The eye, the mirror of the heart

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This editorial refers to ‘Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations’ by J.J. Wang et al., on page 1984

The major health economical burden of cardiovascular disease (CVD) is leading to a swift move from treatment of CVD to diagnosis of early CVD in asymptomatic people. Primary prevention of CVD has been aimed at risk factor identification and treatment, without efforts to document early CVD.

It is well recognized that vascular changes, including atherosclerosis, begin early in life as a silent, asymptomatic disease process. Therefore, identification of early vascular abnormalities in asymptomatic subjects may help identify asymptomatic individuals at risk, before blood pressure is elevated above an ‘arbitrary’ level that we currently identify as hypertension.1 These vascular parameters need to be predictive for cardiovascular morbidity and mortality. A number of non-invasive methods have been introduced to gain better insight into the abnormalities in the wall of the artery that can define the atherosclerotic process. It is important to begin with the recognition that atherosclerosis is a systemic vascular disease that results in functional and structural abnormalities in the entire arterial vasculature. Certain vascular areas, particularly the coronary and cerebral circulations, precipitate most morbid events, and the rate of progression may vary in different vascular beds in different individuals. The retinal circulation may provide a unique and easily accessible vascular bed, which can be studied non-invasively.

Wang et al.2 pooled the data of the Beaver Dam Eye Study and Blue Mountain Eye Study and found a relatively consistent pattern of association between retinal vessel diameter and cardiovascular mortality. In subjects with an age range 43–69 years, both smaller retinal arteriolar and larger retinal venular diameters were significantly associated with a greater risk of coronary heart disease, and were also marginally significantly associated with an increased risk of stroke mortality, independent of age, gender and other vascular risk factors. These associations were not observed in persons aged 70 years and above.

The ocular microcirculation represents a preferential target for many systemic diseases, and changes in vessel structure can pre-date the development of hypertension by many years. NO (nitric oxide) is known to play a pivotal role in the control of ocular blood flow and has been implicated in contributing to development of local ocular and systemic vascular pathology.3 Structural changes in the retinal vasculature have long been recognized as an important predictor of systemic hypertensive damage and life prognosis.4

A lower retinal arteriolar-to-venular ratio (AVR) has been suggested to reflect generalized arteriolar narrowing and to predict the risk of CVD. The contribution of the separate arteriolar and venular diameters to this AVR is unknown. Thus, associations between retinal arteriolar and venular diameters, and the AVR on the one hand, and blood pressure, atherosclerosis, inflammation markers, and cholesterol levels on the other, were examined in the Rotterdam Study.5,6 Especially larger retinal venular diameters were associated in this study with marked progression of periventricular and subcortical white matter lesions independent of other cardiovascular risk factors. Also, persons with larger venular diameters tended to have more incident lacunar infarcts. Generalized retinal arteriolar narrowing at baseline increased the risk of hypertension in a general elderly population and even more so than could be inferred from the AVR only. This association persisted after adjusting for other cardiovascular risk factors and was independent of baseline blood pressure.

The Multi-Ethnic Study of Atherosclerosis (MESA) provided an opportunity to examine the relationship of retinal vascular calibre to a range of cardiovascular risk factors, including biomarkers of inflammation, endothelial dysfunction and pathogen burden, in a large, multi-ethnic population free of clinical CVD at the baseline examination. After controlling for age, gender, race-ethnicity, and centre, Wong et al.7 found that smaller retinal arteriolar calibre was related to hypertension, systolic and diastolic blood pressure, and homocysteine, whereas larger retinal arteriolar calibre was associated with diabetes, current cigarette smoking, and higher levels of plasma fibrinogen. Larger retinal venular calibre was associated with diabetes, current cigarette smoking, obesity (greater body mass index and waist-hip ratio), dyslipidaemia [higher plasma triglyceride and low-density lipoprotein (LDL)-cholesterol, and lower high-density lipoprotein (HDL)-cholesterol], and systemic markers of inflammation [high sensitive C-reactive protein (hsCRP), plasma fibrinogen and interleukin-6.}

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(IL-6), and endothelial dysfunction [soluble intercellular adhesion molecule-1 (sICAM-1) and plasminogen activator inhibitor-1 (PAI-1)]. These findings may provide further insights into the different systemic processes associated with retinal vascular calibre, which has now been shown to predict incident cardiovascular outcomes independently.

These findings may have clinical applications. The results of previous studies provide further evidence that an assessment of retinal vascular calibre may provide information regarding systemic cardiovascular risk. These observations support the value of targeting the microcirculation in treatment of both systemic and ocular diseases. Retinal arteriolar narrowing has been shown to predict coronary heart disease morbidity and mortality, and also stroke. Certain pharmacological agents (e.g. angiotensin-converting enzyme inhibitors) have been suggested to have direct beneficial effects on retinal arteriolar narrowing. Therefore, clinical pharmacological studies of the structure and function of the retinal vessels could be considered as valuable surrogate biomarkers in the development of new therapies in CVD prevention. Our study suggests that an assessment of retinal vascular calibre may offer insights into the contribution of subclinical vascular processes to the development of CVD.

An understanding of the sequential changes that occur in the arterial system is crucial in order to appreciate the temporal influence on the occurrence of CVD and its response to treatment. Diagnostic procedures are currently designed to assess the extent and severity of vascular disease after the development of symptoms or when morbid events occur. The diagnostic challenge must be to detect abnormal structure and function in the vascular system before the development of symptoms or signs of CVD. The findings of independent associations between retinal vessel diameter and coronary heart disease death support the concept that retinal vessel diameter may reflect lifetime cumulative effects of various vascular processes on the microvasculature and thus may be a novel biomarker for CVD risk.

**Conflict of interest:** none declared.

**References**