Retinal Vascular Changes in Pre-Diabetes and Prehypertension

New findings and their research and clinical implications

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The retinal vasculature can be viewed directly and noninvasively, offering a unique and easily accessible "window" to study the health and disease of the human microcirculation in vivo. In the last decade, advances in digital retinal photography and imaging techniques have allowed precise characterization of subtle retinal vascular changes in large populations. These retinal changes can be broadly divided into four groups: *1*) classic retinal vascular changes in diabetes and hypertension (i.e., diabetic and hypertensive retinopathy), *2*) isolated retinopathy signs in individuals with diabetes or hypertension (e.g., microaneurysm, retinal hemorrhage, or cotton wool spot), *3*) changes in retinal vascular caliber, and *4*) changes in retinal vascular architecture (e.g., retinal tortuosity).

New studies in large populations now show that retinal vascular changes are common in the general population and may precede the subsequent development of overt diabetes and hypertension. A consistent pattern of associations is also emerging, showing that specific retinal vascular changes may be related differently to hyperglycemia and blood pressure.

In this review, we summarize recent studies on the retinal vascular changes seen in diabetes and hypertension and speculate on potential research and clinical implications.

CLASSIC RETINAL VASCULAR CHANGES

Diabetic retinopathy

In individuals with diabetes, the classic primary retinal vascular complication—diabetic retinopathy—is well described (1). Diabetic retinopathy signs are broadly divided into nonproliferative and proliferative retinopathy. The prevalence of diabetic retinopathy increases with duration of diabetes. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) showed that the prevalence of diabetic retinopathy is less than 10% in those with diabetes duration of less than 5 years but more than 50% in those with 20 years or longer diabetes (2). The two major risk factors of diabetic retinopathy are hyperglycemia and hypertension, with hyperlipidemia as a possible third major risk factor. The importance of hyperglycemia has been confirmed in epidemiological studies (3), as well as two pivotal clinical trials: the DCCT (Diabetes Control and Complications Trial) in patients with type 1 diabetes (4) and the UKPDS (UK Prospective Diabetes Study) in patients with type 2 diabetes (5). The UKPDS also showed that blood pressure control reduces the risk of retinopathy independent of glycemia levels (6). New data from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) Study now suggest that lipid-lowering therapy may also reduce retinopathy requiring laser treatment (7).

Hypertensive retinopathy

Like diabetic retinopathy, classic hypertensive retinopathy is well characterized. The clinical signs include generalized and focal arteriolar narrowing, arterio-venous nicking, increased retinal arteriolar light reflex (copper or silver wiring), flame- and blot-shaped retinal hemorrhages, cotton wool spots, and, in severe cases, optic disc swelling (8,9). The association of these retinal signs with blood pressure is consistent and seen in both adults (10–20) and children (21), even in individuals without clinical hypertension (13–15, 22–24).

ADVANCES IN ASSESSING RETINAL VASCULAR CHANGES

— Digital retinal photography and new imaging technology have now allowed more precise assessment of the subtle changes seen in the retinal microvasculature (22,25–28). One key development has been methods to objectively quantify retinal vascular caliber. Historically, narrowed retinal arteriolar caliber, an early hypertensive retinopathy sign, has been difficult to measure using the clinical ophthalmoscope (29). Parr, Hubbard, and colleagues (22,30,31) developed techniques to measure retinal vascular caliber from photographs and summarized these as the arterio-venous ratio (AVR). These techniques are now used in large epidemiological studies (20,22,25,27,28) and have substantial reproducibility.

Recent studies suggest the interpretation of the AVR may be overly simplistic. A smaller AVR was thought to reflect generalized retinal arteriolar narrowing, since venular caliber was assumed to be relatively constant (22). Thus, when a low AVR was associated with elevated blood pressure (18,32) and cardiovascular outcomes such as stroke (33,34) and coronary heart disease (35), the associations were initially thought to reflect generalized arteriolar narrowing. Newer analyses, however, suggest a smaller AVR may

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Abbreviations: ARIC, Atherosclerosis Risk In Communities; AVR, arterio-venous ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

not only reflect narrower arterioles but also wider venules (36,37). Furthermore, arteriolar and venular calibers appear to reflect different pathophysiological processes (37,38).

Liew et al. (38,39) have suggested the need to control for venular caliber in statistical models of arteriolar caliber, and vice versa, as venular caliber explains ~30% of the variability in arteriolar caliber (38)—presumably from shared genetic and ocular factors (22).

Improvements in imaging software have also led to quantification of other architectural changes in the retinal vascular network (36,37), as well as "batch processing" of retinal images (20,22, 25,27,28). There remain technical challenges. For example, the impact of magnification error (i.e., eyes of different refraction) requires further study (40).

ISOLATED RETINOPATHY SIGNS

Epidemiology

There is increasing evidence that typical lesions of diabetic retinopathy (microaneurysms, hemorrhages, and cotton wool spots), termed isolated retinopathy signs, are now recognized to be more common than previously thought in people without diabetes and hypertension (41–43). Recent studies using retinal photography to document these signs suggest prevalence rates in the general population of 5–10% (2,13–15,22–24,44) (Fig. 1*A*) and 2.6–8.6% among those without diabetes or hypertension (13–15,22–24) (Fig. 1*B*). Prospective study data have further shown that up to 10% of individuals aged ≥40 years without diabetes may develop these isolated retinopathy signs within 5 years (16,45).

Two studies have reported on the prevalence of retinopathy in individuals with pre-diabetes. In the AusDiab Study, retinopathy signs were seen in 6.7% of individuals with impaired glucose tolerance or impaired fasting glucose (46), whereas in the Diabetes Prevention Program this was seen in 7.9% of individuals with impaired fasting glucose (5.3–6.9 mmol/l) or impaired glucose tolerance, who had no history of diabetes (47).

These isolated retinopathy signs may be transient. Population studies show that between 40 and 70% of these isolated retinopathy signs seen at baseline are not present 3–5 years later (45,48).

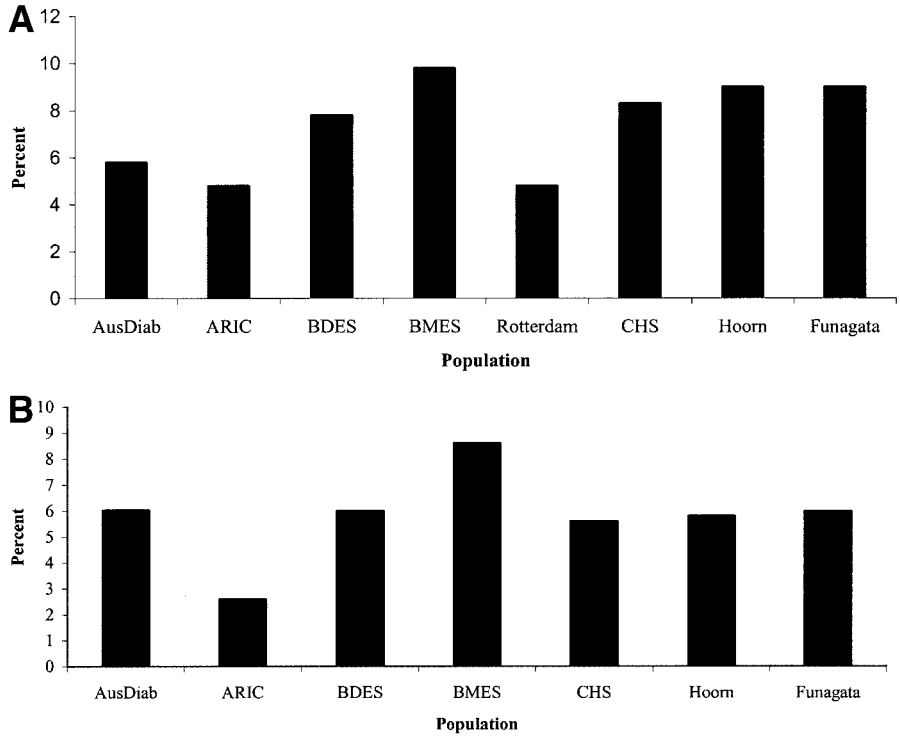

Figure 1—*Prevalence of retinopathy in nondiabetic populations* (A) *and nondiabetic and nonhypertensive populations* (B). *AusDiab: Australian Diabetes, Obesity and Lifestyle Study (year began: 1999–2000,* n = *2,177, aged ≥25 years) (2); ARIC (year began: 1987–1990,* n = *10,954, aged 48–73 years) (22); BDES: Beaver Dam Eye Study (year began: 1988–1990,* n = *4,926, aged 43–84 years) (15); BMES: Blue Mountain Eye Study (year began: 1992–1994,* n = *3,654, aged 49–97 years) (13); CHS: Cardiovascular Health Study (year began: 1989–1990,* n = *2,050, aged 67–97 years) (14), Hoorn (year began: 1989–1992,* n = *626, aged 50–74 years) (23), Rotterdam (year began: 1990–1993,* n = *6,191, aged 55–99 years) (44), and Funagata (year began: 2000–2002,* n = *1,481, aged ≥35 years) (24).*

Risk factors and pathophysiology

The underlying risk factors and pathophysiology of isolated retinopathy signs in nondiabetic and normotensive individuals are poorly understood. Associations of these retinopathy signs with increasing age (15,45), elevated blood pressure (8,13–15,44,47–49), and hyperglycemia (24,44,47,48) have been found. Other possible risk factors include hyperlipidemia (17,23,48), higher BMI (23,24), and systemic inflammation (48,50). We can speculate that isolated retinopathy signs in normotensive and nondiabetic individuals may represent early microvascular damage from a combination of risk factors, including blood pressure and abnormal glucose metabolism, which may reflect an underlying process of developing clinical diabetes or hypertension.

Animal models and human studies suggest that chronic inflammation and glucose-induced arteriolar endothelial dysfunction are related to development of classic diabetic retinopathy (51–53). The association of inflammation and signs of isolated retinopathy in people without diabetes (50) supports the hypothesis that inflammatory processes may also be a possible pathway that underlies early subclinical microvascular disease in the prediabetes or prehypertension state.

Associations with risk of diabetes, hypertension, and cardiovascular diseases

A clinically relevant question is whether signs of isolated retinopathy in individuals without diabetes are markers of the future risk of diabetes (i.e., do these patients require monitoring for the development of diabetes). The evidence here is not consistent. While previous studies suggest that detectable retinopathy precedes the onset of type 2 diabetes by 4–7 years (54), new prospective data from the Blue Mountains (45,55), the Atherosclerosis Risk In Communities (ARIC) (56), and Beaver Dam (57) studies reported no increased risk of diabetes in nondiabetic individuals with signs of retinopathy. However, there are two notable excep-

Table 1—*Associations of retinal vascular changes with diabetes, hypertension, and cardiovascular diseases*

Retinal vascular signs	Associations	Populations	References
Retinopathy	Impaired fasting glucose	ARIC	(67)
	Obesity	Hoorn	(23)
	Blood pressure	ARIC, AusDiab, BDES, BMES, CHS, Funagata, Hoorn, Rotterdam	(2,13–15,22–24,44)
	Incident hypertension	BDES	(57)
	Incident diabetes	ARIC, BDES	(56,57)
	Heart disease	BDES, CHS, ARIC	(14,59,114)
	Nephropathy	ARIC, CHS	(60,61)
	Cerebrovascular disease	ARIC, CHS, BDES	(14,33,34,114–117)
Retinal arteriolar narrowing	Blood pressure	Funagata, BDES, BMES, Rotterdam, ARIC, CHS	(10,22,24,32,37,87)
	Blood pressure in children	SCES, SCORM	(21)
	Measures of atherosclerosis	Rotterdam	(37)
	Waist-to-hip ratio	ARIC	(67)
	Incident hypertension	ARIC, BMES, BDES, Rotterdam	(58,88–90)
	Incident diabetes	ARIC, BDES	(64,65)
	Coronary heart disease	CHS	(98)
Retinal venular dilatation	Impaired fasting glucose	ARIC, MESA	(20,67)
	Measures of atherosclerosis	Rotterdam	(37)
	Obesity in children	SCORM	(69)
	Waist-to-hip ratio	ARIC	(67)
	Hypertriglyceridemia	ARIC	(67)
	Incident obesity	BMES	(118)
	Incident hypertension	BMES	(39)
	Incident impaired fasting glucose	Rotterdam	(66)
	Cerebrovascular diseases	Rotterdam, CHS	(96–98)
	Carotid artery disease	Rotterdam	(37)

AusDiab, Australian Diabetes, Obesity and Lifestyle Study; BDES, Beaver Dam Eye Study; BMES, Blue Mountain Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Sydney Childhood Eye Study; SCORM, Singapore Cohort Study of Risk Factors for Myopia.

tions. First, in the Beaver Dam Study, among individuals aged <65 years at baseline, signs of retinopathy were associated with an increased 15-year incidence of diabetes (odds ratio [OR] 3.68 [95% CI 1.23–10.96]) (57). Second, in the ARIC Study, among participants with a family history of diabetes, signs of retinopathy were also associated with an increased 3-year risk of diabetes (2.3 [1.0–5.3]) (56). Thus, the literature suggests that isolated signs of retinopathy in individuals without diabetes are not necessarily markers of future diabetes risk, except possibly in younger individuals and in those with a family history of diabetes.

Similarly, there is conflicting evidence that isolated signs of retinopathy are markers of future hypertension risk. Data from the Beaver Dam Study showed that among nonhypertensive individuals, those with signs of retinopathy had a higher incidence of hypertension (OR 1.48 [95% CI 1.05–2.07]) (57), but these findings are not supported by other studies (15,45,58).

There is now substantial evidence that isolated microaneurysms, hemorrhages, and cotton wool spots predict the development of clinical cardiovascular and cerebrovascular events independent of traditional risk factors (Table 1). Various population-based studies have shown associations of isolated signs of retinopathy with the risk of stroke (33), congestive heart failure (59), renal dysfunction (60,61), and measures of atherosclerosis (14,62,63). In the ARIC Study, the presence of retinopathy was associated with a threefold higher risk of congestive heart failure in those without previous coronary heart disease (relative risk 2.98 [95% CI 1.50–5.92]) (59). This later association suggests that microvascular disease may be important in the development of diabetic cardiomyopathy in the absence of established coronary artery disease.

RETINAL VASCULAR CALIBER

— The associations and clinical significance of early retinal vascular caliber changes in individuals with diabetes and pre-diabetes, as well as hypertension and prehypertension, are summarized in Table 1.

Associations with diabetes and pre-diabetes

Consistent associations of retinal venular caliber with hyperglycemia, diabetes, and its complications are now emerging (20). Prospective data from three population-based cohorts have shown that changes in retinal vascular caliber may predict the development of type 2 diabetes (64,65) and impaired fasting glucose (66). In two early analyses, an association between smaller retinal AVR and incident diabetes was found in the ARIC Study (OR 1.71 [95% CI 1.13–2.57]; comparing smallest to largest AVR quintile) and the Beaver Dam Study (1.53 [1.03–2.27]; comparing smallest to largest AVR quartile) (64,65). Subsequently, the Rotterdam Study demonstrated that these associations reflected wider retinal venular caliber rather than narrower arteriolar caliber (1.23 [1.02–1.47]; per SD increase in venular caliber) (66). Reanalysis of the ARIC and Beaver Dam studies confirms this finding

(T.Y.W., unpublished data). Thus, it appears that wider retinal venular caliber is a marker of chronic hyperglycemia and the pre-diabetes state and reflects the early microvascular changes that occur in the development of diabetes.

Wider retinal venular caliber has also been linked to the metabolic syndrome and its components (20,37,67). In the Blue Mountains Study, wider retinal venular caliber was associated with the 5-year incidence of obesity among individuals of normal weight at baseline (OR 1.8 [95% CI 1.0–3.1]; comparing largest to lowest venular caliber quintile) (68). Similarly, in children aged 6–8 years, wider retinal venular caliber was also associated with higher BMI (69), suggesting that retinal venular caliber may be influenced by metabolic disorders early in life. There is also evidence that wider venular caliber is associated with various microvascular complications of diabetes, not only diabetic retinopathy (70,71) but also diabetic nephropathy (72).

Despite these observations, the pathophysiological processes underlying the association of wider retinal venular caliber with hyperglycemia, diabetes, and its complications are unclear. It has been speculated that retinal venular widening may be the result of increased blood flow associated with hyperglycemia (73) and retinal hypoxia (74). Alternatively, it may also reflect inflammatory processes implicated in the pathogenesis of impaired glucose metabolism (75), supported by epidemiological findings of wider retinal venules with elevated systemic inflammatory markers (17,20,37,76). Experiments have demonstrated that local inflammatory processes lead to wider retinal venular calibers. For example, administration of lipid hydroperoxide in the vitreous of rats leads to an increase in the retinal venular diameter (77). Similarly, administration of *Escherichia coli* endotoxin in human eyes has been reported to increase retinal venular diameter (78). Finally, retinal venular dilation may be related to endothelial dysfunction, reflecting an increased production of nitric oxide (79) secondary to higher levels of cytokines (80), seen often in association with impaired glucose metabolism (81,82) and diabetes (81).

Associations with hypertension and prehypertension

In distinct contrast to the association of hyperglycemia with retinal venular caliber, there is now substantial evidence that hypertension preferentially affects retinal arteriolar caliber (83) (Table 1). It has long been known that generalized retinal arteriolar narrowing is an early characteristic sign of hypertensive retinopathy (8,84,85). More recent studies using quantitative measurements of retinal vascular caliber have now demonstrated a graded association of narrowed retinal arterioles with increasing blood pressure in different populations of various racial/ethnic groups and age-groups (10,20, 22,24,32,37,86,87).

Of greater significance are prospective findings from four populations that show retinal arteriolar narrowing is a preclinical marker of hypertension risk. The ARIC Study (OR 1.62 [95% CI 1.21–2.18]; comparing smallest to largest AVR quintile) (58), the Beaver Dam Study (1.82 [1.39–2.40]; comparing smallest to largest AVR quartile) (88), the Blue Mountains Study (2.6 [1.7–3.9]; comparing smallest to largest arteriolar caliber quintile) (89), and the Rotterdam Study (1.38 [1.23–1.55]; per SD decrease in arteriolar caliber) (90) all reported that among individuals without hypertension at baseline, those with narrowed retinal arterioles had a higher risk of hypertension in the subsequent 3–10 years, independent of baseline blood pressure levels, BMI, and other known hypertension risk factors.

These observations support the hypothesis that peripheral vascular resistance, reflected by retinal arteriolar narrowing, is an important contributing factor for hypertension development (91). Added support to this hypothesis comes from a recent genome-wide linkage analysis from the Beaver Dam Study, which demonstrated that associations of retinal arteriolar diameter to multiple genetic loci are linked to regulation of blood pressure, endothelial function, and vasculogenesis (92). Thus, retinal arteriolar narrowing may be considered a surrogate marker of an individual's genetic predisposition to hypertension development (93).

Finally, a recent study has shown that the association between higher blood pressure and retinal arteriolar narrowing is detectable in healthy children aged 6–8 years (21), reinforcing the concept that the effects of higher childhood blood pressure may have an adverse effect on the microcirculation (94,95).

Associations with cardiovascular diseases

In addition to their associations with diabetes and hypertension, changes in retinal vascular caliber have also been linked to a range of cardiovascular diseases (Table 1). Wider retinal venular caliber has been associated with carotid artery disease (37), magnetic resonance imaging–detected lacunar infarcts and white matter lesions (96), and clinical stroke events (97,98). In the Cardiovascular Health Study, wider retinal venular caliber was predictive of incident coronary heart disease (rate ratio 3.0 [95% CI 1.6–5.7]; comparing largest to smallest venular caliber quartile) and incident stroke (2.2 [1.1–4.3]), whereas narrower arteriolar caliber was predictive of incident coronary heart disease (2.0 [1.1–3.7]; comparing smallest to largest arteriolar caliber quartile) (98). These findings suggest that both wider venular caliber and narrower arteriolar caliber may be markers of early subclinical cardiovascular disease.

CHANGES IN RETINAL VASCULAR ARCHITECTURE —

New imaging methods have allowed the measurement of other architectural changes in the retinal microvasculature. Hypertension, for example, has been associated with an increase in the retinal arteriolar length-to-diameter ratio (99,100), increased retinal venular tortuosity (99), reduced branching angle at arteriole bifurcations (101), and reduced microvascular density (99,101,102).

Some of these retinal changes have also been shown to be associated with increased cardiovascular risk. For example, the Beaver Dam Study demonstrated that suboptimal arteriolar bifurcation and decreased arteriolar tortuosity are associated with coronary heart mortality (103).

IMPLICATIONS FOR RESEARCH AND CLINICAL MANAGEMENT — It is now well recognized that individuals with impaired glucose metabolism or pre-diabetes have higher mortality from cardiovascular disease (104–106). Similarly, individuals with high to normal blood pressure or prehypertension (107) are more likely to develop cardiovascular events (108,109). To permit appropriate preventative strategies, there is therefore great interest in early detection of individuals with pre-diabetes and prehypertension.

This review suggests that retinal image analysis offers a novel noninvasive

measurement of early changes in the vasculature—not detectable on routine clinical examination—that may allow the identification of individuals at risk of diabetes and hypertension and their subsequent complications. Retinal vascular imaging might also permit physicians to optimize management of individuals with established diabetes and/or hypertension. For example, retinal vascular imaging may allow monitoring of chronic variations in glucose and blood pressure, as well as the presence and severity of subclinical microvascular damage. However, a number of issues should be resolved before retinal vascular imaging can be utilized in clinical practice.

First, despite a large body of data on the associations and risk prediction of retinal vascular caliber measurement in different population-based studies, there is no accepted standardized classification of retinal vascular changes, and a lack of age-, sex-, body size–, and blood pressure–specific normative data. New studies of retinal vascular changes in children, who are generally free of many systemic conditions, may provide these reference data (21,110).

Second, for retinal vascular imaging to be useful for risk stratification, there must be a demonstration of independent predictive value that substantially adds to traditional methods. This has not been conclusively demonstrated. Different analytical methods have hampered the comparison of results between studies, and application-common methods in different studies will allow data pooling to generate more valid risk estimates. Additionally, the role of novel measures of retinal vascular structure (99,103,111–113) in predicting diseases remains to be determined.

Third, the predictive value of retinal vascular imaging is currently based on associations seen in large population-based samples (114–117). It is unclear whether the retinal measurements are sufficiently precise to differentiate risk at an individual level.

Finally, it is unknown whether modification of risk factors (e.g., increased physical activity, reduction in weight) or institution of treatment (e.g., diabetes and antihypertensive medications) may improve retinal vascular measures and whether this is associated with lowered risks of diabetes, hypertension, and their complications. This remains an important area of future research.

In conclusion, measurement of retinal vascular changes using new imaging techniques offers great potential to advance our understanding of the early pathophysiological pathways of diabetes and hypertension development. Recent studies support the concept that the retinal vasculature provides a summary measure of lifetime exposure to various processes involved in the development of diabetes and hypertension. Furthermore, these studies suggest that the effects of glucose and blood pressure on the retinal microvasculature are graded and continuous, and our current definitions of diabetic and hypertensive retinopathy are arbitrary and do not capture early disease. Future research is clearly needed to assess the ability of retinal vascular imaging to provide clinically useful information that adds to existing risk prediction models of diabetes and hypertension.

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