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The Relationship between Retinal Microvascular Abnormalities and Coronary Heart Disease: A Review

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Abstract

Heart disease remains the leading cause of death in the United States despite decades of advancement in its diagnosis and treatment. Due to the limitations of traditional risk stratification for heart disease, evaluation of the retinal vasculature has been proposed as an easily and safely measured adjunct to commonly used screening methods. In this article we provide a comprehensive review of the literature concerning the relationships between retinal microvascular abnormalities and coronary heart disease. We outline details of the most recent large epidemiological studies and discuss their potential implications for clinical practice. Finally, we propose a change to the current guidelines regarding the screening of “low risk” women, a group that is often failed by traditional evaluation algorithms.

Keywords

Coronary heart disease; Retinal microvascular abnormalities; Retinopathy; Risk prediction; Screening

Introduction

Despite enormous advances in its diagnosis and treatment over the past decades, heart disease continues to be the leading cause of death in the United States.[1] The high burden of disease results in human suffering, lost productivity, financial strain, and countless other costs that have led to an increasing focus on risk assessment and primary prevention of coronary heart disease.[2,3,4,5,6] Risk factors for coronary heart disease such as hypertension, elevated low density lipoprotein (LDL) cholesterol, age, cigarette smoking, diabetes mellitus, kidney disease, and others, are well established in both the literature and clinical practice as ways to identify and treat susceptible individuals.[7,8,9,10,11,12] However, there continues to be interest in finding methods and other markers that will allow us to further risk stratify patients. This is especially important for some subgroups of the population, such as women, in whom traditional predictors of risk may not be adequate. For decades, the retinal vasculature has been proposed as an easily and safely measured surrogate for the coronary circulation, but there is conflicting evidence as to its utility in this area.[13,14,15,16,17] This article will examine the current body of literature regarding the

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associations between retinal microvascular changes and coronary heart disease, and explore its potential implications for clinical practice.

Overview of Retinal Microvascular Abnormalities

A detailed description of the pathophysiology of retinal microvascular changes from both hypertension and diabetes is beyond the scope or purpose of this review, and has been described in depth elsewhere.[13,18,19,20,21] However, a basic understanding of terminology is necessary to proceed with a discussion of relationships between retinal vascular changes and coronary heart disease. In a comprehensive 2001 review of retinal microvascular abnormalities and their associations with systemic cardiovascular disease, Wong et al.[13] described useful working definitions for different aspects of retinal vascular pathology, and we will use those same definitions here. Retinopathy specifically refers to changes that are not directly arteriolar, such as cotton wool spots, hemorrhages, microaneurysms, macular edema, and hard exudates. Retinal arteriolar changes such as generalized and focal arteriolar narrowing as well as arteriovenous nicking refer only to pathology involving the retinal arterioles.

Despite early recognition of the relationship between retinal microvascular abnormalities and systemic vascular disease,[22,23] examination of the retina by ophthalmoscopy has not been proven to be a reliable method of assessing the coronary circulation. This is likely due in part to the fact that ophthalmoscopy is not objective nor quantitative.[24,25] In the last few decades, digitized retinal photography and other methods have become accepted as more standardized and objective techniques for characterizing retinal microvascular phenomena.[13,26,27]

Overview of Coronary Microvascular Disease

A discussion of the relationship between retinal microvascular abnormalities and coronary disease necessitates a brief overview of coronary microvascular disease. In the last two decades, significant study has been directed at discovering the pathogenetic mechanisms of coronary microvascular dysfunction as well as the clinical implications of microvascular disease.[28,29] This line of inquiry developed partly because of observations that many patients experience typical angina symptoms in the absence of coronary artery disease detectable by angiography or evidence of structural heart disease.[30] This condition, which has become known as Syndrome X, is relatively common: between 10% and 30% of patients undergoing angiography for typical angina symptoms have “clean” epicardial coronary arteries.[31] Most cases occur in postmenopausal women, and long term survival as well as left ventricular function is usually not adversely affected.[32,33]

To further assess coronary microvascular dysfunction, numerous approaches have been tried with varying results. During angiography, the Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade can be used to measure the intensity and rapidity of radioopacity of myocardial tissue, with higher scores indicating better perfusion and presumably better microvascular function in the myocardium.[34] However, more direct and quantifiable methods calculate coronary flow reserve, which is the difference between flow at maximal hyperemia (vasodilation with adenosine or dipyridamole) and basal flow. Coronary flow reserve can be measured using multiple modalities, including positron-emission tomography, magnetic resonance imaging (MRI), and transthoracic echocardiography.[35,36,37]

It is hypothesized that because retinal vessels are approximately the same magnitude as coronary microvasculature (~100-250μm in diameter) they can serve as representative of processes occurring in coronary microvessels, and therefore serve as a marker for subclinical

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or microvascular coronary disease. As discussed below, however, data are inconsistent about whether retinal microvascular abnormalities can be used as surrogates for systemic or coronary macrovascular and/or microvascular dysfunction.

Relationship Between Retinal Microvascular and Macrovascular Disease

Despite the growing preponderance of evidence associating retinal microvascular abnormalities with coronary heart disease, there still remains a significant lack of understanding about the pathophysiologic mechanisms underlying the relationship between microvascular and macrovascular disease. Several studies have attempted to elucidate the relationship between retinal microvascular dysfunction and large artery atherosclerosis. Using data from the Hoorn study, a population-based cohort with varied degrees of insulin resistance, Van Hecke et al17 hypothesized that microvascular dysfunction may lead to atherosclerosis by inducing endothelial dysfunction of the large vessels. In 256 adults aged 60-85 they compared findings of retinopathy as well as arteriolar and venular diameters with brachial artery endothelium-dependent flow-mediated vasodilation and carotid intima-media thickness. After controlling for other risk factors, this study found no significant association between retinal microvascular abnormalities and endothelium-dependent flow-mediated vasodilation (a marker for endothelial function) or carotid intima-media thickness (a marker for early atherosclerosis). Despite the relatively small size of the study, the authors concluded that retinal microvascular disease is not associated with subclinical atherosclerosis. In contrast, a smaller Chinese study compared central retinal artery blood flow and endothelial-dependent flow-mediated vasodilation between 25 patients with angiographically confirmed coronary artery disease and 30 normal controls. This study found significantly decreased central retinal artery blood flow and decreased brachial artery flow-mediated vasodilation in the patients with coronary artery disease, suggesting a relationship between abnormalities in retinal microcirculation and endothelial dysfunction.38 Other studies have also explored the relationship between retinal microvascular abnormalities and markers for cardiovascular risk and atherosclerosis. In the Atherosclerosis Risk in Communities (ARIC) population, generalized arteriolar narrowing was associated with carotid plaque (but no other markers of atherosclerosis) as well as smoking and inflammatory markers such as white blood cell count, fibrinogen, and low albumin. Arteriovenous nicking was also associated with smoking and inflammatory markers but inconsistently with markers of macroarterial disease.39 Another cross-sectional study, the Multi-Ethnic Study of Atherosclerosis (MESA), examined the relationship between retinal vascular caliber and multiple cardiovascular risk factors. This study found that smaller retinal arteriolar caliber was related to hypertension and higher homocysteine levels, whereas larger venular caliber was associated with diabetes, current cigarette smoking, obesity, dyslipidemia, and systemic markers of inflammation such as C-reactive protein (CRP), fibrinogen, and interleukin-6.40 Similar associations between larger retinal venular caliber and systemic markers of inflammation have been found in other populations.[39,41,42]

Retinal Microvascular Abnormalities and Coronary Arterial Disease

The gold standard for the diagnosis of coronary artery disease is coronary angiography, but its hazards and costs preclude its use in the early evaluation of at-risk patients. Other methods to further risk stratify these patients have been developed and continue to be explored.[43,44] Here, we will summarize the data for and against the use of retinal microvascular abnormalities in the evaluation and risk stratification of patients with coronary artery disease.

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A few studies have found a positive association between retinal microvascular abnormalities and coronary artery disease diagnosed by angiography.[16,45,46] However, these trials did not use objective or quantitative measures of the retinal microvasculature and many did not include a multivariate analysis to control for potential confounders. Furthermore, despite the above positive associations, one Brazilian study in 96 subjects found no association between funduscopic evidence of retinal arteriolar changes and angiographic evidence of coronary disease.[47]

Many more and larger studies have examined the relationship between retinal microvascular changes and the harder endpoints of incident coronary heart disease events and death (Table 1). In general, most of the more recent trials examining these endpoints used standardized grading protocols for quantification of retinal microvascular parameters as described briefly above. With a notable exception,[48] earlier trials found increases in mortality associated with pathologic retinal vascular changes but did not provide data on cause-specific mortality rates and often did not control for confounders.[13,49,50,51,52] However, in the last decade more data on the relationship between retinal microvascular abnormalities and incident coronary heart disease as well as cardiovascular mortality have been forthcoming. As summarized in more detail in Table 1, multiple large population-based studies have found significant associations between retinal microvascular changes and incident coronary disease or cardiovascular death. These trials vary somewhat in the specifics of the retinal abnormalities measured. In the large trials of the general population (ARIC, Blue Mountains Eye Study, and Beaver Dam Eye Study), smaller arteriolar caliber and smaller arteriole to venule ratio consistently showed higher risk of coronary events in middle-aged women but not always in men or elderly subjects.[53,54,55] The consistent associations in women are important because this group is more often classified low/moderate risk by traditional risk scores, and may be a good candidate for further screening. Of note, the ARIC study included over 9,500 subjects, more than all of the other studies combined. And while it is beyond the scope of this review to delve deeply into more specifics about the diabetic population or other populations at high risk for coronary heart disease, some studies have also shown associations between retinal microvascular abnormalities and incident coronary disease in the diabetic, hypertensive, hyperlipidemic, and elderly subgroups even when controlling for other traditional risk factors. 56,[57,58]

Retinal Microvascular Abnormalities and Subclinical/Microvascular Coronary Disease

Given the consistent relationship between retinal microvascular abnormalities and incident coronary heart disease and cardiovascular mortality as evidenced by large population-based cohort studies in the last decade, a few recent studies have attempted to further prove a relationship between the retinal microvasculature and subclinical as well as “microvascular” coronary disease and cardiomyopathy.

In a 2005 study using the ARIC cohort, Wong et al.[59] examined the associations between retinal microvascular abnormalities and incident congestive heart failure events in 11,612 adults aged 49-73 years over a 7 year follow-up period. After controlling for traditional risk factors in multivariate analysis, they found a twofold increased risk of incident heart failure in all persons with signs of retinopathy and a threefold risk in subjects without preexisting coronary heart disease, diabetes, or hypertension. This risk was associated with signs of retinopathy only, and no significant relationship between arteriovenous nicking or focal/generalized retinal arteriolar narrowing was born out after multivariate adjustment. More recently, Cheung et al.[60] analyzed 4,593 adult men and women aged 45-85 years without preexisting cardiovascular disease in the MESA cohort. They compared findings on retinal photographs with left ventricular mass, volume, and remodeling as evidenced by cardiac

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MRI. Their analysis showed an independent association between retinal arteriolar narrowing and retinopathy with MRI findings suggestive of left ventricular remodeling. Also, a significant association between larger retinal venular caliber and left ventricular remodeling was noted in women only. While they differ in the specifics of the retinal findings showing significance, both of these recent trials provide further evidence that the retinal microvasculature may provide information about subclinical heart disease, with especially strong associations in women.

Coronary artery calcification measured by computed tomography has been shown to represent subclinical coronary artery disease and predict future coronary events.[61] In an effort to determine whether retinal vascular changes are associated with subclinical coronary disease, Wong et al.[62] examined 6,147 adults aged 45-84 years from the MESA cohort. They found a significant and independent association between retinopathy and increased coronary artery calcium score when controlling for age, gender, race, and traditional risk factors. This association did not extend to changes in retinal microvascular caliber. In further study of 212 persons in the MESA cohort, Wang et al.[63] sought to relate retinal microvascular caliber with changes in MRI measurements of myocardial blood flow and perfusion reserve. They found an association between lower hyperemic myocardial blood flow and perfusion reserve with smaller retinal arteriolar caliber that was significant after adjustment for age, gender, and race, but that lost significance after adjusting for traditional coronary disease risk factors. These associations were only evident in subjects with no evidence of coronary artery calcium, which makes sense, as myocardial blood flow and perfusion reserve are thought to depend mostly on the degree of upstream epicardial coronary stenosis unless this is absent, in which case they correlate with coronary microvascular function. This study provided further evidence that retinal arteriolar narrowing correlates with coronary microvascular dysfunction and may serve as a marker for coronary microvascular disease in patients who would otherwise be deemed low risk by traditional risk factor assessment

Summary and Conclusions

Despite the best efforts of the medical community and significant advances in diagnosis and management, heart disease remains the number one killer in the United States. Traditional risk factors such as hypertension, hyperlipidemia, diabetes, etc. allow physicians to treat high risk patients, but a substantial proportion of cardiovascular disease is not explained by traditional risk factors alone. Examination of the retinal vasculature has long been proposed as a noninvasive and cost-effective means of further risk-stratifying patients with coronary heart disease. In the past two decades, an increased awareness of the contribution of coronary microvascular disease to the overall heart disease burden has heightened interest in using the retinal microvasculature as a marker for coronary disease. This is especially true for women, who may have a larger component of microvascular processes contributing to their coronary heart disease.[64]

Over the last 8-10 years, the introduction of multiple large, prospective cohort studies examining the relationship between retinal vascular changes and clinical endpoints of coronary disease has provided strong evidence for a positive correlation between the two.[53-58,65] Also, some more recent studies have shown an association between retinal microvascular abnormalities and markers of subclinical or microvascular coronary disease.[59,60,62,63] Of note, all of these trials used highly sophisticated and standardized methods of grading the retinal microvasculature. Also, there is some discordance among the major trials in terms of the specific retinal changes that showed positive correlations. For example, in the ARIC cohort a decreased arteriole to venule ratio and retinopathy was associated with increased incident coronary disease in women but not in men.[55] In the MESA cohort,

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retinopathy (but not retinal vascular caliber) was associated with increased coronary artery calcium scores.[62] Given that MESA also showed a correlation between retinal arteriolar narrowing and decreased myocardial blood flow and perfusion reserve,63 the argument could be made that retinopathy signs may be markers for large artery atherosclerosis while retinal arteriolar narrowing and/or large retinal venular caliber may be markers for coronary microvascular disease.

So when should clinicians start using retinal visualization for coronary disease risk stratification? We would propose that there may be value now in certain subsets of the population (see Table 2). Based on data from the Third National Health and Nutrition Examination Survey (NHANES III), 95% of women under the age of 70 fall into the lowest category of Framingham coronary heart disease risk, meaning that their 10-year *predicted* risk of coronary events is less than 10%.[66] Despite this fact, heart disease remains the leading cause of death in women in the United States, suggesting that further risk stratification in this group is necessary to enable more effective primary prevention strategies. As presented in the data above, most of the larger studies examining the relationship between retinal microvascular abnormalities and coronary events show stronger associations in women. Therefore, we propose that clinicians should consider retinal examination by an ophthalmologist (specifically looking for signs of retinopathy or decreased arteriole to venule ratio) in women with one Framingham risk factor (Table 2). A recent study of women in the MESA cohort showed that a significant proportion of women deemed “low risk” by Framingham had increased coronary artery calcium scores, which were predictive of future coronary events.[67] The fact that retinopathy has been shown to correlate with increased coronary artery calcium scores[62] further supports the use of retinal examination in women who are otherwise deemed “low risk.”

Based on the data available at this point, there are some obvious caveats to such an approach. First, there has been no prospective study that examines whether a new risk score including retinal findings would outperform traditional models of risk factor assessment such as Framingham. Second, if retinal vascular assessment was in fact shown to improve prediction of coronary heart disease risk, it then begets the question of how it could potentially influence therapy. Interestingly, trials within the last decade have shown that intensive glycemic control in patients with diabetes reduces microvascular complications such as retinopathy and nephropathy, but does not consistently improve macrovascular outcomes such as cardiovascular death and myocardial infarction.[68,69,70] By contrast, aggressive LDL-lowering is consistently correlated with improved macrovascular outcomes.[10] This would suggest that otherwise “low risk” women with pathologic retinal findings may benefit from more aggressive blood pressure control and LDL lowering. Obviously, further study into the cost effective and noninvasive potential of using the retinal vasculature in coronary heart disease risk assessment is warranted.

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TABLE 1

Summary of Selected Studies Examining Relationship Between Retinal Microvascular Abnormalities and Incident Coronary Events and Death

Study Population	Study Type	Retinal Vasculature Exam	Endpoints	Conclusions	Reference
1,524 adults with type 2 diabetes, no known CHD or stroke	Population-based prospective cohort (ARIC)	Standardized retinal photographs using the Early Treatment of Diabetic Retinopathy Study severity scale.	Primary: Incident CHD event (MI, death, or revascularization). Secondary: Fatal CHD	Signs of retinopathy associated with twofold risk of incident CHD and threefold risk of fatal CHD (association persisted across subgroups and after controlling for potential confounders).	Cheung et al 2007[56]
3,340 men and women over age 49	Population-based prospective cohort (Blue Mountains Eye Study)	Standardized retinal photographs with computerized assessment of arteriolar and venular calibers, and AVR.	Primary: CHD-related death	After multivariate analysis, larger retinal venular caliber was associated with a 1.5-2x increased risk of CHD death in men and women aged 49-75, but smaller arteriolar caliber only predicted higher risk of fatal CHD in women. No association in aged > 75.	Wang et al 2006[53]
1,992 men and women aged 69-97 years (mean age 79 years)	Population-based prospective cohort (Cardiovascular Health Study)	Standardized retinal photographs with computerized assessment of arteriolar and venular calibers, and AVR. Focal retinal microvascular signs also examined using standardized light box protocol.	Primary: Incident CHD (MI, death). Secondary: Incident stroke	In multivariate analysis, larger retinal venular caliber was associated with increased incident CHD and stroke, while smaller arteriolar caliber was associated with increased incident CHD but not stroke.	Wong et al 2006[57]
126 cases aged 43-74 years who died of CHD and 28 who died of stroke compared with 528 controls	Population-based nested case-control (Beaver Dam Eye Study)	Standardized retinal photographs with computerized assessment of arteriolar and venular LDRs, tortuosity, bifurcation optimality, and bifurcation angles.	Primary: CHD death or stroke death(defined cases)	After multivariate analysis, impaired bifurcation optimality and reduced arteriolar tortuosity was associated with incident CHD. Increased arteriolar LDR was associated with stroke, but not independently of blood pressure.	Witt et al 2006[65]
417 cases (CHD or stroke death) aged 43-84 years with 1,202 age- and gender-matched controls	Population-based nested case-control (Beaver Dam Eye Study)	Standardized retinal photographs with measurements of retinopathy based on Airlie House classification, focal and generalized arteriolar narrowing, AV nicking, and AVR using computerized techniques.	Primary: Cardiovascular disease death (CHD or stroke)	After controlling for traditional risk factors, retinopathy had an OR of 1.8 for any cardiovascular disease death, but only younger subjects (aged 43-74) showed associations between focal/generalized arteriolar narrowing, AV nicking, and CVD death.	Wong et al 2003[54]
9,648 men and women aged 45-64 years with no known baseline CHD	Population-based prospective cohort (ARIC)	Standardized retinal photographs with computerized assessment of AVR, as well as evaluation of retinopathy per the light box protocol.	Primary: Incident CHD event (MI, death, or revascularization)	In multivariate analysis, each SD decrease in AVR was associated with a RR of 1.37 for incident CHD events in women but not men. Also, retinopathy was associated with a RR of 1.83 for incident CHD in women but not men.	Wong et al 2002[55]
560 hypertensive, hyperlipidemic men aged 35-59 years	Prospective cohort (LRC-CPPT)	Direct ophthalmoscopy to identify one or more of: focal/generalized arteriolar narrowing, AV nicking, widened arteriolar light reflex, retinal hemorrhage and exudates, microaneurysms, and disc swelling.	Primary: Incident CHD event (MI or CHD death)	After multivariate analysis, hypertensive retinopathy was associated with a RR of 2.1 for definite CHD events. Generalized or focal arteriolar narrowing was associated with a RR of 2.9 for CHD events.	Duncan et al 2002[58]

Abbreviations: CHD=Coronary Heart Disease, ARIC=Atherosclerosis Risk in Communities, MI=Myocardial Infarction, AVR=Arteriole to Venule Ratio, SD=Standard Deviation, LDR=Length:Diameter Ratio, AV=Arteriovenous, OR=Odds Ratio, RR=Relative Risk, LRC-CPPT=Lipid Research Clinics Coronary Primary Prevention Trial

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Table 2

Proposed Modification of Prevention Strategies Based on Framingham Risk Score

Framingham Risk Class	Men	Women
Low (0-1 Risk Factors)	Traditional Management*	Traditional Management* ***Consider Retinal Exam (especially if one risk factor)**
Moderate (2 or more Risk Factors)	Traditional Management*	Traditional Management*
High (CHD and CHD risk equivalents)	Traditional Management*	Traditional Management*

*Traditional Management denotes risk factor modification as outlined by NCEP ATPIII[9,10] and JNC7[7] guidelines.

CHD = Coronary Heart Disease