

Retinal Vascular Signs in Diabetes and Hypertension — Review

ABSTRACT

The retinal vasculature is a unique site where the microcirculation can be noninvasively imaged *in vivo*. This presents an opportunity to study otherwise inaccessible structural features of the microcirculation. Recently, a number of population-based studies have developed quantitative methods of measuring these retinal signs, and investigated how these signs relate to metabolic disorders such as diabetes, hypertension, obesity, and metabolic syndrome. These studies have reported fairly consistent associations of retinopathy lesions, arteriolar narrowing and venular dilation with these metabolic disorders, suggesting a microvascular component in either the pathogenesis or manifestation of these disorders. Further, several of these signs have been associated with future risk of cardiovascular outcomes, such as coronary heart disease and stroke, independently of traditional risk factors. This review will examine in detail the evidence linking retinal vascular signs with metabolic disorders and discuss their implications for research and clinical practice. (**Arq Bras Endocrinol Metab 2007;51/2:352-362**)

Keywords: Diabetes mellitus; Microcirculation; Retinal vasculature; Cardiovascular disease

RESUMO

Sinais Vasculares Retinianos no Diabetes e Hipertensão.

A vasculatura retiniana apresenta uma oportunidade única de observação não-invasiva da microcirculação e de suas estruturas *in vivo*. Recentemente, uma série de estudos populacionais desenvolveu métodos quantitativos de observação destes sinais retinianos e suas relações com distúrbios metabólicos, tais como diabetes, obesidade, hipertensão arterial e síndrome metabólica. Esses estudos demonstraram associações das lesões retinianas, entre elas estreitamento arteriolar e dilatação venular, com essas alterações metabólicas, sugerindo um componente microvascular na patogênese ou na manifestação destes distúrbios. Ainda, vários destes sinais foram associados com risco de doença cardiovascular, tais como doença arterial coronariana e acidente vascular cerebral independente dos fatores de risco clássicos. Esta revisão discute em detalhes as evidências entre os sinais retinianos e os distúrbios metabólicos e suas possíveis implicações na pesquisa e na prática clínica. (**Arq Bras Endocrinol Metab 2007;51/2:352-362**)

Descritores: Diabetes mellitus; Microcirculação; Vasculatura retiniana; Doença cardiovascular

THE MICROCIRCULATION REPRESENTS the bulk of the circulatory system, yet its role in vascular pathology is poorly understood. In part this is due to difficulties in imaging the microcirculation *in vivo*. The retinal vasculature is a unique site where the microcirculatory vessels are arrayed in a two-dimensional plane amenable to noninvasive high-resolution photography and subsequent in-depth analysis. In the past decade methods have

revisão

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been developed which take advantage of advances in digital photography and image processing software to extract a wealth of data on microvascular structure from retinal images. Recent population-based studies have documented the subtle retinal vascular changes that occur in metabolic disorders such as diabetes, hypertension, obesity and metabolic syndrome, providing new understanding of the microvascular involvement in these disorders. It has now become evident that these retinal vascular changes might be markers of early, pre-clinical stages of these metabolic disorders and may predict their clinical onset. This review provides an update on recent epidemiological studies investigating the relationship of retinal vascular changes in diabetes, hypertension, obesity and metabolic syndrome, and discusses the research and clinical implications of these new findings. Table 1 summarizes key population-based epidemiologic findings to date.

RETINAL VASCULAR SIGNS AND DIABETES

Retinopathy in diabetes

The primary retinal vascular complication in diabetes, diabetic retinopathy, is well described and familiar to most clinicians. Diabetic retinopathy is the leading cause of blindness among working age adults and as such represents a condition of important public health and economic consequence (1). A number of classification systems to grade severity of diabetic retinopathy are currently in use — for research purposes, the Early Treatment Diabetic Retinopathy Study (ETDRS) 100 level scale (or slight modifications) are widely used (2), whereas for clinical practice, a new international 5-stage classification (none, mild, moderate, severe and proliferative) has been proposed and is gaining wide acceptance (3).

There is strong evidence that longer duration of diabetes, poorer control of blood glucose, and elevated blood pressure are the major factors responsible for the onset and progression of diabetic retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a population-based cohort study of diabetes, showed that in persons with type 1 diabetes, the prevalence of diabetic retinopathy ranged from 17% in those with diabetes for less than 5 years to almost 100% in those with diabetes for over 15 years (4). The corresponding figures in persons with type 2 diabetes were 29% and 78% (5). The importance of good glycemic control for delaying the development and progression of diabetic retinopathy has

been confirmed in both epidemiological studies (6) and two landmark clinical trials, the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes (7), and the UK Prospective Diabetes Study (UKPDS) for type 2 diabetes patients (8). The UKPDS has further shown the value of tight blood pressure control in delaying the development of diabetic retinopathy complications and well as other microvascular endpoints (9,10).

Other potential risk factors for diabetic retinopathy include dyslipidemia, obesity, systemic vascular inflammation and endothelial dysfunction (11,12). In the WESDR study (13) and the ETDRS trial (14), participants with dyslipidemia were more likely to have or develop hard exudates, while the Fenofibrate Intervention and Event Lowering in Diabetes Study (15) indicated that lipid lowering therapy might reduce retinopathy requiring laser treatment. There is some evidence that markers of obesity such as high body mass index and greater waist-to-hip ratio are correlated with increased risk of diabetic retinopathy from the DCCT (16), the EURODIAB Prospective Complications studies (17), Diabetes Incidence Study (18), the World Health Organisation Multinational Study of Vascular Disease in Diabetes (19) (referring to type 1 diabetes), as well as the UKPDS (20) and Hoorn Study (in type 2 diabetes) (12). The Hoorn study additionally reported an association of systemic markers of inflammation and endothelial dysfunction with diabetic retinopathy (12).

Diabetes prevalence appears to vary among different ethnic groups, suggesting that the prevalence of diabetic retinopathy may also vary by ethnicity (21). The few studies that have reported on diabetic retinopathy in non-white groups suggest that African-Americans and Hispanics have higher prevalence rates than whites (22-25). Recently, the Multi-Ethnic Study of Atherosclerosis (MESA) study reported diabetic retinopathy prevalence rates among subjects with diabetes: 36.7% in African-Americans, 37.4% in Hispanics, 24.8% in whites, and 25.7% in Chinese-Americans (21). Differences in risk factors such as diabetes duration, glycemic control and hypertension appear to explain the higher prevalence of diabetic retinopathy in African-Americans, but cannot explain the similar prevalence observed in Hispanics, suggesting a role for other as yet unidentified genetic or environmental factors (22-25).

Retinopathy lesions may be markers of diabetic microvascular complications in other vascular beds. In the ARIC study, persons with type 2 diabetes and retinopathy lesions had 4-fold higher risk of incident

Table 1. Cross-sectional and predictive associations of retinal vascular signs.

Retinal vascular sign	Is associated with	May independently predict the risk of incident	Over a period of (years)	Magnitude of risk increase (OR or RR)
Retinopathy	Diabetes/Hyperglycemia DCCT (7), UKPDS (8), WESDR (4-6)	Stroke ARIC (53,90), BMES (66)	3	2-3 fold (up to 20 fold if concurrent with cerebral WMLs) (90)
	Current elevated blood pressure ARIC (76), BDES (74), BMES (33,75), CHS (69), Funagata (77), Hoorn (91)	Coronary heart disease ARIC (73)	3	2-fold in women only
	Metabolic Syndrome MESA (46)	Congestive cardiac failure ARIC (26)	3	2-3 fold
	Impaired Glucose Tolerance AusDiab (34)	Diabetes ARIC (35)	3	2 fold only if positive family history of diabetes, else no increased risk
	Hyperlipidemia ETDRS (14), Hoorn (91,92), Fenofibrate Trial (15), WESDR (13)	Coronary heart disease and stroke mortality BDES (67), Hoorn (93)	10, 11	2-fold
	Obesity DCCT (16), Hoorn (91,92), Funagata (77), UKPDS (20)			
	Systemic inflammatory markers Hoorn (11)	In Diabetes		
	Endothelial dysfunction markers Hoorn (11)	Type 1 Risk of angina, stroke, heart mortality, myocardial infarction, nephropathy, lower limb amputation WESDR (27-30)	3	1.3-2.0 fold
	Carotid Plaque and IMT ARIC (22), CHS (63)	Type 2 Congestive cardiac failure ARIC (26)	20	4-fold
	MRI-defined cerebral infarct ARIC (79)			
Cognitive impairment ARIC (61)				
Renal dysfunction ARIC (60), CHS (62)				
<i>In Diabetes</i> Neuropathy AusDiab (94)				
Carotid stiffness and IMT Chennai (95)				
Hyperhomocysteinemia Hoorn (96)				
Focal arteriolar narrowing	Severity of current elevated blood pressure ARIC (46,68), CHS (69)	Hypertension ARIC (71), BMES (97)	3, 5	1.6-fold
	Obesity ARIC (46)	Coronary heart disease CPP (73)	8	3-fold in men
	Metabolic syndrome ARIC (46)	Coronary heart disease and stroke deaths BDES (67)	10	2-fold in those 43-74 years of age
	MRI-defined cerebral infarcts ARIC (79)			

Table 1. Continuação

		In Diabetes Type 1 Lower limb amputation WESDR (28)	20	3.6-fold
Arteriovenous nicking	Current elevated blood pressure ARIC (46,76), BDES (74), BMES (75), CHS (69), Funagata (77)			
	Past elevated blood pressure ARIC (68), CHS (69)			
	Obesity ARIC (46)			
	Low HDL ARIC (46)			
	Systemic inflammatory markers ARIC (78)			
	Endothelial dysfunction markers ARIC (78)			
	MRI-defined cerebral infarct ARIC (79)			
	Renal dysfunction ARIC (60)			
Venular dilation	Systemic inflammatory markers BDES (44), MESA (45), Rotterdam (43)	Stroke CHS (50), Rotterdam (52)	5, 8.5	2-fold
	Endothelial dysfunction MESA (45)	Coronary heart disease BMES (51), CHS (50)	9, 5	3-fold
	Hyperglycemia BDES (44), MESA (45), Rotterdam (43)	Progression of cerebral small vessel disease Rotterdam (40)	3	—
	Smoking MESA (45)	Diabetes Rotterdam (39)	8.5	1.5-fold
	Higher triglycerides MESA (45)	Obesity BMES (47)	5	2-fold
	Obesity BMES (47), MESA (45), Rotterdam (43), SCORM (48)			
	Carotid IMT Hoorn (98)			
	In Diabetes	In Diabetes Type 1 Incidence of diabetic nephropathy (proteinuria, raised creatinine) WESDR (99)	16	1.5-fold
Retinopathy severity WESDR (100)	Type 2 Stroke CHS (50)	5	2-fold (nonsignificant because of small numbers)	
	Coronary heart disease (CHS50)	5	4-fold	
Narrower arterioles	Current elevated blood pressure ARIC (46,68,76), BDES (74), BMES (75), Funagata (77), MESA (45), Rotterdam (43)	Hypertension ARIC (71), BDES (84), BMES (72), Rotterdam (85)	3, 10, 5, 7	2-3-fold

Table 1. continuação

Past elevated blood pressure ARIC (68), CHS (69)	Coronary heart disease in women ARIC (54), BMES (51), CHS (50), and in both men and women CHS (50)	3, 5, 5	2-fold
Carotid stiffness ARIC (80)	Diabetes (BDES 38, ARIC 37)	10, 3	1.5-1.7 fold [3-fold if hypertension also present (38)]
Estrogen use BDES (81)	In Diabetes		
Medications BDES (82), BMES (83)	Type 1 Myocardial infarction WESDR (29)	20	Approx 2 fold
	Heart disease mortality WESDR (29)	20	2-3 fold
	Lower limb amputation WESDR (28)	20	Unclear if due to narrower arterioles, wider venules or both

ARIC: Atherosclerosis Risk In Communities Study; BDES: Beaver Dam Eye Study; BMES: Blue Mountains Eye Study; Chennai: Chennai Urban Rural Epidemiology Study; CHS: Cardiovascular Health Study; DCCT: Diabetes Control and Complications Trial; Fenofibrate: Fenofibrate Intervention and Event Lowering in Diabetes study; Hoorn: Hoorn Study; MESA: Multi-Ethnic Study of Atherosclerosis; Rotterdam: Rotterdam Study; WESDR: Wisconsin Epidemiologic Study of Diabetic Retinopathy; SCORM: Singapore Cohort Study of the Risk Factors for Myopia
OR, RR: Odds ratio, Relative Risk
WML: White Matter Lesions
IMT: Intima-Media Thickness

congestive cardiac failure, after adjusting for other risk factors (26). The WESDR study showed that in type 1 diabetes, proliferative retinopathy was an independent marker of increased risk of stroke, angina, myocardial infarction, nephropathy, lower limb amputation and mortality (27-30). In persons with type 1 diabetes, the WESDR also showed that other retinal vascular abnormalities also predicted risk of peripheral arterial disease, with small arteriole-to-venule ratio (a measure of either narrower arterioles relative to venules or wider venules relative to arterioles) and focal arteriolar narrowing independently associated with 2–3 fold higher risk of lower limb amputation (28). Small AVR was also associated with approximately twice the risk of myocardial infarction and mortality from heart disease (29).

Retinopathy without diabetes

Interestingly, retinopathy lesions can be found in 10–14% of individuals over 40 years without overt diabetes, and results from the Beaver Dam Eye Study (BDES) (31) and Blue Mountains Eye Study (BMES) (32) show that on average, 1.2–1.8% of persons in this age group without diabetes develop

retinopathy lesions per year. Such ‘nondiabetic’ lesions appear to be transient entities, with 72% regressing over 5 years (32). Their pathogenesis is as yet unclear, although hypertension and elevated plasma glucose (below the diabetic threshold) is believed to play a role (33,34). It might be expected that the presence of retinopathy lesions in persons without diabetes would signal increased risk of overt diabetes, but the data from population-based cohort studies do not support this postulate. In the Atherosclerosis Risk in Communities (ARIC) study, retinopathy lesions were not associated with 3-year incident diabetes except in the subgroup of persons with a positive family history of diabetes, where risk was increased 2-fold (35). Similarly, in the BMES, retinopathy lesions did not confer increased risk of diabetes in 5 years (32).

Venular dilation and diabetes, metabolic disorders

Venular dilation has long been recognized as an early change in diabetic retinopathy (36). Recently, it has become possible to quantify variations in venular calibre between individuals using specialized software, and a

number of intriguing associations have emerged. Wider venules relative to arterioles, as represented by smaller AVR, may predict the development of incident diabetes. The ARIC (37) and BDES (38) have reported 50–70% higher risk of incident type 2 diabetes with small AVR, while in those with hypertension, the risk of incident diabetes with small AVR is increased further to over 3-fold (38). The Rotterdam study examined venular calibre and found wider venules associated with incident impaired fasting glucose and type 2 diabetes (39). These findings shed light on the early microcirculatory changes that occur with diabetic retinopathy, and suggest that retinal photography may potentially help identify persons at risk of developing diabetic complications. The underlying causes of this microvascular change remain unclear, although it has been suggested that venular dilation may be related to retinal hypoxia or venous stasis (40). Experimentally induced hyperglycemia in persons without diabetes can cause venular dilation, suggesting a direct effect of glucose on venular calibre (41). Other influences on venular calibre may include reduced vascular reactivity associated with inflammatory processes and endothelial dysfunction, which occur in impaired glucose tolerance (42). The Rotterdam, (43), BDES (44), and MESA (45) studies provide further evidence supporting a link between venular dilation and inflammation and endothelial dysfunction. These studies reported consistent associations between wider venular caliber and markers of systemic inflammation [high sensitivity C-reactive protein (hsCRP), interleukin-6, higher leukocyte count, higher erythrocyte sedimentation rate, plasma fibrinogen] and endothelial dysfunction [soluble intercellular adhesion molecule-1 (sICAM-1) and plasminogen activator inhibitor (PAI-1)] among older persons with and without diabetes. The ARIC study has also reported a cross-sectional association between wider venular calibre and the metabolic syndrome (46), as well as with some components of the metabolic syndrome (large waist circumference, high triglycerides levels, hyperglycemia) but not others [high blood pressure and low high-density lipoprotein (HDL) cholesterol] (46). The Rotterdam study and BMES reported cross-sectional associations of wider venular calibre with high body mass index (43,47), with the BMES additionally reporting a longitudinal relationship whereby persons with wider venular calibre (in the highest quintile) at baseline were 60–70% more likely to become obese or gain weight over 5-years than persons with venular calibre in the lowest quintile (47). The same cross-sectional relationship between wider venules and obesity has been demonstrated in young children in whom the confounding effects of age, hypertension, and other co-mor-

bidities are of less concern (48). These associations emphasize the close links between retinal venular calibre and metabolic disturbances, and point to a role for impaired microvascular function in the pathology of metabolic syndrome. The exact mechanisms linking these associations are not clear, but may be related to systemic inflammation, endothelial dysfunction, increased blood volume or hormonal changes that occur with metabolic disturbances (49).

Venular calibre may also convey prognostic information on cardiovascular risk independent of traditional risk factors such as hypertension, dyslipidemia, smoking and obesity. In the Cardiovascular Health Study (CHS), persons with diabetes who also had wider venules were 4 times more likely to have an incident coronary heart disease event in the next 5 years, independently of risk factors (50). There was also a suggestion that wider venules in diabetes were associated with at least twice the risk of incident stroke in the same time period, although this association was non-significant due to limited numbers of stroke events (50). In persons without diabetes, wider venules were associated with 80% higher risk of incident coronary heart disease, and non-significantly 60% higher risk of incident stroke, due to small number of events (50). The BMES has also reported an association of wider venules with increased risk of coronary heart disease in men and women between 49–75 years of age inclusive (51). An independent association between wider venules and incident stroke and cerebral infarction (52), as well as progression of cerebral small vessel disease (40), was also reported from the Rotterdam study. These findings confirm and extend earlier reports from the ARIC study that small AVR — in this case most likely representing wider venules relative to arterioles — independently predicted the risk of coronary heart disease (in women) and stroke in both men and women with and without diabetes (53,54).

RETINAL VASCULAR CHANGES, HYPERTENSION AND CARDIOVASCULAR DISEASE

Recognition that a careful clinical examination of the retinal vasculature provides information on hypertension-related tissue damage dates back at least a century when Marcus Gunn described the classic retinal arteriolar changes that occur in hypertension (55). These changes include retinopathy lesions (microaneurysms, hemorrhages and soft exudates, cotton wool spots), focal arteriolar narrowing, arterio-venous nicking, and generalized arteriolar narrowing. As described earlier, many of the same population-based studies that con-

firmed and quantified clinical impressions of a strong relationship between retinal vascular changes and diabetes have also established that hypertension exerts a profound effect on the retinal vasculature. Virtually all studies to date have confirmed the strong, consistent, gradient association between the retinal vascular changes with increasing levels of blood pressure in both adults and children (56,57). Between 8–14% of non-diabetic populations have signs of one or more of these hypertensive retinal vascular lesions (56).

Retinopathy and hypertension

As described earlier, retinopathy lesions are common in the non-diabetic population. The BDES reported a prevalence of 7.8% in older adults (58) without diabetes, while the BMES reported a prevalence of 9.8% (33). Risk factors for retinopathy lesions in persons without diabetes included blood pressure and advancing age, although blood pressure appeared to explain less than half the prevalence observed (33) and was not associated with incident lesions over a 5-year period (32).

There appears to be racial differences in the prevalence of retinopathy lesions in the non-diabetic population, with the lesions twice as common in African-Americans in the ARIC study compared to whites (59). The higher burden of hypertension in the African-American population appears to explain much of this excess (59). The ARIC study also reported cross-sectional associations of retinopathy lesions with concurrent renal dysfunction (60) and cognitive impairment as measured using a series of neuropsychological tests (61). The CHS has also reported the same association of retinopathy with concurrent renal dysfunction (62). These results provide evidence that retinopathy lesions, even in persons without diabetes, may reflect the existence of severe microvascular disease in other systemic vascular beds which contribute to diseases in other organs.

Retinopathy lesions in persons without diabetes also appear to be markers of non-diabetic related systemic microvascular pathology (49). Carotid artery thickening is associated with retinopathy lesions (63) in the absence of diabetes. In the whole cohort of the Atherosclerosis Risk in Communities (ARIC) Study (i.e. persons with and without diabetes), the presence of retinopathy predicted 2–3 fold higher risk of ischemic stroke (53), while the joint presence of retinopathy lesions and cerebral white matter lesions on MRI increases the risk of stroke by almost 20-fold (64). These associations were independent of the effects of age, gender, hypertension, diabetes, smoking, dyslipi-

demia, and other cardiovascular risk factors. In the same population, retinopathy lesions were found to independently predict the risk of congestive heart failure (2-fold higher risk) (65). In the BMES cohort (66), retinopathy lesions in persons without diabetes also predicted almost 2-fold higher risk of stroke and stroke mortality, while in the BDES (67) retinopathy lesions in persons without diabetes was related to 2-fold higher risk of cardiovascular mortality.

Focal arteriolar narrowing

Defined as localized narrowing of the retinal arterioles, this lesion appears to be a transient marker for the severity of concurrent hypertension (56,68,69). Prolonged exposure to elevated blood pressure leads to vasospasm and later, intimal thickening, medial hyperplasia and arteriosclerosis manifesting as either generalized or focal arteriolar narrowing (70). In the ARIC (71) study, the presence of focal arteriolar narrowing was associated with 60% higher risk of incident hypertension 3 years later. The BMES (72) reported findings of similar magnitude, although the results were not statistically significant. The WESDR reported that in persons with type 1 diabetes, focal narrowing predicted 3.5-fold increased risk of low limb amputation, after adjusting for other risk factors (28). An analysis of data from the Lipid Research Clinic's Coronary Primary Prevention Trial suggested that focal narrowing may predict incident coronary heart disease in men, but these findings have not been confirmed elsewhere (73).

Arteriovenous nicking (or nipping)

Arteriovenous nicking is associated with both present and past blood pressure (56,68,69,74–77), as well as markers of metabolic disturbance such as low HDL, obesity (46), inflammation and endothelial dysfunction (78). These associations suggest it may serve as a lasting marker of cumulative microvascular damage from chronically elevated blood pressure and some metabolic disorders. This view is reinforced by reports from the ARIC study that arteriovenous nicking is associated with MRI evidence of cerebral infarcts (79) and renal dysfunction (60). However, arteriovenous nicking does not appear related to risk of incident cardiovascular disease outcomes such as stroke and coronary heart disease, after adjustment for traditional risk factors (56).

Narrower arterioles

Generalized arteriolar narrowing is one of the most evident clinical signs discernable on direct ophthalmoscopy, and has long been interpreted as evidence of chronically elevated blood pressure, both past and pre-

sent (55,56). Recently, it has become possible to quantify the degree of arteriolar narrowing using computer-assisted methods and sophisticated image processing algorithms (76). These methods have been applied to large population-based studies to clarify the relationship of arteriolar narrowing with hypertension and cardiovascular disease. Strong and consistent associations with a dose-response pattern have been reported between narrower arterioles and higher concurrent blood pressure from 7 populations — ARIC (68,76), CHS (69), BDES (74), BMES (75), Rotterdam (43), Funagata (77), and MESA studies (45). Other cross-sectional relationships that have been reported for narrower arteriolar calibre include increased carotid stiffness (ARIC) (80), estrogen therapy use (BDES) (81), and medication use [e.g. topical glaucoma medications in BDES (82), lower or non-aspirin use in BMES (83)].

In the BDES, narrower arterioles prospectively predicted a 3-fold higher risk of incident hypertension over 10 years, independently of other risk factors, which attenuated to a 2-fold high risk after adjustment for baseline systolic and diastolic blood pressure (84). The same association, of similar magnitude, has been reported from the ARIC study (71), the BMES (72), and the Rotterdam study (85). There was some suggestion from the Rotterdam study that narrower venules may also be predictive of incident hypertension, but this was subsequently shown to be a confounding result by arteriolar calibre that is highly correlated with both hypertension and venular calibre (86,87). In the ARIC study, small AVR was associated with 2-fold higher risk of incident coronary heart disease in women (54), findings confirmed from the BMES which additionally showed the relationship to be due to both arteriolar narrowing and venular dilation (51). Recently, the CHS reported that narrower arterioles also predicted a similar magnitude of incident coronary heart disease in both men and women (50). Narrower arteriolar calibre does not appear to be related to risk of stroke (50,52). These results highlight the contribution of microvascular disease to risk of coronary heart disease, and suggest that measurement of retinal vessel calibres may be useful adjuncts for cardiovascular risk prediction.

SUMMARY AND FUTURE RESEARCH

Retinal photography offers a unique opportunity to study in detail structural features of the *in vivo* microcirculation than are otherwise inaccessible to imaging.

Microvascular abnormalities and vessel calibres can be accurately and reliably quantified from high-resolution retinal images. Recently, several large population-based studies have reported strong and consistent associations of retinal vascular signs with metabolic disturbances such as diabetes, hypertension, obesity, and metabolic syndrome, pointing to a microvascular role in these disorders. Prospective associations between retinal vascular signs, particularly venular dilation, and incident cardiovascular outcomes in persons with and without diabetes have also been reported, suggesting that these signs may prove useful adjuncts to cardiovascular risk prediction using traditional risk factors. Nonetheless, several important areas remain inadequately explored. Firstly, the pathophysiological processes leading to retinal vascular signs such as venular dilation, and how these processes link the retinal microcirculation with cardiovascular disease elsewhere, are not clear. Much experimental work is required to elucidate these relationships. Secondly, demonstration of prospective associations with incident cardiovascular outcomes is not sufficient for translation into clinical practice. To be clinically useful, retinal signs must demonstrate additional prognostic information for cardiovascular risk prediction, over and above the contributions from traditional risk factors. Studies examining this issue are currently underway. Finally, the role of genetics in determining retinal vascular structure warrants further study. Much of the variability in arteriolar and venular calibres is believed to be related to genetic factors (88,89) and a number of candidate genes have been postulated (88), but to date no strong evidence implicating specific genes is available. This information will be valuable in revealing the microvascular pathophysiology of hypertension and cardiovascular disease, and to answering the questions of whether retinal vascular signs represent a summary measure of genetic and environmental exposures and live up to their promise as valuable new cardiovascular risk markers.

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