.[28]

Retinal vascular caliber is usually quantified on digitized or digital retinal images with computer-assisted programs, and cannot be accurately measured clinically as yet.[29] However, it is important to be aware of the rapidly growing importance of the role of non-invasive retinal microvasculature analysis on the prediction, prevention and monitoring of cardiovascular diseases, which has the potential for significant impact on morbidity and mortality in the future.[6,28]

The reduction in flicker light-induced retina-arterial vasodilation, which has been shown to be endothelium- and nitric-oxide-dependent, has also been shown to be associated with cardiovascular risk factors, such as diabetes mellitus.[6] Multiple reviews concluded that since endothelial dysfunction precedes the development of morphological vascular changes, the assessment of endothelial function could have a diagnostic value, especially in patients with cardiovascular risk factors.[6,29]

2. Optic nerve

(i) Ischaemic optic neuropathy (ION)

Ischaemic optic neuropathy (ION), a major cause of blindness or severe visual impairment, was discussed in detail in a 2009 review.[30] Non-arteritic anterior ischemic optic neuropathy (NA-AION) is by far the most common type among the 6 distinct clinical categories of ION and one of the most prevalent and visually crippling diseases in the middle-aged and elderly.[30] NA-AION is associated with arterial hypertension, arterial hypotension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atherosclerosis, and arteriosclerosis.[30] The majority of cases present with sudden, painless visual deterioration, particularly loss of the nasal fields, discovered upon waking up in the morning.[30,31] Photophobia is common in bilateral cases.[30] Other signs which may be elicited during clinical examination include relative afferent pupillary defects in unilateral cases, optic disc oedema, splinter hemorrhage on the optic disc or in the peripapillary region, serous retinal detachment, and macular edema.[30]

Arteritic AION (A-AION), although less common, is an ocular emergency that is almost invariably caused by giant cell arteritis (GCA), with the single strongest risk factor being age.[32] GCA, which is associated with increased cardiovascular risk, is mainly a clinical diagnosis and has to be actively sought, especially in elderly patients, based on the American College of Rheumatology 1990 criteria (Table 4), which have a sensitivity of 95.3% and specificity of 90.7%.[33] A-AION requires early diagnosis and immediate treatment with systemic high dose corticosteroids to reduce the risk of further visual loss.[31, 34]

Table 4 – The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis[33]

Old Criteria of 5	Classification Tree of 6 Criteria
• age greater than or equal to 50 years at disease onset. • new onset of localized headache. • temporal artery tenderness or decreased temporal artery pulse. • * elevated erythrocyte sedimentation rate (Westergren) greater than or equal to 50 mm/hour. • biopsy sample including an artery, showing necrotizing arteritis, characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells.	• age greater than or equal to 50 years at disease onset. • new onset of localized headache. • temporal artery tenderness or decreased temporal artery pulse. • biopsy sample including an artery, showing necrotizing arteritis, characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells. • * scalp tenderness. • * claudication of the jaw or tongue or on deglutition.

** = Differences between old and new criteria, either removed or newly added.*

B. AUTOIMMUNE DISEASES

1. Uvea

The uvea consists of the iris, ciliary body and choroid.[35] Uveitis, most often unilateral and idiopathic, is characterized by the potentially sight-threatening intraocular inflammation of the uveal tract, although inflammation of adjacent tissues, such as the retina, optic nerve and vitreous humor may also occur.[36] Uveitis is the commonest ophthalmological finding in the practice of rheumatology and clinical immunology and requires urgent evaluation by ophthalmologists due to the risk of blindness if treatment is delayed.[35]

Classification is most commonly based on the primary anatomical site of inflammation.[37-43] The International Uveitis Study Group has also proposed a simplified clinical classification based on suspicion of infection in order to facilitate the evaluation and diagnosis of uveitis.[40, 44] The presentation of uveitis and its relationship with systemic diseases is summarized in Table 5.[35,40-42,45,46§]

Table 5 – Presentations of Uveitis and Its Relationship with Systemic Diseases

Types of Uveitis	Ocular symptoms and signs	Relationship with systemic diseases
Anterior uveitis	• Eye redness. • Blurred vision. • Photophobia. • Periorbital pain. • Floaters. • Leukocytes in anterior chamber (non-specific). • Haze/Flare, i.e. protein accumulation in aqueous humor (Slit-lamp).	• Dependent on underlying disease course (e.g. ankylosing spondylitis). • Independent of underlying disease course (e.g. inflammatory bowel disease).
Intermediate uveitis	• Similar to posterior uveitis. • Leukocytes in vitreous humor (diagnostic). • Exudates/"snowbanks" (signifies pars planitis; detected by scleral depression).	• Develop systemic disease within 10 years (e.g. multiple sclerosis).
Posterior uveitis	• Blurred vision to severe visual loss. • Floaters. • Flashes. • Less likely to be red and painful. • Evidence of active chorioretinal inflammation (diagnostic).	• Cardinal part of the underlying systemic disease (e.g. Behcet's disease).
Pan uveitis	• Inflammation detected simultaneously of all layers of uvea (anterior chamber, vitreous, retina/ choroid). • Combination of symptoms and signs above.	• Cardinal part of the underlying systemic disease (e.g. Vogt-Koyanagi Harada syndrome and Behcet's disease).

As the underlying systemic causes of uveitis are usually autoimmune or inflammatory diseases, corticosteroids and other immunosuppressants are often indicated and this may lead to side effects, such as cataract, glaucoma, central obesity, metabolic diseases, opportunistic infections, and liver and renal toxicity.

Although more than half of uveitis cases have no identifiable cause, all types of uveitis (based on anatomic classification) can be drug-induced.[47, 48] The culprits can be systemic, intraocular or topical medications that are commonly encountered, such as cidofovir, sulfonamides, bisphosphonates, anti-vascular endothelial growth factor, triamcinolone, metipranolol, theBacillus Calmette-Guérin vaccine and the MMR vaccine.[47] The strength of association between causative drugs and uveitis are scored and categorized according to Naranjo's Classification Criteria.[47, 49]

2. Cornea, Conjunctiva and Eyelid

Many systemic diseases that affect the cornea also involve the conjunctiva. Systemic inflammatory disorders, which might be life-

threatening, such as connective tissue diseases, autoimmune diseases of the lacrimal system, and graft-versus-host-disease (GVHD) can affect the cornea and potentially lead to blindness.[50, 51] Prompt referral to an ophthalmologist consultation is therefore recommended.[50-57]

(i) Keratoconjunctivitis sicca (KCS)

The commonest ocular finding in these patients is keratoconjunctivitis sicca (KCS) [50,51]. KCS can be synonymous with dry eye disease (DED) or refer only to DED caused by aqueous tear deficiency.[50, 58-60] Dry eye disease (DED) is a multifactorial disease that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface, accompanied by increased osmolarity of the tear film and inflammation.[58] The common symptoms are dryness, irritation, foreign body sensation, photophobia, and itching.[61]

DED is usually classified by aetiologies, which can be due to pathological or systemic factors. It is generally divided into aqueous deficiency, which largely depends on lacrimal gland function (e.g. Sjogren syndrome, ageing, sarcoidosis, lymphoma and cicatricial diseases) and evaporative causes (e.g. meibomian gland dysfunction, disorders of lid aperture and globe congruity, contact lens wear, allergic conjunctivitis and vitamin A deficiency).[58,62-63]

DED is usually diagnosed via ocular surface dye staining, fluorescein tear break-up time, the Schirmer test or symptom questionnaires, although newer methods with higher sensitivity and specificity have been reported, e.g. tear film osmolarity, tear fluid protein immunoassays, and fluorescein tear clearance.[64,65] A diagnostic algorithm was designed and deemed better than single test alone.[65,66] McMonnies questionnaire is one of the earliest and most widely used DED screening tools with 87 - 98% sensitivity reportedly and 87 – 97% specificity.[67,68-69]

(ii) Other Corneal/Conjunctival/Eyelid Involvements

In GVHD, apart from KCS, the cornea may show filamentary keratitis, superficial punctate keratitis, corneal ulcers, and peripheral corneal melting which may lead to perforation in severe cases.[51] Severe dry eye syndrome may occur and later develop conjunctival scarring, keratinization, and cicatrization, which can be detected by on clinical examination.[51] Eyelid changes leading to scleroderma-like appearance may occur, including poliosis (loss of melanin in eyelashes), madarosis (loss of eyelashes), vitiligo, lagophthalmos, and entropion.[51] Nevertheless, all the layers of the eye can be involved in ocular GVHD, although posterior eye involvement is very rare.[51]

Peripheral ulcerative keratitis (PUK) although rare, might be an indicator of more severe and widespread systemic vasculitis.[50] Sclerosing keratitis, the peripheral thickening and opacification of the corneal stroma adjacent to the site of inflammation secondary to scleritis, may be associated with rheumatoid arthritis.[50,70] Calcific band keratopathy, a chronic degenerative condition characterized by the deposition of grayish opacities in the superficial layers of the cornea, most frequently in the interpalpebral zone, is commonly associated with chronic ocular inflammatory diseases.[50, 71] It is one of the commonest ocular complications (38%) of juvenile idiopathic arthritis.[72]

3. Sclera

Scleritis is an uncommon, heterogeneous group of diseases characterized by inflammation of the sclera, which may be caused by local or systemic infections or immune mediated diseases.[73,74] Rheumatoid arthritis remains the commonest disease that is associated with all types of scleritis.[74] There are various etiologies of scleritis but the systemic autoimmune or vasculitic diseases are implicated in half of all cases.[74-76] All of these cause scleral inflammation, which results to readily detectable changes in the visible coats of episclera and conjunctiva. However, episcleritis and scleritis may be distinguished based on history and physical examinations.[77] Both scleritis and episcleritis can present as red eye.[77] However, scleritis is more likely to present as a sudden onset of deep, severe periorbital pain with radiation to the temple and jaw and often wakes patients at night. 50% of cases have underlying systemic symptoms. By contrast, episcleritis is usually painless and less likely to have systemic symptoms.[77]

4. Orbit, Extraocular muscles and Eyelids

(i) Graves' Ophthalmopathy (GO)

Graves' ophthalmopathy (GO), also known as thyroid eye disease, is the commonest (25%)

extra-thyroidal manifestation of Grave's Disease (GD).[78] Bilateral GO usually occurs simultaneously or within 18 months of hyperthyroidism in GD, although occasionally GO and GD can happen separately with many years in between.[79] Clinical presentations of GO and GD are described in table 6.[80] Cigarette smoking is the strongest modifiable risk factor of GO and exists in dose-dependence relationship, so smoking history should be taken in detail.[81]

Table 6 – Clinical Presentations of Grave's Ophthalmopathy (GO) and Grave's Disease (GD)

Diseases	Symptoms	Signs
GO	• Dryness. • Gritty ocular sensation, • Photophobia. • Excessive tearing, • Double vision. • Pressure sensation behind the eyes. • Pain.	• Edema and erythema of the periorbital tissues and conjunctivae. • Proptosis. • Corneal ulcer (due to lagophthalmos). • Upper eyelid retraction. • Lid lag on downgaze (von Graefe sign). • Absence of forehead creases on upgaze (Joffroy sign). • Poor convergence (Möbius sign). • Extraocular muscle restriction (Ballet sign). • Relative afferent pupillary defect. • Visual field loss. • Color vision deficiency.
GD	• Heat intolerance. • Restlessness. • Fatigability. • Increased appetite. • Weight loss. • Palpitations. • Diarrhea. • Amenorrhea. • Irregular menstrual period.	• Goiter (simple and diffuse). • Tremor. • Arrhythmia (e.g. atrial fibrillation). • Proximal muscle weakness. • Thyroid acropachy (clubbing of the fingers and toes). • Pretibial myxedema (a nodular or diffuse thickening of the pretibial skin).

Conclusion

There are multiple systemic diseases and therapies that are associated with ocular problems in all parts of the eye. A high index of suspicion is necessary to actively detect these conditions and refer patients timeously when indicated to allow the highest possibility of visual recovery. In addition, the role of retinal microvascular analysis, including retinal vascular caliber, fractals, arteriovenous ratio and flicker light-induced retina-arterial vasodilation, should be further pursued to improve the prediction, prevention and management of cardiovascular disease worldwide.

What are known already:	What this study adds/ highlights:
• Ocular diseases with cardiovascular associations include diabetic retinopathy, retinal venous and artery occlusion, hypertensive retinopathy, transient monocular visual field loss, and ischemic optic neuropathy. • Ocular diseases with autoimmune assocations include uveitis, dry eye disease/ keratoconjunctivitis sicca, ocular graft-versus-host-disease, peripheral ulcerative keratitis, sclerosing keratitis, calcific band keratopathy, scleritis, and Graves' Ophthalmopathy. • The commoner systemic diseases that have ocular associations are cardiovascular diseases (diabetes mellitus, hypertension and hyperlipidemia) and autoimmune or inflammatory diseases (rheumatoid arthritis, spondyloarthropathies, inflammatory bowel diseases, Wegener granulomatosis).	• Vision is actually considered more important than lifespan or loss of a limb in the majority of people. • Retinal microvascular analysis has the potential to develop an important role in the prediction, prevention, monitoring and prognosis of cardiovascular diseases. • Certain medications (systemic, intraocular and topical) are important but often-overlooked causes of uveitis.

References

1. Bausch + Lomb. *Globally, We Are Losing Sight of Our Eye Health, a New Public Opinion Poll Reveals.* [Online] Available from http://www.bausch.com/our-company/NewsRoom/2012-archive/barometer [Accessed on 23rd March 2015]
2. World Health Organization. *Visual impairment and blindness.* [Online] Available from http://www.who.int/mediacentre/factsheets/fs282/en/ [Accessed on 23rd March 2015]
3. Jaffe GJ, Caprioli J. Optical coherence tomography to detect and manage retinal disease and glaucoma. American journal of ophthalmology. 2004;137(1):156-69.
4. Michelson EL, Morganroth J, Nichols CW, MacVaugh H, 3rd. Retinal arteriolar changes as an indicator of coronary artery disease. Arch Intern Med. 1979;139(10):1139-41.
5. Tedeschi-Reiner E, Strozzi M, Skoric B, Reiner Z. Relation of atherosclerotic changes in retinal arteries to the extent of coronary artery disease. Am J Cardiol. 2005;96(8):1107-9.
6. Flammer J, Konieczka K, Bruno RM, Virdis A, Flammer AJ, Taddei S. The eye and the heart. Eur Heart J. 2013;34(17):1270-8.
7. Wilkinson CP, Ferris FL, 3rd, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677-82.
8. Medscape. *Diabetic Retinopathy Clinical Presentation.* [Online] Available from http://emedicine.medscape.com/article/1225122-clinical#showall [Accessed on 21st June 2015]
9. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984;102(4):527-32.
10. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796-806.
11. Grauslund J. Eye complications and markers of morbidity and mortality in long-term type 1 diabetes. Acta ophthalmologica. 2011;89 Thesis 1:1-19.
12. Rogers SL, Tikellis G, Cheung N, Tapp R, Shaw J, Zimmet PZ, et al. Retinal arteriolar caliber predicts incident retinopathy: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Diabetes Care. 2008;31(4):761-3.
13. Masters BR. Fractal analysis of the vascular tree in the human retina. Annu Rev Biomed Eng. 2004;6:427-52.
14. Grauslund J, Green A, Kawasaki R, Hodgson L, Sjolie AK, Wong TY. Retinal vascular fractals and microvascular and macrovascular complications in type 1 diabetes. Ophthalmology. 2010;117(7):1400-5.
15. Kolar P. Risk factors for central and branch retinal vein occlusion: a meta-analysis of published clinical data. Journal of ophthalmology. 2014;2014:724780.
16. Medscape. *Retinal Vein Occlusion Clinical Presentation.* [Online] Available from http://emedicine.medscape.com/article/798583-clinical#showall. [Accessed on 21st June 2015]
17. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 2000;98:133-41; discussion 41-3.
18. Wong TY, Mitchell P. Hypertensive retinopathy. The New England journal of medicine. 2004;351(22):2310-7.
19. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens. 1999;17(2):151-83.
20. Wong TY, McIntosh R. Hypertensive retinopathy signs as risk indicators of cardiovascular morbidity and mortality. Br Med Bull. 2005;73-74:57-70.
21. Fisher CM. Observations of the fundus oculi in transient monocular blindness. Neurology. 1959;9(5):333-47.
22. Petzold A, Islam N, Hu HH, Plant GT. Embolic and nonembolic transient monocular visual field loss: a clinicopathologic review. Survey of ophthalmology. 2013;58(1):42-62.
23. Gautier JC. Amaurosis fugax. The New England journal of medicine. 1993;329(6):426-8.
24. Marshall J, Meadows S. The natural history of amaurosis fugax. Brain. 1968;91(3):419-34.
25. Hayreh SS, Zimmerman MB. Fundus changes in central retinal artery occlusion. Retina (Philadelphia, Pa). 2007;27(3):276-89.
26. World Health Organization. *The top 10 causes of death.* [Online] Available from http://www.who.int/mediacentre/factsheets/fs310/en/ [Accessed on 23rd March 2015]
27. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.
28. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. Survey of ophthalmology. 2009;54(1):74-95.
29. Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, et al. The assessment of endothelial function: from research into clinical practice. Circulation. 2012;126(6):753-67.
30. Hayreh SS. Ischemic optic neuropathy. Progress in retinal and eye research. 2009;28(1):34-62.
31. Hayreh SS, Podhajsky PA, Zimmerman B. Nonarteritic anterior ischemic optic neuropathy: time of onset of visual loss. American journal of ophthalmology. 1997;124(5):641-7.
32. Nordborg E, Nordborg C. Giant cell arteritis: epidemiological clues to its pathogenesis and an update on its treatment. Rheumatology (Oxford, England). 2003;42(3):413-21.
33. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122-8.Borchers AT, Gershwin ME. Giant

cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmunity reviews. 2012;11(6-7):A544-54.
34. Selmi C. Diagnosis and classification of autoimmune uveitis. Autoimmunity reviews. 2014;13(4-5):591-4.
35. International Uveitis Study Group. *What is uveitis.* [Online] Available from http://www.iusg.net/page7/What_is_Uveitis.html [Assessed on 29th March 2015]
36. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. American journal of ophthalmology. 1987;103(2):234-5.
37. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. American journal of ophthalmology. 2005;140(3):509-16.
38. Khairallah M. Are the Standardization of the Uveitis Nomenclature (SUN) Working Group criteria for codifying the site of inflammation appropriate for all uveitis problems? Limitations of the SUN Working Group classification. Ocular immunology and inflammation. 2010;18(1):2-4.
39. UpToDate. *Uveitis: Etiology, clinical manifestations and diagnosis.* [Online] Available from http://www.uptodate.com.eproxy1.lib.hku.hk/contents/uveitis-etiology-clinical-manifestations-and-diagnosis?source=search_result&search=uveitis+etiology&selectedTitle=1%7E15 [Accessed on 21st June 2015]
40. Zein G, Berta A, Foster CS. Multiple sclerosis-associated uveitis. Ocular immunology and inflammation. 2004;12(2):137-42.
41. Pan D, Hirose T. Vogt-Koyanagi-Harada syndrome: review of clinical features. Seminars in ophthalmology. 2011;26(4-5):312-5.
42. Mat MC, Sevim A, Fresko I, Tuzun Y. Behcet's disease as a systemic disease. Clinics in dermatology. 2014;32(3):435-42.
43. Deschenes J, Murray PI, Rao NA, Nussenblatt RB. International Uveitis Study Group (IUSG): clinical classification of uveitis. Ocular immunology and inflammation. 2008;16(1):1-2.
44. Max R, Lorenz HM, Mackensen F. [Ocular involvement in spondyloarthropathies: HLA B27 associated uveitis]. Zeitschrift fur Rheumatologie. 2010;69(5):397-402.
45. Trikudanathan G, Venkatesh PG, Navaneethan U. Diagnosis and therapeutic management of extra-intestinal manifestations of inflammatory bowel disease. Drugs. 2012;72(18):2333-49.
46. Moorthy RS, London NJ, Garg SJ, Cunningham ET, Jr. Drug-induced uveitis. Current opinion in ophthalmology. 2013;24(6):589-97.
47. Shifera AS, Kopplin L, Lin P, Suhler EB. Drug-induced uveitis. Int Ophthalmol Clin. 2015;55(2):47-65.
48. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
49. Gomes BA, Santhiago MR, Jorge PA, Kara-Jose N, Moraes HV, Jr., Kara-Junior N. Corneal Involvement in Systemic Inflammatory Diseases. Eye & contact lens. 2015.
50. Nassar A, Tabbara KF, Aljurf M. Ocular manifestations of graft-versus-host disease. Saudi journal of ophthalmology : official journal of the Saudi Ophthalmological Society. 2013;27(3):215-22.
51. Sotozono C, Ueta M, Koizumi N, Inatomi T, Shirakata Y, Ikezawa Z, et al. Diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis with ocular complications. Ophthalmology. 2009;116(4):685-90.
52. Sotozono C, Ang LP, Koizumi N, Higashihara H, Ueta M, Inatomi T, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. Ophthalmology. 2007;114(7):1294-302.
53. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. The New England journal of medicine. 1994;331(19):1272-85.
54. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310(16):1721-9.
55. Mahmood AR, Narang AT. Diagnosis and management of the acute red eye. Emerg Med Clin North Am. 2008;26(1):35-55, vi.
56. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Survey of ophthalmology. 1999;43(5):379-96.
57. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5(2):75-92.
58. Adatia FA, Michaeli-Cohen A, Naor J, Caffery B, Bookman A, Slomovic A. Correlation between corneal sensitivity, subjective dry eye symptoms and corneal staining in Sjogren's syndrome. Canadian journal of ophthalmology Journal canadien d'ophtalmologie. 2004;39(7):767-71.
59. de AFGB, Santhiago MR, de Azevedo MN, Moraes HV, Jr. Evaluation of dry eye signs and symptoms in patients with systemic sclerosis. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2012;250(7):1051-6.
60. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol. 2012;130(1):90-100.
61. Tavares Fde P, Fernandes RS, Bernardes TF, Bonfioli AA, Soares EJ. Dry eye disease. Seminars in ophthalmology. 2010;25(3):84-93.
62. Alves M, Angerami RN, Rocha EM. Dry eye disease caused by viral infection: review. Arq Bras Oftalmol. 2013;76(2):129-32.
63. Bron AJ. Diagnosis of dry eye. Survey of ophthalmology. 2001;45 Suppl 2:S221-6.
64. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. Cornea. 2000;19(5):644-9.

65. Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea. 1998;17(1):38-56.
66. McMonnies C, Ho A, Wakefield D. Optimum dry eye classification using questionnaire responses. Adv Exp Med Biol. 1998;438:835-8.
67. McMonnies CW, Ho A. Patient history in screening for dry eye conditions. J Am Optom Assoc. 1987;58(4):296-301.
68. Gothwal VK, Pesudovs K, Wright TA, McMonnies CW. McMonnies questionnaire: enhancing screening for dry eye syndromes with Rasch analysis. Investigative ophthalmology & visual science. 2010;51(3):1401-7.
69. Zlatanovic G, Veselinovic D, Cekic S, Zivkovic M, Dordevic-Jocic J, Zlatanovic M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. Bosn J Basic Med Sci. 2010;10(4):323-7.Jhanji V, Rapuano CJ, Vajpayee RB. Corneal calcific band keratopathy. Current opinion in ophthalmology. 2011;22(4):283-9.
70. Paroli MP, Abbouda A, Restivo L, Sapia A, Abicca I, Pivetti Pezzi P. Juvenile idiopathic arthritis-associated uveitis at an Italian tertiary referral center: clinical features and complications. Ocular immunology and inflammation. 2015;23(1):74-81.
71. Wakefield D, Di Girolamo N, Thurau S, Wildner G, McCluskey P. Scleritis: Immunopathogenesis and molecular basis for therapy. Progress in retinal and eye research. 2013;35:44-62.
72. Wakefield D, Di Girolamo N, Thurau S, Wildner G, McCluskey P. Scleritis: challenges in immunopathogenesis and treatment. Discovery medicine. 2013;16(88):153-7.
73. Sainz de la Maza M, Molina N, Gonzalez-Gonzalez LA, Doctor PP, Tauber J, Foster CS. Clinical characteristics of a large cohort of patients with scleritis and episcleritis. Ophthalmology. 2012;119(1):43-50.
74. Watson PG, Hayreh SS. Scleritis and episcleritis. The British journal of ophthalmology. 1976;60(3):163-91.
75. Hakin KN, Watson PG. Systemic associations of scleritis. Int Ophthalmol Clin. 1991;31(3):111-29.
76. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. The Journal of clinical endocrinology and metabolism. 2013;98(4):1443-9.
77. Wiersinga WM, Smit T, van der Gaag R, Koornneef L. Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. Journal of endocrinological investigation. 1988;11(8):615-9.
78. Bahn RS. Graves' ophthalmopathy. New England Journal of Medicine. 2010;362(8):726-38+74.
79. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. JAMA. 1993;269(4):479-82.