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The Diabetic Eye: A Window to the Heart & Vascular System

Caroline J. Magri[1]* and Stephen Fava[2]

[1]Department of Cardiac Services, Mater Dei Hospital, Tal-Qroqq, Msida MSD2090, Malta
[2]Diabetes & Endocrine Centre, Department of Internal Medicine, Mater Dei Hospital, Tal-Qroqq, Msida MSD2090, Malta

Abstract

Diabetic retinopathy is a serious complication of diabetes mellitus that could potentially lead to blindness. There is growing interest in the association between this important microvascular complication and cardiovascular morbidity and mortality. In this review article, the authors analyse the currently available data that link diabetic retinopathy with cardiovascular events in both type 1 and type 2 diabetic patients, including its association with coronary heart disease, heart failure, cerebrovascular disease and cardiac autonomic neuropathy. Important retinal signs that suggest underlying cardiovascular disease are discussed together with possible underlying pathophysiological mechanisms. The clinical implications involved are considered together with future studies. The latter should address not only possible pathological mechanisms, including genetic contribution, but also the implementation of diabetic retinopathy assessment as a risk stratification tool as well as novel therapeutic agents that might be beneficial both in the management of diabetic retinopathy and cardiovascular disease in general.

Introduction

Diabetic retinopathy is an important microvascular complication of diabetes mellitus, highly prevalent in both type 1 and type 2 diabetic subjects and a leading cause of blindness in developed countries [1]. The underlying pathological mechanisms are various and still incompletely understood. Both experimental and clinical studies have shown that sustained hyperglycemia secondary to long-standing diabetes ultimately leads to retinal hypoxia with consequent unregulated expression of various growth factors and uncontrolled retinal neovascularization in diabetic patients [2].

There is increasing interest in the association between microvascular and macrovascular disease in diabetic patients, as evidenced by the considerable number of studies showing an association between diabetic retinopathy (DR) and cardiovascular disease (CVD). The purpose of this review is to analyse the current data with regard to the association of DR and the different presentations of CVD, the possible pathophysiological pathways linking the two complications as well as clinical implications.

A systematic review of published literature was performed using Medline and Embase as computerized databases. The search included all published papers up to 16th June, 2012. The terms "diabetic retinopathy" and "cardiovascular disease", "ischaemic heart disease", "cardiovascular morbidity", "cardiovascular mortality", "heart failure" and "stroke" were used in the search strategy.

Diabetic Retinopathy & Cardiovascular Disease

The association between DR and cardiovascular morbidity and mortality has been studied in various populations, as shown in table 1. More than 20 years ago, the Framingham Heart and Eye Study showed that DR was associated with prevalent cardiovascular disease [3]. Consequent epidemiological studies showed conflicting results with some reporting an increased coronary heart disease (CHD) risk among diabetic individuals with retinopathy whilst controlling for confounding risk factors [4-6] while others suggesting that the association of DR with CHD was mainly due to shared risk factors [7-9]. In the more recent Atherosclerosis Risk in Communities (ARIC) Study, whereby the occurrence of DR was evaluated by standardized assessment of retinal photographs rather than fundoscopy, DR was associated with a twofold higher risk of incident CHD and threefold higher risk of fatal CHD, independent of glycaemic levels, cardiovascular risk factors, and large-vessel atherosclerosis. This association appeared to be graded with retinopathy severity and was significant in both genders. Furthermore, the association of DR with incident CHD remained significant after additional adjustments for inflammatory markers [hazard ratio (HR) 2.08, 95% confidence interval (CI) 1.39-3.12], carotid artery intima-media thickness (IMT) (HR 1.99, 95% CI 1.30 –3.04), and nephropathy (HR 1.91, 95% CI 1.18-3.08) [10].

In the latest meta-analysis by Kramer et al. [11], it was shown that the presence of any degree of DR increased the chance for all-cause mortality and/or cardiovascular events by 2.34 (95% CI 1.96-2.80) compared with type 2 diabetic subjects without DR. In patients with type 1 DM (n=4,438), the corresponding odds ratio was 4.10 (1.50-11.18). Importantly, these associations remained significant after adjusting for traditional cardiovascular risk factors.

This strong association between DR and CHD events can be explained by an increased incidence of more diffuse and severe coronary atherosclerosis in subjects with DR as compared to diabetic subjects without retinopathy [12]. Higher degrees of coronary calcification might also play a role [13]. In the Veterans Affairs Diabetes Trial, Reaven et al. have indicated an important relationship between DR and extent of coronary atherosclerosis as measured by computed tomography-detectable coronary artery calcium (CAC) such that individuals with proliferative DR were approximately six-fold more likely to have CAC >400 than those with no proliferative DR, even following adjustment for other CVD risk factors [14]. In addition, it has been shown that coronary flow reserve is significantly restricted in patients with diabetes mellitus (DM), and its reduction is more marked in those with diabetic retinopathy, especially in advanced retinopathy

***Corresponding author:** Dr. Caroline J. Magri, Department of Cardiac Services, Mater Dei Hospital, Jesmel, Imdina Road, Zebbug, ZBG05, Malta, Tel: (+356) 79258763/(+356) 79847431; Fax: (+356) 25454154; E-mail: cjmagri013@yahoo.com

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Reference	Study	Population	Follow-up	Study end-points	Relative risk (95% CI)	Adjusting factors
Hiller et al. [3]	Framingham Heart & Eye Study	206 type 2 DM	N/A (cross-sectional study)	Cardiovascular events, i.e. CHD, intermittent claudication, congestive heart failure, and stroke	14.3 (2.7-101.9) For ages 52-64 years	Sex, duration of diabetes, age at diagnosis of diabetes, and history of insulin treatment
Miettinen et al. [4]		1,059 Finnish type 2 DM subjects	7 years	CHD death or nonfatal myocardial infarction	2.12 (1.02-4.39) for PDR	Age, area, sex, total cholesterol, HDL cholesterol, triglycerides, smoking, hypertension, urinary protein, A1c
Klein et al. [7]	Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)	996 younger onset (<30 years of age at diagnosis & taking insulin) & 1370 older-onset DM patients	16 years	All-cause & cause-specific mortality	All-cause mortality: mild NPDR 1.34 (1.29–1.71) and PDR 1.89 (1.43–2.50); CHD mortality: mild NPDR 1.21 (0.95–1.53) and PDR 1.43 (0.94–2.17); stroke mortality: mild NPDR 1.30 (0.92–1.85) and PDR 1.88 (1.03–3.43)	Age, sex, duration of diabetes, A1C, systolic blood pressure, prior CVD, smoking (pack-years), diuretic use
Fuller et al. [50]	World Health Organization Multinational Study of Vascular Disease in Diabetes	1390 type 2 DM	12 years	CVD mortality	1.2 (0.8–1.8) in men and 2.7 (1.8–4.1) in women	Age, duration of diabetes, systolic blood pressure, cholesterol, smoking, proteinuria, electrocardiographic abnormalities, glucose
Faglia et al. [5]	Milan Study on Atherosclerosis (MiSAD)	735 Italian type 2 DM	5 years	Cardiac death, myocardial infarction, resting angina, and effort angina	2.37 (1.06–5.31)	Age, sex, diabetes duration
Van Hecke et al. [8]	Hoorn Study	631 nonDM & DM subjects	10.7 years (median)	All-cause and CVD mortality	All-cause mortality in DM subjects 2.05 (1.23–3.44); CVD mortality in DM subjects 2.20 (1.03–4.70)	Age & sex
Cusick et al. [9]	Early Treatment Diabetic Retinopathy Study (ETDRS)	2267 type 2 DM	5 years	All-cause mortality	Moderate NPDR 1.27 (0.94–1.72); Severe NPDR 1.48 (1.03– 2.15); mild PDR 1.28 (0.80– 0.06); moderate/ high PDR 2.02 (1.28–3.19)	Age, sex, BMI, A1C, total cholesterol, triglycerides, fibrinogen, cigarette smoking, daily insulin use, the use of antihypertensive medications, other baseline diabetes complications
Targher et al. [64]	Valpolicella Heart Diabetes Study	248 type 2 DM developed CVD & 496 type 2 DM control subjects	5 years	Nonfatal CHD (i.e. MI and coronary revascularization), ischemic stroke, or cardiovascular death	NPDR 1.8 (1.2–2.3); PDR 4.1 (2.0–8.9)	Age, sex, BMI, smoking history, plasma lipids, A1C, diabetes duration, diabetes treatment
Juutilainen et al. [6]		824 Finnish type 2 DM (425 men, 399 female)	18 years	All-cause, CVD & CHD mortality	Men: all-cause mortality 1.34 (0.98 –1.83), CVD mortality 1.30 (0.86 –1.96), & CHD mortality 1.18 (0.74 –1.89) for BDR, 3.05 (1.70 –5.45), 3.32 (1.61– 6.78), & 2.54 (1.07– 6.04), respectively, for PDR; Females: 1.61 (1.17–2.22), 1.71 (1.17–2.51), and 1.79 (1.13–2.85), respectively, for BDR, 2.92 (1.41– 6.06), 3.17 (1.38 –7.30), and 4.98 (2.06 –12.06), respectively, for PDR	Current smoking, hypertension, total cholesterol, HDL cholesterol, glycaemic control of diabetes, duration of diabetes, and proteinuria
Cheung et al. [10]	Atherosclerosis Risk in Communities Study (ARIC)	214 American type 2 DM	7.8 years	Incident CHD events, i.e. myocardial infarction, fatal CHD, or coronary revascularisation	Incident CHD: 2.07 (1.38-3.11) Fatal CHD: 3.35 (1.4-8.01)	Age, sex, race, study centre, fasting glucose, A1C, duration of diabetes, blood pressure, antihypertensive treatment, cigarette smoking, BMI, and lipid profile,

Liew et al. [65]	Blue Mountains Eye Study	199 Australian type 2 DM	12 years	CHD deaths	2.21 (1.2-4.05)	Age, gender, smoking, hypertension
Gimeno-Orna et al. [51]		458 type 2 DM	6.7 years	Nonfatal or fatal CVD (i.e. unstable angina including revascularization, nonfatal/ fatal MI, TIA, nonfatal /fatal stroke, lower-leg amputation, terminal CHF, sudden death).	NPDR 1.71 (1.1-2.66); PDR 2.95 (1.1-3.56)	Age, gender, blood pressure, smoking status, total cholesterol/HDL ratio, A1c, body mass index, diabetes duration, insulin treatment, baseline coronary heart disease, stroke or lower-leg ischemia, baseline UAE, and glomerular filtration rate

Abbreviations: A1c: Glycated Haemoglobin; BDR: Background Diabetic Retinopathy; BMI: Body Mass Index; CHD: Coronary Heart Disease; CHF: Congestive Heart Failure; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; MI: Myocardial Infarction; NPDR: Non-Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy; TIA: Transient Ischaemic Attack; UAE: Urinary Albumin Excretion

Table 1: Studies investigation the association between diabetic retinopathy and cardiovascular disease.

[15]. Impaired coronary vasoreactivity might also play a role [16] as well as lower collateral coronary score [17].

DR has also recently been shown to be associated with myocardial perfusion abnormalities in subjects with cardiac and noncardiac chest pain [18]. Furthermore, Tryniszewski et al. showed that the extent of heart muscle perfusion defect was significantly related with the severity of DR [19]. These studies suggest that ophthalmological assessment for the presence of DR can be a useful risk assessment tool of ischaemic heart disease.

Diabetic Retinopathy & Heart Failure

A limited number of studies report an association between DR and heart failure. Analysis of the Framingham Eye Study showed that type 2 DM subjects aged 52-64 years had an increased risk of developing CVD, i.e. coronary heart disease, intermittent claudication, congestive heart failure, and stroke (odds ratio [OR] 14.3, 95% CI 2.7-101.9) [3]. In the general population constituting the ARIC Study, participants with retinopathy had an increased incidence of CHF compared with those without retinopathy that persisted following multifactorial adjustment for a number of risk factors including diabetes status (relative risk [RR] 1.96; 95% CI 1.51-2.54) [20]. In a more recent analysis of the ARIC study, it was shown that, after 9-year follow-up period, type 2 DM subjects with retinopathy were more likely to develop heart failure (as noted from hospital stay and death records) than subjects without retinopathy (cumulative incidence of 21.6% vs. 8.5%) [21]. This association remained significant after controlling for age, gender, race, smoking, diabetes duration, insulin use, blood pressure, lipid profile, and other risk factors (HR 2.71; 95% CI: 1.46 to 5.05). In addition, following further adjustments for glycaemic control, carotid atherosclerosis, and serum markers of endothelial dysfunction, the increased risk among subjects with DR persisted (HR 2.20, 95% CI: 1.08 to 4.47).

It has been suggested that DR indicates small vessel disease throughout the cardiovascular system that leads to increased impedance burden on the heart with consequent systolic and diastolic dysfunction [21]. Alternatively, small vessel disease within the myocardium leads to diastolic dysfunction which, over the years leads to systolic dysfunction and ultimately overt heart failure. Interestingly, Takeda et al. have recently shown that DR is associated with LV diastolic dysfunction as assessed by the diastolic index of echocardiographic colour kinesis in diabetic subjects with preserved ejection fraction (≥ 50%) [22]. However, this was a small retrospective cross-sectional study (n=63), multivariate adjustment was not performed and no difference was found in diastolic dysfunction between subjects with and without DR when assessed using transmitral flow velocity and tissue Doppler imaging of the mitral annulus. A larger prospective study is desirable.

Diabetic Retinopathy & Cerebrovascular Disease

A number of studies have shown an association between DR and stroke in both type 1 [23,24] and type 2 [23,25] diabetic patients. Recently, using the ARIC database, in a population-based, prospective cohort study of 1617 middle-aged persons with type 2 DM followed-up for 7.8 years, it was shown that the presence of DR was associated with an increased risk of ischaemic stroke (HR 2.34, 95% CI 1.13-4.86), even after adjustment for age, gender, race, centre, 6-year mean arterial blood pressure, anti-hypertensive treatment use, fasting glucose, insulin treatment, duration of diabetes, high-density lipoprotein and low-density lipoprotein cholesterol levels and cigarette smoking status [25]. The ARIC study also showed that retinopathy is independently associated with poorer cognitive function in middle-aged persons without stroke [26] whilst a sub-study of the ARIC cohort in which participants had cranial magnetic resonance imaging (MRI) scans, showed that retinopathy is independently associated with sulcal and ventricular enlargement on MRI in healthy, middle-aged people [27]. Large studies addressing the association of retinopathy with cognitive decline and dementia in a specific diabetic population are lacking; these would be highly informative since they would support a possible contribution of small vessel disease in the pathogenesis of a wide spectrum of cerebrovascular conditions in diabetes.

Diabetic Retinopathy & Cardiac Autonomic Neuropathy

Studies have shown an association between DR and cardiac autonomic neuropathy (CAN) in both type 1 and type 2 diabetic patients. CAN is closely linked with mortality secondary to cardiovascular conditions [28,29]. In a cohort of 162 type 1 DM patients followed for 15 to 21 years, Krolewski et al. showed a relationship between abnormal cardiac autonomic tests and proliferative DR [30]. Likewise, in type 2 DM, CAN as assessed by R-R interval variability and resting heart rate (HR) was also associated with DR severity [31,32].

Furthermore, Kramer et al. have shown an association between early autonomic dysfunction (as evidenced by reduced HR response during exercise) and DR [33]. In this cross-sectional study of 72 type 2 and 40 type 1 DM patients, lower maximum HR increase (OR 1.62, 95% CI 1.03-2.54; p=0.036), and lower HR recovery at 2 (OR 2.04, 95% CI 1.16-3.57; p=0.012) and 4 min (OR 2.67, 95% CI 1.37-5.20; p=0.004) were associated with DR in the 72 type 2 DM patients studied, after adjusting for confounding factors, i.e., glycated haemoglobin levels (HbA1c), DM duration, systolic blood pressure, age, albuminuria,

and estimated workload in metabolic equivalents (METs). In type 1 DM patients, the absence of an increase in HR at intervals of 10 beats per minute each during exercise was associated with a significantly increased risk of DR (OR 2.01, 95% CI 1.1-3.69; p=0.02) when adjusted for DM duration, HbA1c and diastolic blood pressure. Similar findings were shown recently in a cross-sectional study of 84 type 1 DM patients conducted by Almeida et al. [34]. It has been suggested that CAN and DR are linked via abnormal BP regulation whereby autonomic dysfunction may lead to abnormal autoregulation of retinal vessels, resulting in abnormal BP patterns adversely affecting the retinal blood supply [33]. This merits further study.

Retinal Prognosticators

A number of studies have revealed that cardiovascular morbidity and mortality increase with worsening diabetic retinopathy [21,24]. Clinically significant macular oedema was also found to be associated with decreased survival in subjects with older-onset DM [35]. Other retinal findings worth further investigation in a specific diabetic population include retinal vascular caliber and retinal arteriole: venule ratio (AVR). In a diabetic cohort, it was shown that generalized as well as focal retinal arteriolar narrowing were associated with an increased risk of developing lower extremity amputation over a 20-year follow-up period [36]. In addition, AVR has been shown to be associated with the incidence and progression of DR [37]. In the WESDR study [38], AVR was associated with myocardial infarction while both the severity of retinopathy and AVR were associated with heart disease mortality.

Interestingly, in a population-based cohort study of 3654 Australians, it was shown that wider venules were associated with CHD death [RR 1.8 (95% CI 1.1 to 2.7) and RR 2.0 (95% CI 1.1 to 3.6) per standard deviation (SD) increase in venular calibre for men and women, respectively, after adjustment] in people aged 49-75 years. In addition, in females of same age range, smaller AVR and narrower arterioles were associated with CHD death (RR 1.5, 95% CI 1.1 to 2.2, and RR 1.9, 95% CI 1.0 to 3.5 per SD decrease in AVR and arteriolar calibre, respectively, after adjustment) [39].

The ever-increasing development in ophthalmic imaging will enable more accurate assessment of the retina and will probably provide useful information with regards the clinical management of important systemic complications in the diabetic population.

Pathophysiologic Mechanisms

The studies demonstrating a relation between DR and CVD were largely cross-sectional studies. Consequently, the mechanisms linking microvascular disease, as evidenced by retinopathy, to an increased risk of CVD in diabetic subjects are still hypothetical and remain to be elucidated. It is possible that subjects with DR have a greater burden of cardiovascular risk factors compared to those without DR, leading to an increased predisposition to develop CHD. However, in the majority of studies outlined, the association between DR and CHD remained statistically significant following multivariate adjustment for possible confounding risk factors. Another explanation is that DR is an early sign of inflammation and endothelial dysfunction that ultimately leads to CHD [40]. Thus, in diabetic individuals, retinopathy was associated with inflammatory activity and endothelial dysfunction as evidenced by a positive association with levels of C-reactive protein (CRP) and soluble intercellular adhesion molecule-1 (sICAM-1) [41]. It has been suggested that this generalised vascular dysfunction increases arterial or arteriolar wall permeability and leakage, leading to retinopathy or nephropathy in small arteriolar or capillary beds and facilitating entry and accumulation of lipids in large arteries, leading to atherosclerosis formation [42]. However, the Hoorn Study failed to show any association between retinal microvascular abnormalities and large artery endothelial dysfunction (assessed using endothelium-dependent flow-mediated dilation) and intima-media thickness [43]. The role of endothelial dysfunction merits further investigation, preferably in larger diabetic populations.

Other possible mechanisms include insulin resistance, sympathetic overdrive, oxidative stress and endothelin [21]. Advanced glycation end-products (AGEs) have also gained increasing interest in view that they can cause both micro- and macrovascular complications in DM through the formation of cross-links between molecules in the basement membrane of the extracellular matrix and by engaging the receptor for AGEs (RAGE). The latter leads to upregulation of the transcription factor nuclear factor-kappaβ and its target genes. Monocyte activation ensues as well as increased endothelial permeability to macromolecules. AGEs block nitric oxide activity in the endothelium and cause the production of reactive oxygen species, thus contributing to the development of atherosclerosis and various complications in diabetic patients [44].

Additionally, rheological mechanisms could contribute to the pathophysiological mechanisms. Increased blood viscosity, reduced red blood cell deformability, reduced blood flow and increased platelet aggregability could all play a role and lead to micro- and macrovascular complications in DM [45]. In keeping with this, Coppola et al. have shown that whereas the blood viscosity normally decreases during the postprandial period in normal individuals, it does not in aged type 2 diabetic subjects, thus pointing to the occurrence of alterations in the regulation of the haemorrheological equilibrium in the postprandial period in type 2 diabetic patients [46]. This could lead to atherothrombosis via increased vascular resistance with consequent shear-stress damage at the blood-endothelial surface and increased plasma protein interaction with the endothelium in the post-stenotic recirculation zones [45,47].

Circulatory mechanisms could also play a role. These include abnormalities both in the coronary microcirculation as well as generalised microvascular disease. Thus, DR could be a marker of generalised microvascular disease, including the coronary microcirculation, secondary to vascular endothelial dysfunction acting in combination with a systemic inflammatory milieu and oxidative stress that is highly prevalent in diabetic subjects [42]. Thus, DR was shown to be associated with intima-media thickness (IMT) and arterial stiffness (measured by assessing augmentation index) in an Asian-Indian type 2 DM population [48].

It has been suggested that genetic mechanisms might provide a link between DR and CVD (reviewed by 46). Studies have shown associations of some genetic markers with either severe retinopathy or resistance to retinopathy [49]. Interestingly, a number of candidate genes associated with DR have also been shown to play a role in the pathogenesis of CVD, e.g. HLA (human leukocyte antigen), β-AR (beta-adrenoreceptor), ACE (angiotensin-converting enzyme), NPY (neuropeptide Y) and NOS2A (inducible nitric oxide synthase) genes (46). More studies are needed to clarify the actual contribution of DR to the pathophysiology of CVD; this is crucial from aetiological, preventive and therapeutic aspects.

Some studies have found DR to be associated with CVD independently of nephropathy [4,6,50,51]. This is important in view of the known associations between DR and nephropathy and between

DR and CVD. These findings therefore indicate that DR has prognostic implications additional to those associated with diabetic nephropathy (DN). Although both DR and DN are classified as microvascular diseases, they have varying underlying pathophysiologies. This indicates that DR and DN furnish different, although overlapping, prognostic information.

Clinical Implications

In view of the fact that retinopathy lesions can be readily evaluated with direct ophthalmoscopy which is both widely used and available, assessment for DR can be a very useful tool in risk stratification of diabetic subjects. This is important since current cardiovascular risk prediction tools for diabetic populations are inaccurate and unsatisfactory, as shown by the systematic review performed by Brindle et al. [52]. There is therefore the need to identify more strong predictors and biomarkers of CVD in the diabetic population [52]. The additional gain in risk assessment by adding DR status to the currently used methods of risk prediction still needs to be assessed in further studies [42]. However routine screening for DR is well-established in preventing visual loss and hence even a small gain would be cost-effective. On the other hand, measurement of vessel caliber is not routinely done and requires special equipment and expertise.

Undoubtedly, the presence of DR should lead to a more thorough assessment of the cardiovascular system, both in symptomatic and asymptomatic patients, to enable early implementation of medical and/or interventional treatment, together with closer follow-up. In keeping with this, DR has been shown to be a predictor of adverse cardiovascular events following percutaneous coronary intervention [53,54] and coronary artery bypass grafting [55,56].

The possible therapeutic implications of the association between DR and CHD have been reviewed by Cheung et al. [42]. It is still questionable whether specific therapies targeted at the microcirculation, such as angiotensin-converting enzyme inhibitors, may have additional benefits in decreasing the progression of DR [57]. Another important point to consider is the use of agents to suppress vascular endothelial growth factors (VEGF) (e.g., pegatanib, ranibizumab, bevacizumab). Whereas various studies have shown the beneficial effects of anti-VEGF therapies in the management of macular oedema [58-60] and neovascularization [61,62] in diabetic patients, it is possible that repeated administrations of these agents leads to cardiovascular morbidity. The main systemic side-effects following intravitreal administration of these agents include thrombosis, hemorrhage, hypertension, proteinuria, while the less frequent side-effects include cerebrovascular accidents, myocardial infarction, transient ischemic attacks, deep vein thrombosis, pulmonary embolism and thrombophlebitis (reviewed by Semeraro et al. [63]). Therefore, clinicians should prescribe these agents with caution, and especially so in subjects with DR who are at high risk of CVD, until further studies will help elucidate the benefits and risks associated with this novel treatment.

Conclusions

Diabetic retinopathy is not only a serious microvascular diabetes-related complication that may potentially lead to blindness, but it may also indicate increased risk of adverse cardiovascular events. Various studies have shown its association with fatal and non-fatal CHD, CHF, cerebrovascular disease as well as cardiac autonomic neuropathy. However, the underlying mechanisms linking DR with cardiovascular events are still incompletely understood. Future research should thus aim at addressing this important issue, including any possible genetic mechanisms. Furthermore, studies should try to assess whether there is a difference in the prognostic significance of DR in type 1 and type 2 DM patients since most of the studies showing a strong positive association between DR and CVD were conducted in type 2 DM subjects. Finally the implementation of DR assessment as risk stratification tool should also be assessed. In the meantime, clinicians should thoroughly assess all diabetic patients with retinopathy from a cardiovascular point of view and provide intensive medications where necessary with the aim of decreasing the CVD morbidity and mortality associated with this condition.

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