

# Retinal Microvascular Signs In Adults With Hypertension: Systemic Associations And Risk Reduction

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## Abstract

Eyes are the portals through which one can glimpse signs of certain health problems. Retinal microvascular signs are common fundus findings in the general population; even in individuals without hypertension or diabetes. This paper provides new insights into the clinical significance of retinal microvascular signs in adults with elevated blood pressure so as to aid in identifying susceptible individuals with certain retinopathy signs who need further referral and systemic assessment for appropriate risk reduction therapy. It provides evidence based information on the systemic associations of hypertensive retinopathy signs, classification of these signs, clinical guidelines for hypertension management and critiques some famous 'population-based' studies describing the relationship of retinal microvascular signs, as quantified from fundus photographs, to various systemic diseases in the general population and discusses their relevance in context of current hypertension management.

## BACKGROUND

Eyes are the windows to the soul, as an ancient English proverb has it. They are portals through which one can glimpse signs of certain health problems; not only eye disorders like cataracts and glaucoma, but also systemic illnesses like diabetes mellitus, cardiovascular disease and even impending stroke. Interestingly, the signs of these diseases are visible in, on, or around the eyes long before physical symptoms appear. Eyes truly are unique in the sense that they are the only place in the body where one can see a bare nerve, artery and vein without doing any cutting. The apparent condition of these structures reflects the disease processes occurring in the eye and probably occurring in the rest of the body as well. (King, 2008) Retinal microvascular signs, like generalized retinal arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, retinal haemorrhages, microaneurysms and cotton wool spots are common fundus findings in the general population; even in individuals without hypertension or diabetes. (Kovach, 2012) This paper enumerates what eye signs might be saying about one's health in order to provide new insights into the systemic associations and clinical significance of retinal microvascular signs in adults with elevated blood pressure. The authors have reviewed several population based studies that used retinal photography to quantify retinal microvascular signs and computer-imaging

techniques to define generalized retinal arteriolar narrowing in highly consistent research settings. Thus, their findings can be validated and standardized to aid in identifying susceptible individuals with certain retinopathy signs who need further referral and systemic assessment for appropriate risk reduction therapy of subclinical and clinical stroke, cognitive impairment, renal dysfunction and cardiovascular mortality.

## LITERATURE SEARCH

The authors conducted a structured review of recent studies on the systemic associations of retinal microvascular signs and their implications in current hypertension management, with special reference to 'population based' researches. Data sources were Medline, Embase, Cochrane, Sciverse scopus, Google Scholar and Gray literature database. Keywords used for the search were based on MeSh terms: cardiovascular disease, cerebrovascular disease, coronary heart disease, epidemiology, hypertensive retinopathy, retinal arteriolar disease, retinal microvascular abnormalities and stroke. Search was restricted to articles published in English and publications from 1979 onwards using search engines of PubMed, Science Direct, MD consult, Ovid.

## META-ANALYSIS

The initial search resulted in a total of 366 abstracts retrieved from these databases. Inclusion criteria were studies based on clinical significance of hypertensive retinopathy signs,

classification of these signs, reviews of hypertensive retinopathy, clinical guidelines for hypertension management, population-based studies describing the relationship of retinal microvascular signs, as quantified from fundus photographs, to various systemic diseases in the general population. 46 papers met our inclusion criteria, based on context relevance. Further literature search was done through 'reference list harvesting', 'citation alerts' and 'related articles feature'. All the abstracts were first reviewed to exclude the duplicate or incongruous studies. Complete articles were accessed for appropriate studies, followed by comprehensive content exploration and subsequent reflective synthesis of their findings on a generalized 5 point scale covering the following sub-domains: Retinal signs, Systemic associations, Study type, Researchers, Study period, Strength of association. The studies were categorized in terms of Atherosclerosis Risk in Communities Study (ARIC), Cardiovascular Health Study (CHS) and Screening type Eye Study (ES). Systemic associations established by these studies were graded in terms of strength (Strong/Moderate/Weak) through Relative risk / Odds ratio (2.0 =Strong, 1.5 to 2.0 =Moderate, <1.5 =Weak). Grading was done independently by two reviewers and a final consensus was reached for any conflicting scores before charting the results.

**RESULTS**

A meta-analysis of systemic associations of retinal microvascular signs in previous population-based studies on hypertensive subjects is presented in Table 1.

**Table 1A**

A meta-analysis of systemic associations of retinal microvascular signs in previous population-based studies on hypertensive subjects is presented in Table 1.

Retinal signs	Systemic associations	Study type*	Researchers and study period	Strength of association **	
Retinal haemorrhages	Current blood pressure	ARIC ES	Sharrett et al., 2009 Wang et al., 2012 Wong et al., 2003a Wong et al., 2002a	Strong	
		CHS			
Microaneurysm	Carotid artery disease	ARIC CHS	Klein et al., 2010 Wong et al., 2003c	Strong	
Arterio-venous nicking	Current blood pressure	ARIC ES	Sharrett et al., 2009 Wang et al., 2003, Klein et al., 1994, Klein, et al., 1997 Wong et al., 2002a	Strong	
		CHS			
	Past blood pressure	ARIC CHS	Sharrett et al., 1999 Wong et al., 2002a	Strong	
	Inflammatory markers	ARIC	Klein et al., 1999	Weak	
		ARIC	Klein et al., 1999		
	Endothelial dysfunction		ARIC ES	Wong et al., 2004a Leung et al., 2005	Weak
	Metabolic syndrome		ARIC ES	Wong et al., 2011a, 2002b Mitchell et al., 2001	Weak
Incident clinical stroke		ARIC	Wong et al., 2002b	Moderate	
Subclinical cerebral disease		ARIC	Wong et al., 2004b	Moderate	
Focal arteriolar narrowing	Renal dysfunction	ARIC ES	Sharrett et al., 1999 Wang et al., 2006, 2003, Klein et al., 1994, 1997	Weak	
		CHS	Wong et al., 2002a		

**Table 1B**

A meta-analysis of systemic associations of retinal microvascular signs in previous population-based studies on hypertensive subjects is presented in Table 1.

Generalized arteriolar narrowing	Incident hypertension	ARIC ARIC ES	Wong et al., 2004c Wong et al., 2004c Smith et al., 2007	Moderate
	Metabolic syndrome	ARIC	Wong et al., 2004a	Weak
	Current blood pressure	ARIC ES	Sharrett et al., 1999 Wang et al., 2003, Klein et al., 1994	Strong
		CHS	Wong et al., 2002a, Ikram et al., 2004	
	Inflammatory markers	ARIC ES	Klein et al., 1999 Ikram et al., 2004	Weak
	Carotid atherosclerosis	ARIC ES	Klein et al., 2006 Liao et al., 2004 Ikram et al., 2009	Moderate
	Metabolic syndrome	ARIC ES	Wong et al., 2004a Leung et al., 2005	Weak
	Incident clinical stroke	ARIC ES	Wong et al., 2011a, 2002b Mitchell et al., 2012	Weak
	Incident heart disease	ARIC	Wong et al., 2002c	Moderate
	Cardiovascular mortality	ES	Wong et al., 2003b	Weak

\* Atherosclerosis Risk in Communities Study (ARIC)  
Cardiovascular Health Study (CHS)  
Eye Study (ES)  
\*\* Relative risk / odds ratio >2.0 (Strong), 1.5 to 2.0 (Moderate), <1.5 (Weak).

**Synthesis**

Certain common findings emerged from a systemic analysis of the results of previous population based studies. They are as follows: Hypertensive retinopathy signs carry substantial clinical significance for past, present and even future health related events of their subjects. (Table2) Retinal haemorrhages, microaneurysms and cotton wool spots are associated with considerable risk of subclinical and clinical stroke, cognitive impairment, renal dysfunction and cardiovascular mortality; independent of BP and cardiovascular risk factors like age, gender, diabetes, smoking, body mass index. A consistent pattern of association between retinal microvascular signs and ischaemic heart disease has not yet been demonstrated unequivocally. Evidence suggests that patients with some retinopathy signs like retinal haemorrhages, microaneurysms and cotton wool spots may benefit from a careful systemic evaluation and appropriate risk reduction therapy. In individuals whose BP is 20/10 mmHg above the systolic and diastolic BP target, initiation of therapy using pharmacological agents like Thiazide diuretics and ACE

inhibitors should be considered.

**Table 2**

Classification of retinal microvascular signs, their systemic associations and management. \*

Grades	Description	Systemic associations	Suggested management
Mild	Generalized arteriolar narrowing and focal arteriolar narrowing, arterio-venous nicking, arteriolar wall opacity (silver-wiring)	Moderate and weak associations with stroke, ischaemic heart disease, cardiovascular mortality	Routine care Closer monitoring of blood pressure. Better control of blood pressure in persons with known hypertension.
Moderate	Retinal haemorrhage (dot, dot or flame-shaped), microaneurysms, cotton wool spot, hard exudates	Strong association with stroke, cognitive decline, congestive heart failure, renal dysfunction, and cardiovascular mortality	May require physician referral Need to exclude diabetes. Possible indication for treatment of hypertension and other risk factors in persons without known hypertension. Better control of blood pressure and risk factors in persons with known hypertension
Malignant	Moderate retinopathy signs plus optic disc swelling	Associated with mortality	Urgent treatment of hypertension by plasma agents.

\* Grades do not imply a sequential temporal relationship of mild to moderate or moderate to malignant.

**DISCUSSION**

The list of systemic diseases that can have ocular manifestations is a long one; in addition to diabetes, hypertension and cardiovascular disease, it also includes aneurysms, HIV, cancer, and certain rare hereditary diseases. Hypertension still remains one of the leading causes of morbidity and mortality worldwide, (Wolf-Maier et al., 2003) despite increasing recognition of its importance and development of new therapeutic agents to control blood pressure (BP). Retinal microvascular signs are common fundus findings in general adult hypertensive population. These signs include generalized and focal arteriolar narrowing, arteriovenous (AV) nicking, isolated retinal haemorrhages, microaneurysms and cotton wool spots; and are traditionally referred to as hypertensive retinopathy. (Tso and Jampol, 1982 ; Yalvac et al., 2010). The WHO clinical guidelines for hypertension management have been updated. There has also been a series of population-based studies describing the relationship of retinal microvascular signs quantified from fundus photographs, to various systemic diseases in the general population. New hypertension guidelines in United States, as per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure updated its recommendation of hypertension management in 2003 (Chobanian et al., 2003; Jones and Hall, 2004). The main features of the report were: Individuals older than 50 years , systolic BP >140 mmHg are at a stronger cardiovascular risk factor than diastolic BP; Individuals who are normotensive at 55 years still have a 90% lifetime risk of developing hypertension; Individuals with systolic BP 120

## CONCLUSION

Retinal microvascular signs differ in their associations with systemic diseases. Isolated retinal haemorrhages, microaneurysms and cotton wool spots appear to be associated with risk of subclinical and clinical stroke, cerebrovascular and cardiovascular outcomes, renal dysfunction and mortality. Conversely, systemic associations for generalized retinal arteriolar narrowing, focal arteriolar narrowing and AV nicking appear to be weaker and less consistent. There is no clear evidence that patients with mild retinopathy need immediate physician referral or follow-up at the time. Individuals with moderate retinopathy signs may benefit from a thorough cardio/cerebro/renal systemic assessment and appropriate risk reduction therapy. Patients with malignant retinopathy will continue to need urgent anti-hypertensive treatment. Since the natural history of these signs is not fully understood, it remains unclear if a careful clinical ophthalmoscopic examination is comparable to photographic techniques in detecting subtle retinopathy signs. Recent studies suggest specifically targeting microcirculation for risk reduction in hypertension management. There is an increasing array of anti-hypertensive agents available that may have beneficial effects on microvessel structure and function beyond its primary effect in lowering BP. Further research is needed to evaluate whether these treatment approaches may reverse or even reduce retinopathy signs, and whether this will ultimately reflect in a decreased cardiovascular risk for the patient. All said and done, it still remains open to speculation whether current research methods of assessing retinal status and its systemic implications can be successfully translated into 'everyday' clinical use.

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