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Diabetic retinopathy and systemic vascular complications

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Abstract

Retinopathy is the most common complication of diabetes. The assessment of retinopathy signs presents clinicians a unique opportunity to directly visualize and assess the actual morphology of diabetic microvascular damage. Extensive studies have now shown that people with diabetic retinopathy have excess risks of systemic vascular complications, including subclinical and clinical stroke, coronary heart disease, heart failure, and nephropathy. There is also emerging evidence to suggest that diabetic retinopathy may share common genetic linkages with systemic vascular complications. The extant literature, therefore, supports the theory that diabetic retinopathy reflects widespread microcirculatory disease not only in the eye but also vital organs elsewhere in the body. Being a uniquely specific and non-invasively assessable measure of diabetic microvascular damage, retinopathy may also be envisioned as a novel biomarker of vascular disease risk in asymptomatic patients with diabetes. This review summarizes recent studies on the systemic associations of diabetic retinopathy, and discusses their pathophysiological significance and clinical implications.

Keywords: Retinopathy; Stroke; Heart failure; Coronary heart disease; Nephropathy; Complications; Microvascular disease; Macrovascular disease; Cardiovascular disease prediction; Mortality

Contents

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1. Introduction

Diabetic retinopathy is the most common and specific microvascular complication of diabetes (Mohamed et al., 2007). While its adverse impact on vision is well known (Frank, 2004), the importance of retinopathy signs beyond visual impairment is less well recognized. Two decades ago, the Framingham Heart and Eye Study proposed that diabetic retinopathy signs may reflect generalized microangiopathic processes that affect not only the eyes but also organs elsewhere in the body (Hiller et al., 1988). In recent years, utilizing standardized retinal photography and methods to evaluate retinopathy lesions (Hubbard et al., 1999), studies have more precisely quantified the associations of diabetic retinopathy with a diverse range of systemic vascular complications. Both non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) have now been linked with major clinical diseases such as stroke, coronary heart disease, heart failure, and nephropathy (Wong et al., 2001b), as well as newer subclinical measures of cardiovascular disease such as coronary artery calcification and cardiac remodeling (Cheung et al., 2007a; Wong et al., 2007a). Therefore, apart from being a manifestation of microvascular damage in the retina, diabetic retinopathy should be viewed as a biomarker of underlying widespread deleterious effects of abnormal glucose metabolism on the systemic microcirculation. This review summarizes the systemic associations of diabetic retinopathy, discusses hypothesized pathophysiological mechanisms, and highlights potential clinical applications and areas of future research.

2. Diabetic retinopathy and mortality

It has long been known that in persons with diabetes, the presence of retinopathy is associated with an increased risk of mortality (Table 1). Studies suggest that this association is more consistently seen in patients with type 2 as compared to type 1 diabetes, reflecting older age and possibly the higher prevalence of cardiovascular risk factors in type 2 diabetes.

In persons with type 2 diabetes, the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), a large population-based study in the United States, demonstrated that both NPDR and PDR were associated with a 34% to 89% excess risk of death after 16 years of follow-up (Klein et al., 1999a). Importantly, this association was independent of age, sex, diabetes duration, glycemic control, and other survival-related risk factors. Consistent with this finding are subsequent data from other studies, largely in Caucasian populations (Cusick et al., 2005; Henricsson et al., 1997; Juutilainen et al., 2007; Rajala et al., 2000; Van Hecke et al., 2003), but also in Asians (Sasaki et al., 1997) and Mexican-Americans (Hanis et al., 1993).

This association is less consistently seen in persons with type 1 diabetes who are younger. Although some studies suggest retinopathy also predicts poorer survival in persons with type 1 diabetes, the association may be explained by concomitant cardiovascular risk factors (Klein et al., 1992, 1999a; van Hecke et al., 2005). In the Early Treatment Diabetic Retinopathy Study, a large clinical trial with a relatively short follow-up, retinopathy was shown to have no association with mortality in type 1 diabetes (Cusick et al., 2005). Some (Klein et al., 2004a; Torffvit et al., 2005), but not all (Rajala et al., 2000) investigators suggest that, besides the traditional cardiovascular risk factors, coexisting nephropathy (e.g., end-stage renal disease) is a major determinant for the poorer survival in type 1 diabetic patients with retinopathy.

The association of diabetic retinopathy with mortality is principally due to an increased risk of cardiovascular disease in persons with retinopathy (Figs. 1–3). The World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO-MSVDD) consists of a large cohort of type 1 and 2 diabetic persons who were followed

Table 1
Selected studies on the relationship of diabetic retinopathy and mortality

Study	Population	Follow-up	Retinal status	Associations[a]	References
WESDR	1370 T2DM	16-year	NPDR	+	Klein et al. (1999a)
			PDR	++	
ETDRS	2267 T2DM	5-year	Moderate–severe NPDR	+	Cusick et al. (2005)
			Moderate–severe PDR	+++	
Finnish	824 T2DM	18-year	NPDR in men	+	Juutilainen et al. (2007)
			NPDR in women	+++	
			PDR in men	++	
			PDR in women	+++	
WESDR	996 T1DM	16-year	Moderate NPDR or PDR	+ (NS)	Klein et al. (1999a)
ETDRS	1444 T1DM	6-year	Severe NPDR	+ (NS)	Cusick et al. (2005)
			Moderate/severe PDR	+ (NS)	
EURODIAB	2237 T1DM	8-year	PDR	+++ (NS)	van Hecke et al. (2005)

WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]Adjusted hazard rate or relative risk <1.5 (+), 1.5–2.0 (++), >2.0 (+++); (NS), not statistically significant.

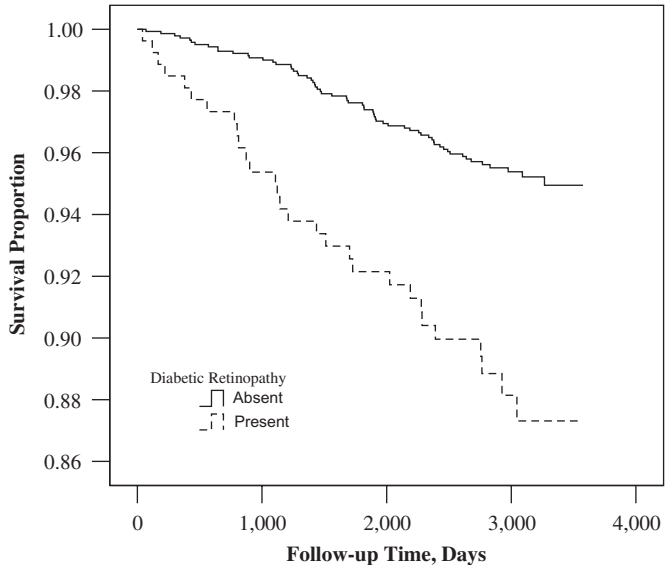

Fig. 1. Stroke free survival in participants with (dashed line) and without (solid line) diabetic retinopathy (Cheung et al., 2007c).

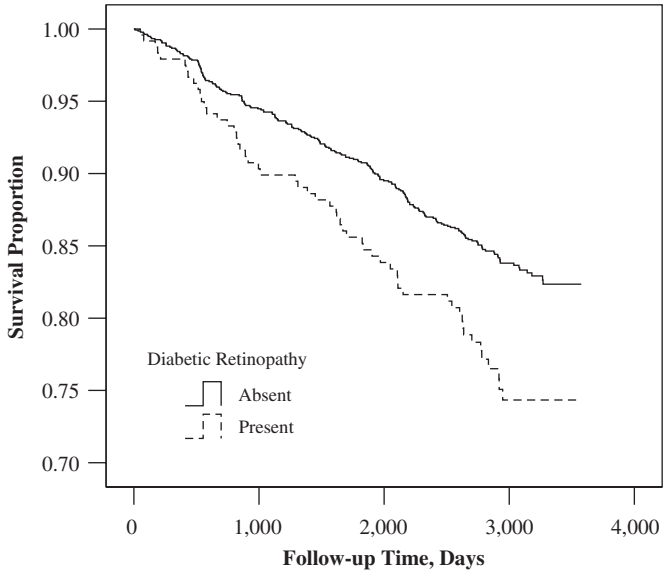

Fig. 2. Coronary heart disease free survival in participants with (dashed line) and without (solid line) diabetic retinopathy (Cheung et al., 2007e).

up for 12 years for incidence of fatal and non-fatal cardiovascular outcomes (Fuller et al., 2001). In the WHO-MSVDD, the presence of diabetic retinopathy predicted higher risk of cardiovascular disease and mortality (Fuller et al., 2001). This association remained significant even after adjusting for traditional cardiovascular risk factors, and was stronger in women than men, and confined to persons with type 2, but not type 1, diabetes (Fuller et al., 2001). While the presence of retinopathy itself seems to signify an increased mortality risk, studies have also shown a "dose-dependent" association between increasing severity of diabetic retinopathy and increasing cardiovascular disease risk (Henricsson

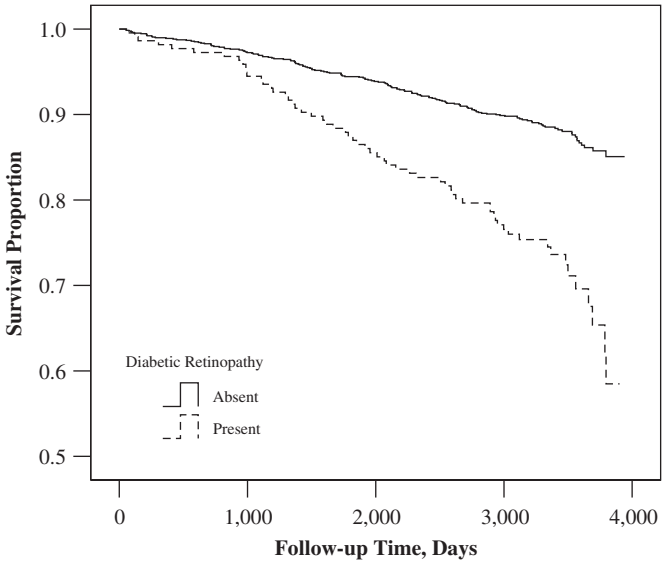

Fig. 3. Heart failure free survival in participants with (dashed line) and without (solid line) diabetic retinopathy (Cheung N, unpublished data, the Atherosclerosis Risk in Communities Study).

et al., 1997; Jager et al., 2001; Juutilainen et al., 2007; Klein et al., 2002a; Rajala et al., 2000; Targher et al., 2006; Van Hecke et al., 2003, 2005).

3. Diabetic retinopathy and cerebrovascular disease

Stroke and other cerebrovascular diseases (e.g., vascular dementia) are major contributors of morbidity and mortality in people with diabetes. Over the past decade, despite the significant progress made in stroke prevention and treatment, most advances have been confined to the management of strokes that are caused by large vessel disease (e.g., carotid atherosclerosis) (Greenberg, 2006). However, up to one-third of symptomatic strokes can be attributed to disease of the small arteries/arterioles in the cerebral circulation (Greenberg, 2006), especially in people with diabetes (Alex et al., 1962; Aronson, 1973; Bell, 1994; Fisher, 1965, 1968). Relatively little is known about these small vessel pathologies due to the paucity of non-invasive methods to study the cerebral microcirculation (Bamford and Warlow, 1988; Wardlaw et al., 2001).

Because the retinal and cerebral vasculatures share similar embryological origin, anatomical features and physiological properties (Patton et al., 2005; Wong, 2004), vascular lesions seen in eyes with diabetic retinopathy may mirror similar pathological disease processes in the cerebral microcirculation. Indeed, there is a strong and consistent level of evidence that retinopathy signs are associated with both clinical and subclinical stroke, independent of cerebrovascular risk factors (Table 2).

Since the 1970s, physicians have observed that the presence of retinopathy is associated with stroke, particularly in persons with hypertension (Goto et al., 1975; Nakayama et al., 1997; Okada et al., 1976; Petitti and Bhatt, 1995; Schneider et al., 1993; Svardsudd et al., 1978;

Table 2
Selected studies on the relationship of diabetic retinopathy and stroke

Study	Population	Follow-up	Retinal status	Associations[a]	References
WESDR	996 T1DM	4-year	PDR in T1DM	+ + +	Klein et al. (1992)
	1370 T2DM		PDR in T2DM	+ + +	
WESDR	1370 T2DM	16-year	Mild NPDR	+ (NS)	Klein et al. (1999a)
			PDR	+ +	
WESDR	996 T1DM	20-year	DR severity	+ +	Klein et al. (2004a)
ARIC	1617 T2DM	8-year	Any DR	+ +	Cheung et al. (2007c), Wong et al. (2002a)
WHO-MSVDD	1126 T1DM	12-year	DR in T1DM men	+ (NS)	Fuller et al. (2001)
	3179 T2DM		DR in T1DM women	+ (NS)	
			DR in T2DM men	+ + +	
			DR in T2DM women	+ + +	

WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy; ARIC, Atherosclerosis Risk in Communities Study; WHO-MSVDD, World Health Organization Multinational Study of Vascular Disease in Diabetes; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]Adjusted hazard rate or relative risk <1.5 (+), 1.5–2.0 (+ +), >2.0 (+ + +); (NS), not statistically significant.

Tanaka et al., 1985). New population-based studies, using standardized photographic evaluation of retinal images to ascertain retinopathy lesions, have confirmed these early observations (Table 2). In the WESDR, PDR was associated with incident stroke mortality in both type 1 and 2 diabetes, independent of diabetes duration, glycemic control and other risk factors (Klein et al., 1992, 1999a, 2004a). In type 1 diabetes, increasing retinopathy severity was also associated with higher stroke risk (Klein et al., 2004a). These findings are consistent with data from the WHO-MSVDD in both men and women with type 2 diabetes (Fuller et al., 2001).

More recently, the Atherosclerosis Risk in Communities (ARIC) Study, a large prospective cohort study of 1617 middle-aged white and black Americans with type 2 diabetes, showed that the presence of NPDR, even of the mildest phenotype (presence of retinal microaneurysms and/or retinal hemorrhages only), was associated with a two- to three-fold higher risk of ischemic stroke (Fig. 1) (Cheung et al., 2007c; Wong et al., 2001a). In a sub-study of the ARIC cohort in which participants had cranial magnetic resonance imaging (MRI) scans, a synergistic interaction between the presence of retinopathy and the presence of MRI-defined cerebral white matter lesions on subsequent risk of clinical stroke development was seen. Participants with retinopathy or white matter lesions alone had about two-fold increase in stroke risk, but participants with both retinopathy and white matter lesions had more than 18 times higher stroke risk than those without either finding (Wong et al., 2002a). This confirms the theory that subclinical cerebrovascular disease may be more severe or extensive in persons with both cerebral and retinal markers of microvascular pathology compared to those without these markers. Findings from the ARIC study are further reinforced by data from the Cardiovascular Health Study of an older population (Wong et al., 2003b) and other studies (Petitti and Bhatt, 1995; Wong et al., 2003a). Finally, there is new evidence that diabetic retinopathy signs are associated with stroke risk even in persons without clinically defined diabetes (Mitchell et al., 2005) and in persons with impaired glucose tolerance (Wong et al., 2005a).

Apart from stroke events, diabetic retinopathy has also been linked with other cerebrovascular disorders. For example, among the ARIC study participants without clinical stroke, retinopathy lesions were related to cognitive decline (Wong et al., 2002b), and MRI detected cerebral atrophy (Wong et al., 2003c). In the CHS and other studies, retinopathy was also modestly associated with cognitive dysfunction and dementia (Baker et al., 2007; Tekin et al., 2004).

The importance of the reported associations of retinopathy signs with stroke, white matter lesions, cerebral atrophy, and cognitive impairment is that it directly supports a possible contribution of small vessel disease, evident in the retina, in the pathogenesis of a wide spectrum of cerebrovascular conditions in persons with diabetes. In addition, because diabetic retinopathy is usually the result of a disruption in the blood-retinal-barrier, it is possible to infer that these cerebral conditions may also be related to a breakdown of the blood-brain-barrier (Wardlaw et al., 2003).

4. Diabetic retinopathy and heart disease

Similar to stroke, microvascular dysfunction has also emerged as an important pathogenic factor in the development of diabetic heart disease (Camici and Crea, 2007). However, there are no simple and non-invasive techniques for the assessment of coronary microcirculation (Duran and Taffet, 2007), and studies that have traditionally evaluated the role of coronary microvascular dysfunction in diabetic heart disease have been limited to small clinic-based samples using highly specialized methods (Di Carli et al., 2003; Factor et al., 1980; Li et al., 2006; Miura et al., 2003; Pitkanen et al., 1998).

Two decades ago, the Framingham Heart and Eye Study proposed that retinopathy signs may reflect a generalized

microangiopathic process that affects the myocardium in people with diabetes (Hiller et al., 1988). This hypothesis is supported by earlier studies, based on ophthalmoscopic examinations, linking retinopathy signs with ischemic T-wave changes on electrocardiogram (Breslin et al., 1966a,b), severity of coronary artery stenosis on angiography (Michelson et al., 1979), histological evidence of microvascular disease in the myocardium (Factor et al., 1980), and incident clinical coronary heart disease events (Duncan et al., 2002).

Recent population-based studies using standardized photographic grading of retinopathy have produced stronger evidence in support of previous observations. It is now clear that diabetic retinopathy signs are associated with an increased risk of myocardial infarction and coronary heart disease (Fig. 2) and heart failure (Fig. 3) (Table 3). The ARIC study showed that the presence of retinopathy was associated with two-fold higher risk of incident coronary heart disease (and myocardial infarction), three-fold higher risk of fatal coronary heart disease, and four-fold higher risk of congestive heart failure, independent of diabetes duration, glycemic control, smoking, lipid profile, and other risk factors (Cheung et al., 2007e,f; Wong et al., 2005b). The population-attributable risk of retinopathy to heart failure has been estimated to be 30.5% in people with diabetes without a previous history of myocardial infarction and hypertension, suggesting that nearly one-third of these diabetic cardiomyopathy cases was related to microvascular dysfunction (Wong et al., 2005b).

There is a graded, dose-dependent association of increasing diabetic retinopathy severity with increasing coronary heart disease risk (Cheung et al., 2007e). These findings are consistent with data from the WHO-MSVDD (Fuller et al., 2001) and other studies showing associations of not only NPDR but also PDR with ischemic heart disease (Faglia et al., 2002; Juutilainen et al., 2007; Miettinen et al., 1996).

Similar to the associations with cardiovascular mortality and stroke, the association of retinopathy with coronary heart disease risk is not consistently present in younger persons with type 1 diabetes. In the WESDR type 1 diabetes cohort, while NPDR, PDR, and retinopathy severity were all associated with an excess risk of deaths from ischemic heart disease, these associations were not significant after adjusting for cardiovascular risk factors, including nephropathy (Klein et al., 1992, 1999a, 2004a). In the EURODIAB study of type 1 diabetes, retinopathy was also not significantly associated with incident coronary heart disease after multivariate adjustments (Soedamah-Muthu et al., 2004).

In addition to population studies, there are clinical studies that suggest the presence of retinopathy can be used as an indicator of silent myocardial ischemia and help guide investigative approaches in diabetic patients with suspected heart disease (Araz et al., 2004; Gokcel et al., 2003; Janand-Delenne et al., 1999; Naka et al., 1992; Norgaz et al., 2005; Yoon et al., 2001). For example, retinopathy may be a valuable prognostic predictor for diabetic patients undergoing cardiac revascularization procedures. Studies show that compared to patients without diabetic retinopathy, patients with retinopathy are more likely to sustain major adverse cardiac events or complications (e.g., death, myocardial infarction, heart failure, in-stent restenosis, etc.) after percutaneous coronary intervention or coronary artery bypass surgery, even after factoring effects of age, gender, diabetes duration, insulin use, and other factors that may affect prognosis after these procedures (Briguori et al., 2005; Kim et al., 2002; Ono et al., 2002, 2006). Thus, it may be important to assess retinopathy status to assist in clinical decision-making for revascularization strategies in diabetic patients with established coronary heart disease (Ohno et al., 2006).

The association of retinopathy with clinical heart disease is well supported by the observed links between diabetic retinopathy and subclinical coronary micro- and

Table 3
Selected studies on the relationship of diabetic retinopathy and heart disease

Study	Population	Follow-up	Retinal status	Associations[a]	References
ARIC	1524 T2DM	8-year	Any DR	+ + (CHD)	Cheung et al. (2007e)
ARIC	627 T2DM	7-year	Any DR	+ + + (CHF)	Wong et al. (2005b)
WHO-MSVDD	1126 T1DM	12-year	DR in T1DM men	+ + +	Fuller et al. (2001)
	3179 T2DM		DR in T1DM women	+ +	
			DR in T2DM men or women	+ +	
Finnish	824 T2DM	18-year	NPDR in men	+ (NS)	Juutilainen et al. (2007)
			NPDR in women	+ +	
			PDR in men or women	+ + +	
Finnish	1040 T2DM	7-year	NPDR	+ (NS)	Miettinen et al. (1996)
			PDR	+ + +	
WESDR	996 T1DM	20-year	DR severity	+	Klein et al. (2004a)

WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy; ARIC, Atherosclerosis Risk in Communities Study; WHO-MSVDD, World Health Organization Multinational Study of Vascular Disease in Diabetes; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure.

[a]Adjusted hazard rate or relative risk <1.5 (+), 1.5–2.0 (+ +), >2.0 (+ + +); (NS), not statistically significant.

macro-vascular pathology. Pathological and radiological studies have shown that persons with retinopathy are more likely to have myocardial arteriolar abnormalities (Factor et al., 1980), coronary perfusion defects (Giugliano et al., 1993; Ioannidis et al., 2004; Yoon et al., 2001), poorer coronary flow reserve (Akasaka et al., 1997) and lower coronary collateral score (Celik et al., 2005), than those without retinopathy. The presence of retinopathy signs has also been associated with higher degrees of coronary artery calcification (Wong et al., 2007a; Yoshida et al., 1999) and more diffuse/severe coronary artery stenosis on angiograms (Norgaz et al., 2005), two established measures of subclinical coronary atherosclerotic burden.

5. Diabetic retinopathy and nephropathy

Diabetic nephropathy is the other major classic microvascular complication of diabetes. Experimental studies show a high correlation of pathological changes in the retinal vasculature with those in the renal vasculature (Chavers et al., 1994; Nag et al., 1980). In the Renin–Angiotensin System Study of young people with type 1 diabetes, severity of retinopathy was positively associated with biopsy-proven renal anatomical features of preclinical diabetic glomerulopathy (Klein et al., 2005). Furthermore, epidemiological studies have consistently demonstrated that diabetic retinopathy is associated with microalbuminuria and clinical nephropathy, independent of hypertension and other shared risk factors (Cruickshanks et al., 1993; Edwards et al., 2005; Klein et al., 1992, 1995, 1999b, 2002a; Wong et al., 2004a).

In the WESDR, persons with type 1 diabetes with more severe retinopathy at baseline had an elevated 4-year risk of nephropathy (Klein et al., 1999b). Moreover, the presence of specific diabetic retinopathy signs, such as retinal hemorrhages, microaneurysms, and cotton wool spots, were associated with higher risk of renal dysfunction in the ARIC study (Wong et al., 2004a). Similarly, in the Cardiovascular Health Study, the presence of retinopathy was independently associated with gross proteinuria (Klein et al., 2002a) and progression of renal impairment (Edwards et al., 2005). These findings confirm that retinopathy and nephropathy share similar microvascular pathogenic pathways related to abnormal glucose metabolisms and other processes (e.g., inflammation, endothelial dysfunction) and support the clinical recommendation to monitor renal function in diabetic persons with signs of retinopathy.

6. Diabetic retinopathy and neuropathy

Unlike nephropathy, the relationship between diabetic retinopathy and neuropathy is less clear. There are few studies showing that retinopathy may be related to neuropathy risk in people with diabetes (Dyck et al., 1999; Savage et al., 1996) or even abnormal glucose metabolism (Barr et al., 2006). In a longitudinal study of 264 diabetic individuals, the presence of more severe microvascular diseases, including retinopathy, was associated with more severe diabetic polyneuropathy (Dyck et al., 1999). Recently, the Australian Diabetes Obesity and Lifestyle Study, a population-based study of Australian adults aged 25 years or more, reported a significant association between retinopathy and neuropathy in persons without clinical diabetes but with abnormal glucose metabolism (Barr et al., 2006). In the WESDR, as compared to persons with no or minimal retinopathy at baseline, those with severe NPDR or PDR had a higher risk of incident lower leg amputation, a complication partly related to diabetic somatic neuropathy (Klein et al., 1992; Moss et al., 1999).

7. Wider retinal venules and systemic vascular complications

Retinal venular dilation has long been suggested as a characteristic sign of early diabetic retinopathy (Frank, 2004). However, this vascular feature is less well described in comparison to other morphologically more distinct retinopathy lesions (e.g., microaneurysms, blot hemorrhages, soft exudates), largely because of difficulties in quantifying retinal venular dilation in clinical settings.

Advances in retinal image-analysis have allowed precise measurements of retinal vascular caliber from digitized or digital photographs (Hubbard et al., 1999; Patton et al., 2006; Wong et al., 2004b). Using this technique, wider (or dilated) retinal venular caliber has been associated with higher risks of diabetic retinopathy progression and incident PDR in the WESDR (Klein et al., 2004b, 2006b). Further, there is now evidence to suggest that wider retinal venules may also have associations with major systemic vascular diseases (Cheung et al., 2007d; Klein et al., 2007; Wang et al., 2006a,b, 2007; Wong et al., 2006a). Wider retinal venular caliber has been shown in several studies to predict higher risks of stroke, coronary heart disease, and nephropathy in several population-based studies, even after factoring the effects of concomitant risk factors (Cheung et al., 2007b; Klein et al., 2007; Wang et al., 2006a, 2007; Wong et al., 2006a). In addition, data from these new studies suggest that wider retinal venular caliber is a biomarker of early retinal as well as systemic microvascular damage caused by hyperglycemia-related processes (e.g., impaired vascular tone autoregulation, inflammation, endothelial dysfunction) (Nguyen et al., 2007; Nguyen and Wong, 2006). These findings provide further support for the link between early retinopathy signs and systemic vascular complications.

8. Pathogenic links between retinopathy and systemic vascular complications

Despite the increasingly abundant evidence that diabetic retinopathy is associated with a range of systemic vascular complications, the underlying pathophysiological mechanisms remain obscure (Krentz et al., 2007). This reflects, at

least in part, an incomplete understanding of the pathogenesis of diabetic retinopathy itself (Frank, 2004).

Nevertheless, several mechanisms have been hypothesized. First, in people with type 2 diabetes, the presence of retinopathy may simply indicate a more adverse cardiovascular profile. It is known that compared to those without retinopathy, diabetic persons with retinopathy are more likely to have concomitant cardiovascular risk factors, such as hypertension and dyslipidemia, which can all increase their risk of systemic vascular complications (Klein et al., 1984a,b, 2002a,b). However, this is unlikely the case as many studies have demonstrated that traditional cardiovascular risk factors cannot fully explain the observed associations (Cheung et al., 2007c,e; Juutilainen et al., 2007; Klein et al., 1999a, 2004a; Miettinen et al., 1996), suggesting the existence of other biological mechanisms. Additionally, even if the systemic associations of diabetic retinopathy are purely due to shared risk factors, the importance of these associations with diabetic retinopathy should not be overlooked (see Section 10).

Second, it has been suggested that retinopathy is a manifestation of generalized vascular dysfunction caused by endothelial dysfunction or genetically determined alterations in the basement membrane metabolism associated with hyperglycemia (the Steno hypothesis) (Deckert et al., 1989; Parving et al., 1996). These vascular effects increase arterial or arteriolar wall permeability and leakage. It is hypothesized that in small arteriolar or capillary beds, retinopathy and nephropathy may develop as a result. In large arterial wall, increased permeability facilitates entry and accumulation of lipids, thus promoting the pathogenic cascade of atherosclerosis formation. Such a hypothesis, although appearing attractive, requires further validation in experimental studies.

Third, another possibility is that microvascular disease, evident as retinopathy lesions in the eye, may be present in other tissue and play a causal role in the development of atherosclerotic disease in people with diabetes. This is based on the observations that diabetic retinopathy is related not only to classic microvascular complications (e.g., nephropathy), but also complications of predominantly macrovascular etiology (e.g., coronary heart disease) (Table 3). There is now a large body of literature indicating that retinopathy is associated with several direct subclinical measures of large artery atherosclerosis, including carotid artery intima-media thickness or carotid plaque, arterial stiffness, coronary artery calcification, as well as atherosclerotic lesions detected from angiograms (Klein et al., 2002a; Norgaz et al., 2005; Rema et al., 2004; Wong et al., 2003b, 2007a; Yoshida et al., 1999). Based on the complex pathophysiological interactions between diabetic microvascular and macrovascular disease (Krentz et al., 2007; Stokes and Granger, 2005), a possible mechanism that may causally link retinopathy to the development of atherosclerosis is shown in Fig. 4. The microvasculature, which encompasses the majority of endothelial surface area, has been suggested to contribute to atherogenesis by creating a systemic inflammatory milieu (Stokes and Granger, 2005). In the presence of hyperglycemia (or other cardiovascular risk factors), the endothelial cells lining the microvasculature, including the retinal microcirculation, experience oxidative stress and become activated. This in turn promotes adhesive interactions between (and the activation or priming of) circulating inflammatory cells. Cytokines derived from the activation of these cells augments an uncontrolled synthesis of inflammatory mediators by blood and endothelial cells. The resultant surge of inflammatory mediators into the systemic circulation may act in concert with the flow disturbances and other physical factors that are unique to lesion-prone arteries to initiate the development of a nascent atheroma. As the disease progresses, this eventually evolves into a more complex atherosclerotic lesion that gives rise to clinical manifestation of cardiovascular disease (e.g., myocardial infarction). Thus, microvascular disease (indicated by the presence of retinopathy) may play a critical intermediate pathogenic role, by providing the inflammatory drive, in the development of atherosclerosis in people with diabetes. Support for this hypothesis is derived from numerous clinical and experimental studies showing that inflammation is a key factor in the development of diabetic retinopathy and atherosclerotic disease (Hansson, 2005; Ishida et al., 2003; Toda and Nakanishi-Toda, 2007).

Finally, there is a circulatory mechanism that may also provide a causal link for diabetic retinopathy and cardiovascular disease (Cheung et al., 2007a; Cheung and Wong, 2007). Microvascular disease is known to play an important role in the pathogenesis of diabetic cardiomyopathy, a complex and unique disease entity that is independent of coronary atherosclerosis and hypertension (Boudina and Abel, 2007). Recently, in the Multi-Ethnic Study of Atherosclerosis, diabetic retinopathy was found to be associated with left ventricular concentric remodeling, a known precursor for heart failure development (Cheung et al., 2007a). This finding is consistent with the ARIC study, which demonstrated a strong association of retinopathy with clinical congestive heart failure in people with diabetes (Wong et al., 2005b). Both studies offer good support for a pathogenic link between diabetic retinopathy and cardiomyopathy. It is possible that diabetic retinopathy may represent widespread systemic microcirculatory (resistance vessel) disease, which places an increased impedance burden, in part through reflected waves, on the diabetic heart. The excess load may in turn compromise the efficiency of cardiac performance (e.g., ventricular emptying and cardiac contractility), predisposing the development and manifestation of diabetic cardiomyopathy (Cheung et al., 2007a; Cheung and Wong, 2007).

9. Genetic links between retinopathy and systemic vascular complications

There is a great deal of interest in identifying the genetic factors involved in the development of systemic vascular

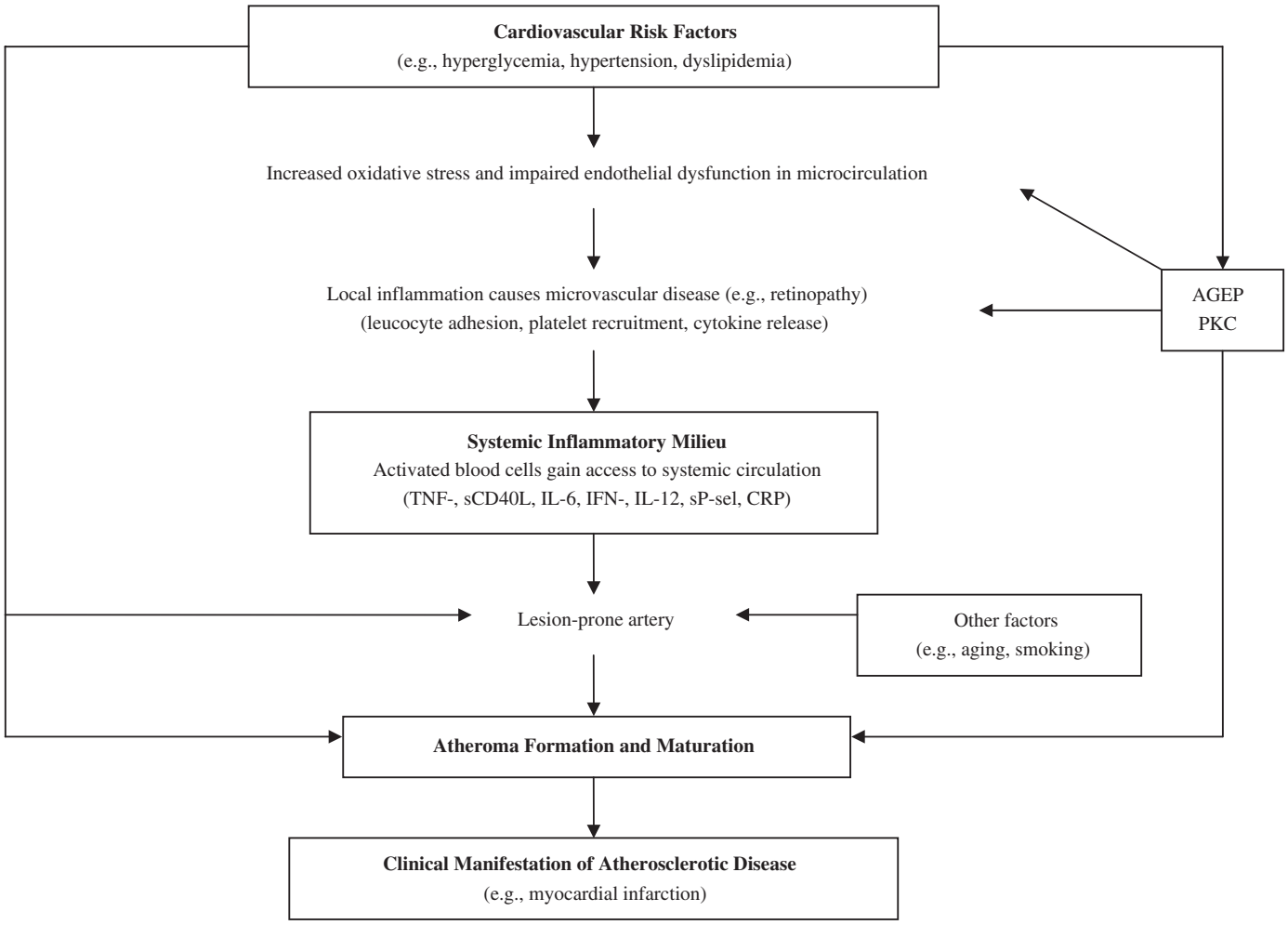

Fig. 4. Potential mechanisms linking diabetic microvascular (retinopathy) to macrovascular (atherosclerosis) disease. Cardiovascular risk factors increase oxidative stress, which activates the endothelial cells lining the microvasculature. The resultant imbalance between superoxide and nitric oxide leads to endothelial dysfunction, which is further augmented by advanced glycation end-products (AGEP) and protein kinase C (PKC) activation. This promotes the expression of adhesion molecules, leucocyte and platelet recruitment, and subsequent generation of inflammatory mediators. These mediators, along with activated leucocytes and platelets, gain access into the systemic circulation, where they prime, initiate, or exacerbate an inflammatory response in those lesion-prone large arteries that are rendered vulnerable to oxidative stress and inflammation due to chronic exposure to flow disturbances or cardiovascular risk factors. The inflammatory mediators derived from the microcirculation work in concert with other immune cells within the wall of lesion-prone arteries, leading to development of the nascent atheroma, which continues to mature and give rise to clinical manifestation of atherosclerotic disease.

disease, as knowledge of these genes may open new avenues for preventative and therapeutic strategies. However, previous studies have largely focused on the genetic associations of large vessel atherosclerotic disease (Nabel, 2003; Samani et al., 2007). There is less research on the genetic determinants of small vessel microvascular disease. Thus, understanding the genetic basis of diabetic retinopathy may uncover important insights into genetic etiology of systemic diabetic microangiopathy.

Twin studies and family-based analyses of diabetic populations have shown significant familial aggregation in retinopathy risk, and ethnic variations in retinopathy frequency do not appear to be solely attributable to environmental and biological risk factors (Alcolado, 1998; Cunha-Vaz and Bernardes, 2005; Fong et al., 2003; Simonelli et al., 2001; Warpeha and Chakravarthy, 2003). In addition, previous studies have found associations of some genetic markers with either severe retinopathy or absence of retinopathy (Table 4) (Looker et al., 2007). These findings indicate the presence of genetic determinants for predisposition or resistance to retinopathy development in people with diabetes. Importantly, several candidate genes associated with diabetic retinopathy have also been implicated in the pathogenesis of cardiovascular disease (Table 4). Additional studies, which are currently underway (e.g., the ARIC study and the Multi-Ethnic Study of Atherosclerosis), will determine whether retinopathy is a useful vascular phenotype for genetic association studies of systemic vascular diseases.

Table 4
Potential shared genetic associations of diabetic retinopathy and systemic vascular complications

Genes (or products)	Implicated in vascular complications	Associated with diabetic retinopathy
AR2 (aldose reductase)	Stroke (Watarai et al., 2006)	Demaine et al. (2000), Ichikawa et al. (1999), Kao et al. (1999)
HLA (human leukocyte antigen)	CHD (Palikhe et al., 2007)	Agardh et al. (1996), Cisse et al. (1998), Falck et al. (1997)
IgG (immunoglobulin subclass heavy chains)	Nephropathy (Jennette et al., 2006)	Stewart et al. (1993)
TNF (tumour necrosis factor in MHC)	Stroke (Hoppe et al., 2007)	Hawrami et al. (1996)
β-AR (beta adrenoreceptor)	CHD (Barbato et al., 2005)	Sakane et al. (1997)
PON1 (paraoxonase 1)	Stroke (Ranade et al., 2005)	Kao et al. (1998)
$\alpha 2\beta$ (alpha-2-beta integrin)	Stroke (Abumiya et al., 2000)	Matsubara et al. (2000)
NPY (neuropeptide Y)	CHD (Pettersson-Fernholm et al., 2004)	Niskanen et al. (2000)
ACE (angiotensin-converting enzyme)	CVD (Schunkert, 1997)	Hanyu et al. (1998), Matsumoto et al. (2000), Nagi et al. (1995), Rabensteiner et al. (1999)
IGF-1 (insulin growth factor 1)	Stroke (van Rijn et al., 2006)	Rietveld et al. (2006)
NOS2A (inducible nitric oxide synthase)	Cardiomyopathy (Dawson et al., 2005)	Warpeha et al. (1999)

CVD, cardiovascular disease; CHD, coronary heart disease.

10. Clinical significance of retinopathy in systemic disease screening

Understanding the relationship of diabetic retinopathy with systemic vascular diseases is clinically important not only to ophthalmologists, but also to physicians and others who treat and counsel patients with diabetes.

The assessment of cardiovascular risk in persons with diabetes is a key component of clinical care, allowing the implementation of targeted preventive treatments for patients who are asymptomatic but at high risk of systemic vascular complications. However, current cardiovascular risk prediction for diabetic populations is inaccurate and unsatisfactory (Brindle et al., 2006a,b; Guzder et al., 2005; Jurgensen, 2006; Stephens et al., 2004). A recent systematic review of data from more than 70,000 participants showed that the "classic" Framingham risk scores significantly underestimate the absolute risk of cardiovascular disease in diabetic populations (Brindle et al., 2006a). There is, therefore, clearly a need to identify additional predictors and biomarkers of cardiovascular disease risk in people with diabetes (Jurgensen, 2006). A major clinical challenge in risk prediction is that individual susceptibility to systemic vascular complications varies greatly. While some diabetic patients are particularly prone to develop complications, others appear to have a degree of "vascular resilience" despite long duration of disease. Therefore, to improve risk prediction, merely assessing traditional cardiovascular risk factors is inadequate, and a personalized and specific marker of underlying vascular disease may be more useful.

Being a common, uniquely specific, and non-invasively assessable measure of diabetic microangiopathic burden, retinopathy could serve as a useful biomarker to improve risk stratification in people with diabetes. This is supported by the strong biological rationale and consistent associations of diabetic retinopathy with both subclinical (Fig. 5) and clinical

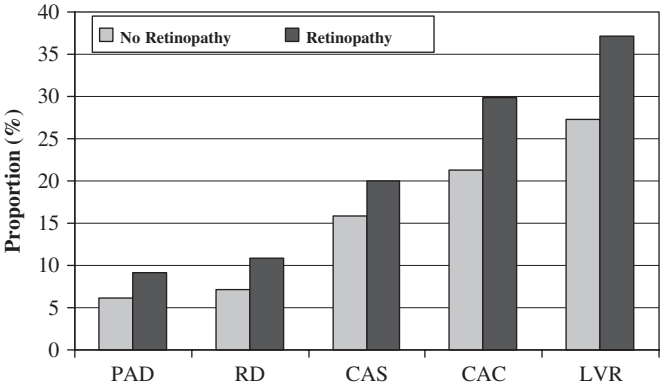

Fig. 5. Frequency of systemic vascular diseases in association with diabetic retinopathy (PAD, peripheral artery disease; RD, renal dysfunction; CAS, carotid artery stenosis; CAC, coronary artery calcification; LVR, left ventricular concentric remodeling) (Cheung N, unpublished data, the Multi-Ethnic Study of Atherosclerosis).

(Tables 2 and 3) vascular diseases. Thus, incorporating retinal assessment into the currently available cardiovascular risk prediction tools (Donnan et al., 2006; Lee et al., 2006) may improve the precision of risk prediction for cardiovascular disease in people with, and possibly also without, diabetes (Duprez, 2007; St Clair and Ballantyne, 2007; Wang et al., 2007). In fact, in certain clinical settings this is already the case. For example, retinopathy may guide pre-operative assessment and counseling of diabetic patients planning for elective cardiac revascularization procedures (Briguori et al., 2005; Kim et al., 2002; Ohno et al., 2006; Ono et al., 2002, 2006). However, to determine the cost-effectiveness of routine retinal evaluation, further studies are needed to examine the additional gain in risk assessment by adding retinopathy (and its severity) status to the currently used methods of prognosis prediction (e.g., Framingham risk score).

Apart from people with diabetes, there is emerging evidence that typical signs of early diabetic retinopathy

(e.g., microaneurysms, blot hemorrhages, hard exudates, and cotton wool spots) are relatively common in people without clinically diagnosed diabetes. Studies have reported high prevalence (up to 14%) and incidence (6–10%) rates of these retinopathy signs in non-diabetic populations (Chao et al., 2007; Cugati et al., 2006a; Klein et al., 1997; Yu et al., 1998). Retinopathy signs in people without diabetes have also been associated with a similar spectrum of cardiovascular disease, including stroke (Cooper et al., 2006; Mitchell et al., 2005; Wong et al., 2001a), ischemic heart disease (Hirai et al., 2007), congestive heart failure (Wong et al., 2005b), and renal dysfunction (Edwards et al., 2005; Wong et al., 2004a). Additionally, these retinopathy signs may also signify increased risks of diabetes, especially among persons with a family history of diabetes (Cugati et al., 2006b; Klein et al., 2006a; Wong et al., 2006b). These "non-diabetic" retinopathy signs may therefore reflect the adverse influences of long-standing but subtle abnormalities in glucose metabolism, blood pressure dysregulation, and other processes on the systemic circulatory system. Additional research is needed to further delineate the pathogenic basis and prognostic significance of these retinopathy signs in people without diabetes.

11. Therapeutic implications

The close relationship between diabetic retinopathy and systemic vascular disease may allow the development and use of common therapeutic strategies. The effectiveness of targeting systemic vascular risk factors in prevention of diabetic retinopathy is clearly demonstrated in several large randomized clinical trials in which controlling traditional cardiovascular risk factors (e.g., hyperglycemia, hypertension, dyslipidemia) reduces both the risk of retinopathy and cardiovascular disease in people with diabetes (UK Prospective Diabetes Study Group, 1998; Keech et al., 2005; Mohamed et al., 2007; Nathan et al., 2005; Wong et al., 2007b; Wong and Mitchell, 2007).

The question of whether specific systemic vascular therapies targeted at the microcirculation may have additional benefits in reducing retinopathy is less certain. The EURODIAB Controlled Trial of Lisinopril in Insulin-dependent Diabetes Mellitus (EUCLID) evaluated the effects of the angiotensin-converting enzyme (ACE) inhibitor lisinopril on diabetic retinopathy progression in normotensive, normoalbuminuric patients with type 1 diabetes. Lisinopril reduced the progression of diabetic retinopathy by 50% and progression to PDR by 80% over 2 years (Chaturvedi et al., 1998). The authors speculated that ACE inhibitors might have an additional benefit on diabetic retinopathy progression independent of blood pressure lowering. However, data from other studies did not find ACE inhibitors to be superior to non-specific blood pressure medications (UK Prospective Diabetes Study Group, 1998; Estacio et al., 2000; Schrier et al., 1996). In the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial, routine administration of a fixed combination of angiogensin converting enzyme inhibitor and diuretic reduced cardiovascular mortality, but not retinopathy risk (Patel et al., 2007).

Concurrently, it is important for ophthalmologists and physicians to be aware of potential systemic vascular effects of new diabetic retinopathy treatments. In recent years, the development of agents used to suppress vascular endothelial growth factors (VEGF) (e.g., pegatanib, ranibizumab, bevacizumab) have revolutionized the management of neovascular age-related macular degeneration (Wong et al., 2007c) and there is now emerging evidence that these anti-VEGF agents may also be useful in the management of diabetic retinopathy. Several clinical trials have demonstrated beneficial effects of anti-VEGF therapies for diabetic patients with macular edema (Arevalo et al., 2007; Chun et al., 2006; Cunningham et al., 2005; Scott et al., 2007) and neovascularization (Adamis et al., 2006; Avery et al., 2006). Although these treatments may poise imminent clinical application, the long-term systemic safety of anti-VEGF agents remains uncertain (Gillies and Wong, 2007; Wong et al., 2007c). VEGF plays a vital role in the maintenance of cardiovascular homeostasis, such as regulating the formation of collateral vessels that are critical to the viability of ischemic myocardium (Ferrara, 2001), a process that is particularly important in people with diabetes (Chou et al., 2002). Experimental studies have shown that impaired VEGF function is the seminal event in the pathogenesis of diabetic cardiomyopathy (Yoon et al., 2005), a major cause of heart failure in people with diabetes. These studies highlight the importance of normal physiological VEGF levels in the systemic circulatory system. Such levels may be hampered by the use of anti-VEGF therapies for diabetic retinopathy. While current anti-VEGF agents are administered intravitreally for treating diabetic retinopathy, it is known that systemic absorption of such agents occur (van Wijngaarden et al., 2005). Prolonged systemic exposure of anti-VEGF agents, due to the lengthy half-lives of some agents (e.g., 10 days for bevacizumab) and repeated administrations, may be associated with higher risks of systemic vascular complications, such as stroke and non-ocular hemorrhage (Gillies and Wong, 2007; Wong et al., 2007c). In patients with diabetic retinopathy, this could be an even more profound issue because of their preexisting excess cardiovascular risk associated with diabetes. It is therefore imperative to be cautious in prescribing anti-VEGF therapies to patients with diabetic retinopathy, and both clinicians and patients need to recognize that the true balance of risks and benefits will not be clear until data from long-term surveillance and new clinical trials become available.

12. Future research

This review on the systemic associations of diabetic retinopathy indicates several lines of future research. First, it remains inconclusive as to whether the associations of retinopathy with systemic vascular complications are

indeed causal in nature. Most hypothesized mechanisms discussed herein are based on observational clinical studies, which provide little direct evidence for the underlying mechanistic pathways. Additional experimental studies are needed, preferably with a specific focus to elucidate the pathophysiology of diabetic retinopathy. A better understanding in this aspect may shed light into the complex pathogenesis of diabetic vascular complications.

Second, the literature clearly indicates that diabetic retinopathy signs are not confined exclusively to people with clinically diagnosed diabetes. Typical signs of early diabetic retinopathy are relatively common in people without diabetes or hypertension (Chao et al., 2007; Cugati et al., 2006a; Klein et al., 1997; Yu et al., 1998). While there is some evidence that these retinopathy signs are associated with systemic vascular complications (Hirai et al., 2007), including incident diabetes and hypertension (Klein et al., 2006a; Wong et al., 2006b), data on this type of retinopathy remain relatively sparse. Further studies are needed to determine their pathophysiological basis and prognostic significance.

Third, as the review shows, the associations of diabetic retinopathy with systemic vascular complications appear to be most evident in middle-aged to older people with type 2 diabetes. Less consistent results have been seen in studies of younger people with type 1 diabetes (Tables 1 and 2). This could be due to a number of reasons related to methodological issues (e.g., insufficient length of follow-up, lack of power to detect associations due to generally smaller samples) or biological differences (e.g., better cardiovascular profile in younger participants, variations in susceptibility or resilience to systemic vascular complications). These uncertainties deserve further attention and should be addressed in future studies.

Finally, currently available risk prediction tools for systemic vascular diseases in persons with diabetes lack precision (Brindle et al., 2006a). Assessing the integrity of the vasculature by screening for retinopathy lesions may offer a means to obtain more relevant and "personalized" information regarding the patients' microvascular health. This "personalized" information (presence or absence of retinopathy) may correlate more closely with and be incorporated into the assessment of individual susceptibility to systemic vascular diseases (Turner et al., 2007), facilitating more precise quantification of the vascular effects of cardiovascular risk factors. Nevertheless, the clinical value of retinopathy assessment in the prediction of systemic vascular complications is yet to be fully determined. There is need for studies that are geared to examine the ability of retinopathy signs to provide incremental predictive information above and beyond the currently available risk prediction models.

13. Conclusion

In summary, diabetic retinopathy is a common microvascular complication that is not only a serious threat to vision, but may also signify an increased risk of morbidity and mortality attributable to systemic vascular complications. Retinopathy may, therefore, represent vascular damage and injury not only in the eyes but also in other vital organs such as the brain, heart, and kidneys in people with diabetes. For ophthalmologists, physicians, and other healthcare providers, it is important not to overlook the broader associations and clinical implications of diabetic retinopathy.

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