

REVIEW ARTICLE

Association between diabetic eye disease and other complications of diabetes: Implications for care. A systematic review

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The aim of this systematic review was to examine the associations between diabetic retinopathy (DR) and the common micro- and macrovascular complications of diabetes mellitus, and how these could potentially affect clinical practice. A structured search of the PubMed database identified studies of patients with diabetes that assessed the presence or development of DR in conjunction with other vascular complications of diabetes. From 70 included studies, we found that DR is consistently associated with other complications of diabetes, with the severity of DR linked to a higher risk of the presence of, or of developing, other micro- and macrovascular complications. In particular, DR increases the likelihood of having or developing nephropathy and is also a strong predictor of stroke and cardiovascular disease, and progression of DR significantly increases this risk. Proliferative DR is a strong risk factor for peripheral arterial disease, which carries a risk of lower extremity ulceration and amputation. Additionally, our findings suggest that a patient with DR has an overall worse prognosis than a patient without DR. In conclusion, this analysis highlights the need for a coordinated and collaborative approach to patient management. Given the widespread use of DR screening programmes that can be performed outside of an ophthalmology office, and the overall cost-effectiveness of DR screening, the presence and severity of DR can be a means of identifying patients at increased risk for micro- and macrovascular complications, enabling earlier detection, referral and intervention with the aim of reducing morbidity and mortality among patients with diabetes. Healthcare professionals involved in the management of diabetes should encourage regular DR screening.

KEYWORDS

diabetes complications, diabetic retinopathy

1 | INTRODUCTION

Diabetic retinopathy (DR) is the most common complication of diabetes and remains the leading cause of blindness among working-age individuals in most developed countries.^{1,2} DR has long been considered a microvascular complication of diabetes; however, growing evidence suggests that abnormalities in retinal function can be detected in patients without any evidence of microvascular abnormalities, and the American Diabetes Association defined DR as a highly specific neurovascular complication.^{3,4}

DR is characterized by degeneration of endothelial cells and pericytes in retinal capillaries, which leads to ischaemia and the formation of microaneurysms.⁵ In the advanced stage of the disease, pathologic proliferation of retinal vessels occurs via upregulation of proangiogenic mediators, particularly vascular endothelial growth factor (VEGF).⁵ The resulting alterations of the retinal microvasculature and increased leakage from the retinal vessels may lead to sight-threatening vision loss.⁵ As the number of adults with diabetes worldwide is projected to increase from 415 million to 642 million by 2040,⁶ DR represents a significant global health threat. According to recent estimates, DR

accounts for 2.6 million cases of moderate to severe vision impairment worldwide, and this figure is expected to rise to 3.2 million by 2020.⁷

A pooled analysis of data from 35 studies conducted in the United States, Europe, Asia and Australia estimated that in 2010, worldwide, the number of patients with diabetes who had DR or vision-threatening DR (VTDR) was 92.6 and 28.4 million, corresponding to prevalence rates of 34.6% and 10.2%, respectively.¹ The global number of patients with diabetes who have retinopathy in the general population is projected to reach 191 million by 2030.⁸

Longer duration of diabetes is a major risk factor for DR.⁹ One study estimated that individuals who have type 1 diabetes mellitus (T1DM) for 20 years or more are 2.7 times more likely to develop retinopathy (relative risk [RR], 2.69; 96% confidence interval [CI], 2.47-2.93), and are 8.7 times more likely to have VTDR (RR, 8.69; 96% CI, 7.10-10.63), compared with individuals who have type 2 diabetes mellitus (T2DM) for less than 10 years.¹ However, more recently, DR has also been reported with various prevalence rates in patients with newly diagnosed diabetes mellitus.²

Treatment of DR significantly improved after the introduction of pharmacological agents with anti-VEGF activity. In phase III clinical trials of patients with diabetic macular oedema (DMO), a complication of DR, anti-VEGF therapy improved visual acuity from baseline and lowered the risk of progression to proliferative DR (PDR), indicating that VEGF inhibitors can interfere with the underlying pathogenesis of retinopathy.^{10,11} However, delayed DR screening and detection can hamper treatment. In one UK study, there was a significant trend ($P = 0.0004$) relating time from diagnosis of T2DM to detection of worsening retinopathy at screening.¹²

The consequences of delayed detection of DR extend beyond suboptimal visual acuity outcomes; increasing evidence links retinopathy to other microvascular complications of diabetes, most notably nephropathy and cardiac autonomic neuropathy (CAN).¹³⁻¹⁶ Retinopathy has also been linked to macrovascular comorbidities, including stroke, myocardial infarction and, potentially, heart failure.¹⁷⁻¹⁹ Additionally, a recent meta-analysis of epidemiological observational studies found that patients with diabetes who have DR are at increased risk of all-cause mortality, compared with patients with diabetes who do not have retinopathy (risk ratio [RR], 2.33; 95% CI, 1.92-2.81).¹⁹

With regard to the link between DR and cardiovascular events, Alonso et al. conducted a cross-sectional study of patients with T2DM who did not have renal deficits or prior history of cardiovascular disease (CVD). They found that the percentage of patients with carotid plaques, a risk factor for ischaemic stroke,²⁰ was higher among those with DR than among those without DR (68.0% vs 52.2%; $P = 0.0045$).¹⁷ Other research has demonstrated that, not only is DR associated with future cardiovascular events, but also that the risk of these events increases with increasing severity of DR (hazard ratio [HR], 1.49; 95% CI, 1.12-1.97 for mild retinopathy and HR, 2.35; 95% CI, 1.47-3.76 for severe retinopathy).¹⁸ Similar associations have been observed between DR and cerebrovascular events.²¹⁻²³

Our analysis aimed to further elucidate the relationships between DR and micro- and macrovascular complications, and to identify any examples where the presence of DR increases the risk of having or developing other complications of diabetes. Irrespective of the directionality of any such relationships, that is, whether DR is antecedent

to or develops after other complications, an increased awareness and understanding of these relationships can help promote timely referral and discussion between ophthalmologists and the other healthcare professionals involved in the management of these co-morbidities, including diabetologists, cardiologists, vascular surgeons and nephrologists. There is currently a lack of communication between the diverse healthcare disciplines involved in the treatment of patients with diabetes, which can lead to a breakdown in the care pathway and contributes to suboptimal patient outcomes. DR screening can be performed effectively outside the ophthalmologist's office by trained personnel (eg, primary care physician's office, optometrist, mobile unit). Indeed, this approach is generally deemed more practical and efficient than screening at ophthalmology offices.²⁴ The identification of patients with DR and a greater understanding of the wider relevance of DR may provide an opportunity to identify patients who are at increased risk of the presence or development of other diabetic complications, thus forming the basis for enhanced inter-disciplinary communication with the aim of improving patient outcomes.

2 | MATERIALS AND METHODS

2.1 | Research questions

The aim of this study was to answer the following research questions:

- Is there a link between DR and the micro- and macrovascular complications of diabetes?
- Does DR increase the risk of other complications of diabetes?
- What is the clinical significance of the associations between DR and other complications of diabetes?

2.2 | Literature search strategy

A literature search of the PubMed database was performed using a structured approach to identify relevant studies. The search term combination used was: ((((((diabetes) OR diabetic) OR diabetes mellitus) AND (((retinopathy) OR eye disease) OR macular disease))) AND (((((((neuropathy) OR neurological complication*)) OR (((nephropathy) OR renal disease) OR microalbuminuria) OR kidney disease)) OR (((((coronary heart disease) OR myocardial ischemia) OR cardiovascular disease) OR cardiovascular event*)) OR myocardial infarction) OR atherosclerosis)) OR (((((((cerebrovascular accident) OR cerebral infarction) OR cerebral ischemia) OR cerebrovascular disease) OR stroke) OR cerebrovascular event*)) OR transient ischemic attack)) OR (((((((intermittent claudication) OR vasculopathy) OR peripheral artery disease) OR ulcer) OR gangrene) OR peripheral vascular disease) OR necrosis) OR amputation))) AND (((((((risk) OR risk factor) OR association) OR correlation) OR logistic regression) OR predictive) OR predictor) OR predictive factor) OR link) OR relationship)).

Diabetes search terms were restricted to title content, and the remaining search terms were limited to title and abstract. Only peer-reviewed original research studies and reviews were included, and no geographical, date or language restrictions were applied.

2.3 | Study selection

Inclusion criteria were: (a) studies involving a population of patients with diabetes, with no restriction on clinical characteristics, glycated haemoglobin [HbA1c] and comorbidity or treatment history, and (b) studies that evaluated the presence or development of DR in conjunction with other vascular complications of diabetes.

2.4 | Data extraction

For the first stage of the selection process, identified titles were screened for relevance. If the publication passed this stage, the abstract was read to verify relevance, and if this was confirmed, the full text of the paper was assessed against the inclusion and exclusion criteria. Extracted information included study design, population characteristics, conclusions and limitations. Precedence was given to studies specifically designed to investigate the relationship between DR and other complications of diabetes, and to studies in which statistical analyses were adjusted for confounding factors.

3 | RESULTS

3.1 | Study selection

Of 3028 potentially relevant papers initially identified through the PubMed search, 2418 were excluded because they were not relevant to the research questions. The abstracts of the remaining 610 papers were read, which led to the exclusion of an additional 330 papers. This resulted in a total of 280 papers of which the full text was assessed for relevance. Of these papers, 71 met the criteria for inclusion in the structured review.

3.2 | DR and other microvascular complications of diabetes

A correlation was found between DR and other microvascular complications of diabetes, specifically, nephropathy and neuropathy. A summary of the findings of the reviewed studies that examined the

TABLE 1 Studies describing the association between DR and nephropathy and renal decline

Reference Study population	Study design (n)	Independent variable	Dependent variable	OR/HR/RR (95% CI)	P value
El-Asrar ¹⁴ T1DM & T2DM	Cross-sectional (648)	DR	Nephropathy	All: OR = 4.37 (2.19-8.71) T1DM: OR = 8.02 (1.95-33) T2DM: OR = 2.48 (1.02-6.03)	<0.05 <0.05 <0.05
		Mild to moderate NPDR Severe NPDR PDR		OR = 3.78 (1.86-7.67) OR = 7.17 (2.43-20.61) OR = 23.56 (8.49-66.11)	<0.05 <0.05 <0.05
P. Rossing ¹⁵ T1DM	Prospective (537)	DR	Progression to microalbuminuria/ macroalbuminuria	RR = 1.90 (1.26-2.88)	<0.01
Parving ²⁵ T2DM	Cross-sectional (32208)	DR	Microalbuminuria/ macroalbuminuria	OR = 1.49 (1.38-1.62)	<0.0001
Karlberg ²⁶ T1DM	Prospective (184)	PDR	Nephropathy	OR = 2.98 (1.18-7.51)	0.02
Kramer 2013 ²⁷ T1DM	Retrospective (1365)	DR progression Nephropathy development	Nephropathy development DR progression	HR = 1.72 (1.30-2.27) HR = 1.62 (1.23-2.13)	<0.001 0.001
Romero-Aroca 2012 ²⁸ T1DM	Prospective (110)	DR Microalbuminuria Overt nephropathy	Overt nephropathy STDR STDR	OR = 3.92 (2.97-7.69) OR = 5.98 (1.83-19.53) OR = 6.202 (1.35-28.34)	0.030 0.003 0.019
Romero-Aroca 2011 ²⁹ T1DM	Prospective (334)	Overt nephropathy	DMO	HR = 0.68 (0.51-0.90)	0.008
Hammes 2015 ³⁰ T2DM	Longitudinal (64784)	Microalbuminuria Macroalbuminuria	DR Severe DR DMO DR Severe DR DMO	OR = 1.16 (1.11-1.20) OR = 1.20 (1.14-1.27) OR = 1.31 (1.09-1.58) OR = 1.28 (1.12-1.39) OR = 1.51 (1.36-1.67) OR = 2.77 (2.11-3.66)	<0.0001 <0.0001 <0.0001 <0.0001 <0.0001 <0.0001
Jeng ³¹ T1DM & T2DM	Longitudinal (53453)	Nephropathy	NPDR PDR Progression from NPDR to PDR	HR = 5.01 (4.68-5.37) HR = 9.70 (8.15-11.50) HR = 2.25 (1.68-3.02)	<0.001 <0.001 <0.001
Savage ³² T2DM	Cross-sectional (947)	Macroalbuminuria	Increasing severity of DR Progression to PDR	OR = 2.89 (1.73-4.61) OR = 3.92 (2.02-7.63)	0.0001 0.0001
Takagi ³³ T2DM	Prospective (1802)	DR	Microalbuminuria Decrease in eGFR	HR = 1.57 (1.17-2.12) HR = 1.36 (1.08-1.71)	<0.003 0.008
Moriya ³⁴ T2DM	Retrospective (1475)	DR + microalbuminuria	Macroalbuminuria	HR = 11.55 (5.24-25.45)	<0.01

Abbreviations: CI, confidence interval; DMO, diabetic macular oedema; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NPDR, non-proliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy; RR, relative risk; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

relationship between DR and these microvascular complications is presented in Tables 1 and 2.

3.2.1 | Nephropathy

Diabetic nephropathy affects approximately 40% of patients with diabetes and is characterized by increased urinary albumin excretion (UAE). It is categorized into stages, microalbuminuria (UAE >20 µg/min and ≤199 µg/min) and macroalbuminuria (UAE ≥200 µg/min), and it is associated with increased mortality.³⁵ Glomerular filtration rate (GFR), a measure of renal function, is also used to assess the presence of diabetic nephropathy.³⁵ Overall, risk estimates from the reviewed studies suggest a correlation between DR and nephropathy, and between DR and declining renal function (Table 1).

DR and albuminuria

In a cross-sectional study of patients with T1DM or T2DM, the presence and severity of DR were significantly predictive of nephropathy.¹⁴ Multivariate logistic regression showed that nephropathy was the only complication of diabetes independently associated with DR, and that retinopathy increased the likelihood of developing nephropathy by 4.37 times. However, the predictive value of DR was strongest for T1DM.¹⁴ These findings have been confirmed in other studies that identified DR as a significant independent predictor of progression to micro- or macroalbuminuria in patients with T1DM¹⁵ or T2DM²⁵. Risk of nephropathy has been shown to increase with DR severity,¹⁴ and PDR was identified as a significant independent marker of incident nephropathy in a 25-year follow-up study in T1DM.²⁶

Interestingly, data from the Diabetes Control and Complications Trial (DCCT) in T1DM demonstrated that progression of DR independently increases the risk of development of nephropathy, and also showed that the development of nephropathy increases the risk of DR progression.²⁷ Although a previous study demonstrated that these two complications influence the incidence of each other,³⁶ a retrospective study in T2DM demonstrated that the association between DR and diabetic nephropathy is unidirectional and that renal injury precedes retinal damage.³⁷ Accordingly, several studies have shown that nephropathy is a risk factor for DR, including severe forms of retinopathy.^{28,30-32} Concerning T1DM, a 20-year prospective study by Romero-Aroca et al. found that both micro- and macroalbuminuria correlated with the development of VTDR but not with the development of any DR.²⁸ In the same study, DR was a significant risk factor for nephropathy.²⁸ Notably, in a 10-year prospective analysis of patients with T1DM, macroalbuminuria was identified as a significant independent risk factor for the development of DMO, but not of DR.²⁹ Concerning T2DM, Hammes et al. analysed data from 6478 patients. The presence of microalbuminuria was found to independently increase the risk of DR, severe DR and DMO, and the risk further increased in the presence of macroalbuminuria.³⁰ However, research has also shown that nephropathy did not affect development or progression of DMO, although it was an independent risk factor for DR, PDR and the progression from non-proliferative DR (NPDR) to PDR.³¹ Previously, macroalbuminuria, but not microalbuminuria, had been found to be significantly associated with increasing severity of DR and with progression from NPDR to PDR in T2DM.³²

TABLE 2 Studies describing the association between DR and diabetic neuropathy

Reference Study population	Study design (n)	Independent variable	Dependent variable	OR/HR (95% CI)	P value
Kostev ³⁸ T2DM	Retrospective (45633 [German cohort only])	DR	Neuropathy	OR = 2.96 (2.08-4.22)	<0.05
Jurado ³⁹ T2DM	Cross-sectional (307)	DR	DPN	OR = 5.18 (2.70-10.00)	0.000
Abougambou ⁴⁰ T2DM	Prospective (1077)	Neuropathy	DR	OR = 2.91 (2.21-3.82)	<0.001
Lin ⁴¹ DPN	Retrospective (5031 [+20 124 controls])	DPN	Any DR NPDR PDR	HR = 5.41 (4.92-5.94) HR = 5.63 (5.11-6.21) HR = 3.67 (2.57-5.23)	<0.001 <0.001 <0.001
Zander ⁴² T1DM & T2DM	Cross-sectional (33659)	Neuropathy	Maculopathy	T1DM: OR = 3.5 (NR) T2DM: OR = 3.1 (NR)	<0.01 <0.01
Witte ⁴³ T1DM	Prospective (956)	DR	CAN	OR = 1.70 (1.11-2.60)	0.01
Ko ⁴⁴ T2DM	Prospective (1021)	DR	CAN	OR = 1.51 (1.03-2.23)	0.036
Voulgari ⁴⁵ T1DM & T2DM	Cross-sectional (600)	DR	CAN	T1DM: OR = 1.13 (1.04-1.41) T2DM: OR = 1.24 (1.16-1.35)	0.01 0.008
Huang ¹⁶ T2DM	Cross-sectional (174)	NPDR PDR	CAN	OR = 2.73 (1.14-6.54) OR = 11.19 (4.15-30.16)	0.024 <0.001
H. T. Chen ⁴⁶ T2DM	Cross-sectional (674)	PDR	CAN	OR = 6.85 (2.32-20.20)	<0.001
Gaspar ⁴⁷ T1DM & T2DM	Retrospective (187)	DR	Orthostatic hypertension	T1DM: OR = 8.09 (1.65-39.62) T2DM: OR = 4.08 (1.83-9.10)	<0.01 <0.001

Abbreviations: CAN, cardiac autonomic neuropathy; CI, confidence interval; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; HR, hazard ratio; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OR, odds ratio; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

DR and declining renal function

In a single-centre observational cohort study by Takagi et al., the presence of DR was a common predictor of both albuminuria onset and decreased estimated GFR (eGFR) in patients with T2DM.³³ In earlier research, also involving patients with T2DM, Rossing et al. found a significant correlation between degree and presence of DR at baseline and increased rate of eGFR decline.⁴⁸ Interestingly, in the Japan Diabetes Complications Study, patients with T2DM who had both microalbuminuria and DR at baseline had the highest risk of developing macroalbuminuria and displayed significantly faster eGFR decline ($-1.92 \text{ mL min}^{-1} 1.73 \text{ m}^{-2} \text{ y}^{-1}$; $P < 0.01$) compared with those with one of the two complications ($-0.69 \text{ mL min}^{-1} 1.73 \text{ m}^{-2} \text{ year}^{-1}$; $P < 0.01$) or with neither complication ($-0.54 \text{ mL min}^{-1} 1.73 \text{ m}^{-2} \text{ y}^{-1}$; $P < 0.01$).³⁴

3.2.2 | Neuropathy

DR was found to be associated with two neuropathies: diabetic peripheral neuropathy (DPN) and CAN (Table 2). DPN is estimated to affect 30% to 50% of individuals with diabetes; it is characterized by peripheral nerve injury and manifests most commonly as distal symmetric polyneuropathy (DSP). Symptoms of DSP include pain, numbness and weakness in the lower limbs, which may lead to falls.⁴⁹ Diabetic symmetric polyneuropathy is also a major risk factor for foot ulcers and amputations.⁴⁹ Concerning CAN, reported prevalence rates among individuals with diabetes vary from 17% to 66% in T1DM, and from 31% to 73% in T2DM.⁵⁰ Nerve injury occurs in both the autonomic and peripheral nervous systems, increasing the likelihood of experiencing heart rate abnormalities that progress to resting tachycardia, as well as orthostatic hypotension, ischaemia, CVD, chronic kidney disease and anaemia.⁵⁰ Additionally, individuals with diabetes who have CAN are at increased risk of mortality compared with those without.⁵⁰

DR and DPN/DSP

In a retrospective study of longitudinal data from patients with newly diagnosed T2DM, collected from nationwide general practitioners in Germany and the UK, the presence of microvascular complications, defined as DR plus nephropathy, was found to be independently associated with neuropathy; in particular, DR was identified as a significant risk factor for neuropathy in the German cohort.³⁸ Furthermore, the longitudinal Rochester Diabetic Neuropathy Study demonstrated that DR severity was an independent risk factor for DPN severity in patients with T1DM.⁵¹ A positive correlation between DPN and DR was also found in the cross-sectional North Catalonia Diabetes Study, in which the presence of retinopathy, together with age, HbA1c and plasma levels of high-density lipoprotein cholesterol, was used in a model to evaluate the risk of DPN. Based on these four parameters selected by logistic regression analysis, the sensitivity and specificity of the model for diagnosis of DPN was 74.2% and 74.9%, respectively.³⁹

Other studies, including a prospective analysis of patients with T2DM in Malaysia, showing that neuropathy is an independent risk factor for progression of retinopathy,⁴⁰ found neuropathy to be a predictor of DR onset and progression. Similarly, in a retrospective

population-based study in Taiwan, patients with DPN exhibited an increased risk of DR and advanced DR compared with a matched cohort of patients with diabetes who did not have DPN.⁴¹ Notably, when stratified according to DR severity, the risk of DPN was greater in patients with PDR than in those with NPDR.⁴¹ A significant association has also been found between diabetic maculopathy and neuropathy in both patients with T1DM and patients with T2DM, taking into account both peripheral neuropathy and CAN.⁴²

DR and CAN

In the EURODIAB Prospective Complications Study, Witte et al. investigated potential risk factors for CAN in patients with T1DM.⁴³ They found that the presence of DR or PDR at baseline was significantly associated with CAN incidence ($P < 0.05$) after controlling for sex, diabetes duration and HbA1c; 17% of 956 patients developed the complication over the 7.3 years of follow-up, corresponding to an incidence rate of 23.4 per 1000 person-years. The association remained significant after multivariate regression analyses.⁴³ A similar conclusion was drawn from a seven-year follow-up study of patients with T2DM who had normal cardiac autonomic function at baseline. Logistic regression revealed that the presence of DR was predictive of CAN progression after adjusting for age, hypertension, smoking and diabetes duration.⁴⁴

Overall, the above findings are consistent with those of a cross-sectional study by Voulgari et al. indicating that the odds of CAN are independently increased by the presence of DR in both T1DM and T2DM patient populations,⁴⁵ and with the results of a study of patients with T2DM showing that increasing DR severity is associated with a higher risk of developing CAN.¹⁶ A significant positive correlation between DR severity and risk of CAN in patients with T2DM was also reported by Chen et al. after adjusting for age, sex, diabetes duration and HbA1c.⁴⁶ Additionally, after logistic regression analysis, the authors identified PDR as the most significant single risk factor for CAN.⁴⁶

Of note are the results of a 10-year follow-up study that found DR to be significantly more prevalent in individuals with diabetes who have orthostatic hypertension, a major clinical feature of CAN, compared with individuals without.⁴⁷

3.3 | DR and macrovascular complications of diabetes

In addition to the microvascular complications described above, the presence of DR has also been associated with development of the macrovascular complications of diabetes, specifically, cerebrovascular complications (stroke, cerebral infarction/haemorrhage), cardiovascular complications (atherosclerosis, cardiovascular events, coronary heart disease [CHD]) and peripheral complications (foot ulcers, lower extremity amputations, peripheral arterial disease [PAD]). The key findings of the reviewed studies examining the relationship between DR and various types of macrovascular complications of diabetes are presented in Tables 3–5.

TABLE 3 Studies describing the association between DR and cerebrovascular complications

Reference Study population	Study design (n)	Independent variable	Dependent variable	OR/HR/RR (95% CI)	P value
Petitti ⁵² T1DM & T2DM	Case-control (2124)	DR	Ischaemic stroke	RR = 4.0 (1.0-14.5)	<0.05
Cheung 2007 ⁵³ T1DM & T2DM	Prospective (1617)	DR	Ischaemic stroke	HR = 2.34 (1.13-4.86)	<0.05
B. E. Klein ⁵⁴ T1DM	Prospective (996)	DR/step	Stroke	OR = 1.6 (1.1-2.3)	0.01
Hägg 2013 ²² T1DM	Observational follow-up (4803)	Severe DR	Stroke Cerebral infarction Cerebral haemorrhage	HR = 3.0 (1.9-4.5) HR = 2.7 (1.6-4.4) HR = 3.9 (1.7-8.9)	<0.05 <0.05 <0.05
Hägg 2014 ²¹ T1DM	Observational follow-up (4803)	Severe DR	Haemorrhagic stroke	HR = 2.99 (1.18-7.55)	0.021
Kawasaki 2013 ⁵⁵ T2DM	Prospective (2033)	Mild to moderate DR	Stroke	HR = 1.69 (1.03-2.80)	0.04
Hankey ²³ T2DM	Prospective, observational (9795)	History of DR	Small-artery ischaemic stroke	HR = 1.82 (1.08-3.07)	0.03
Cheung 2010 ⁵⁶ T1DM & T2DM	Prospective (810)	DR	Incident cerebral infarct Incident lacunar infarct	OR = 7.35 (1.72-31.34) OR = 5.32 (1.23-23.03)	NR
Lip ⁵⁷ T1DM & T2DM	Registry (8962)	DR	Stroke/thromboembolism	RR = 1.21 (0.80-1.84)	0.37
Chou ⁵⁸ T1DM & T2DM	Registry (50180)	DR	Ischaemic stroke	HR = 1.11 (0.95-1.30)	0.204

Abbreviations: CI, confidence interval; DR, diabetic retinopathy; HR, hazard ratio; NR, not reported; OR, odds ratio; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

3.3.1 | Cerebrovascular complications

An early case-control study identified DR as a risk factor for non-embolic ischaemic stroke in individuals with diabetes, independent of smoking, blood pressure and other complications of diabetes.⁵² The findings were later supported by a population-based, prospective study of patients with diabetes that found DR to be significantly correlated with incident stroke, although no association was identified between DR grade and increasing risk of ischaemic stroke.⁵³ This differs from the results of the Wisconsin Epidemiologic Study of Diabetic Retinopathy in T1DM, which demonstrated an association between DR severity and increased odds of stroke.⁵⁴ Similarly, in the Finnish Diabetic Nephropathy (FinnDiane) Study, severe DR independently increased the risk of stroke, cerebral infarction and cerebral haemorrhage in patients with T1DM who were followed for 9 years, and the risk increased if patients had concomitant diabetic nephropathy.²² Further analysis of this data set revealed severe DR to be independently associated with haemorrhagic stroke but not with ischaemic stroke,²¹ whereas a large prospective study in patients with T2DM who were followed for 5 years found DR to be correlated with small-artery ischaemic stroke, but not with large-artery ischaemic stroke or haemorrhagic stroke.²³ An analysis of data from the Japan Diabetes Complications Study revealed that even patients with mild to moderate NPDR had an increased risk of stroke after adjusting for traditional cardiovascular risk factors.⁵⁵ Furthermore, in the Atherosclerosis Risk in Communities (ARIC) Brain MRI Study, DR was associated with the emergence of subclinical brain infarcts.⁵⁶

3.3.2 | Cardiovascular complications

Increased carotid intima-media thickness (cIMT) is a broadly accepted marker for early or subclinical atherosclerosis,⁵⁹ and several studies have demonstrated an association between DR and this

marker.^{17,60-65} In a cross-sectional analysis of patients with T2DM, DR severity was associated with elevated cIMT after controlling for other risk variables.⁶⁰ These findings are consistent with those from the Chennai Urban Rural Epidemiology Study (CURES-2)⁶¹ and several other cross-sectional investigations.⁶²⁻⁶⁴ Furthermore, Li et al. found the presence of retinal microvascular abnormalities, defined as DR or retinal arteriosclerosis, to be independently associated with increased cIMT in both men and women with T2DM, and with increased carotid plaque presence in men with T2DM.⁶⁶ In research by de Kreutzenberg et al. DR alone, or co-existing with nephropathy, was significantly and independently associated with carotid plaque presence in patients with T2DM,⁶⁷ and Alonso et al. showed DR to be independently correlated with cIMT, carotid artery plaque presence and carotid burden in patients with T2DM.¹⁷

Contrary to the evidence described above, DR presence was not associated with increased cIMT in a cross-sectional study that examined the relationship between DR severity and risk factors for sub-clinical CVD in a cohort of individuals with diabetes who had no history of clinical CVD.⁶⁸ However, the study found that severe retinopathy doubled the odds of a high coronary artery calcium (CAC) score and a low ankle-brachial index (ABI) after adjusting for cardiovascular risk factors, HbA1c, nephropathy and diabetes duration.⁶⁸ A correlation between PDR and high CAC scores was also identified in the Veterans Affairs Diabetes Trial (VADT). Through logistic regression analysis, PDR presence in patients with T2DM was estimated to increase the likelihood of a CAC score greater than 400 by six times, compared with no PDR presence.⁶⁹ It is worth noting, however, that, in a prospective study of individuals with T2DM who were followed for up to 8 years, even mild to moderate DR increased the risk of CHD and stroke.⁵⁵ In addition, in a case-controlled study, the odds ratio of myocardial perfusion defects in an asymptomatic patient who

TABLE 4 Studies describing the association between DR and cardiovascular complications

Reference Study population	Study design (n)	Independent variable	Dependent variable	OR/HR/RR/ β (95% CI)	P value
R. Klein ⁶⁰ T2DM	Cross-sectional (1600)	cIMT	DR	OR = 1.09 (1.01-1.17)	0.02
Rema ⁶¹ T2DM	Cross-sectional (600)	cIMT	DR	OR = 3.60 (1.51-8.46)	0.004
Liu ⁶² T2DM	Cross-sectional (1607)	cIMT	DR	OR = 1.84 (1.02-3.31)	0.043
Saif ⁶³ T2DM	Cross-sectional (140)	cIMT	DR	NR	<0.0001
Son ⁶⁴ T2DM	Cross-sectional (142)	cIMT	DR	OR = 6.57 (1.68-25.71)	0.007
L. X. Li ⁶⁶ T2DM	Cross-sectional (2870)	DR	cIMT	All: β = 0.078 (0.080-0.262) Men: β = 0.067 (0.026-0.269) Women: β = 0.087 (0.058-0.334)	<0.001 0.018 0.005
			Carotid plaques	All: OR = 1.72 (1.32-2.24) Men: OR = 2.17 (1.54-3.05)	<0.001 <0.001
de Kreutzenberg ⁶⁷ T2DM	Cross-sectional (662)	DR	Carotid plaques	OR = 3.44 (1.71-7.57)	0.0011
Alonso ¹⁷ T2DM	Cross-sectional (312)	DR	ICA-IMT Carotid plaques Plaque burden	NR OR = 1.71 (1.03-2.85) OR = 3.17 (1.75-5.75)	0.017 0.0366 <0.0001
Kawasaki 2011 ⁶⁸ T1DM & T2DM	Cross-sectional (972)	VTDR	CAC Low ABI	OR = 2.33 (1.15-4.73) OR = 2.54 (1.08-55.99)	<0.05 <0.05
Reaven ⁶⁹ T2DM	Cross-sectional (204)	PDR	CAC	OR = 9.0 (1.7-49.2)	0.011
Kawasaki 2013 ⁵⁵ T2DM	Prospective (2033)	Mild NPDR Mild to moderate NPDR	CHD CHD Any CVD	HR = 1.62 (1.02-2.58) HR = 1.69 (1.09-2.63) HR = 1.92 (1.33-2.75)	0.04 0.02 <0.01
Gimeno-Orna ⁷⁰ T2DM	Prospective (458)	NPDR PDR	Incident CVD	HR = 1.61 (1.20-2.60) HR = 2.95 (1.10-3.56)	0.017 0.019
Roy 2007 ⁷¹ T1DM	Prospective (483)	Moderate DR Severe DR	CVD	OR = 3.19 (1.19-8.57) OR = 3.88 (1.39-10.80)	0.01 0.01
Targher ⁷² T2DM	Prospective (406)	DR PDR	Incident CVD	Men: HR = 1.61 (1.20-2.60) Women: HR = 1.67 (1.30-2.80) Men: HR = 3.75 (2.00-7.40) Women: HR = 3.81 (2.20-7.30)	All <0.001
Park ⁶⁵ T2DM	Prospective (557)	DR	CHD	OR = 2.39 (1.63-3.51)	<0.001
Torffvit ⁷³ T1DM	Prospective (462)	STDR	CVD	RR = 4.40 (NR)	<0.05
Cheung 2007 ⁵³ T2DM	Prospective (1524)	Any DR Any DR ^a Mild/moderate DR Severe DR Severe DR	Incident CHD Fatal CHD	HR = 1.99 (1.33-3.00) HR = 1.91 (1.18-3.08) HR = 1.89 (1.22-2.92) HR = 2.57 (1.25-5.27) HR = 5.38 (1.54-18.82)	NR
Gerstein ¹⁸ T2DM	Prospective (3433)	Change in retinal severity	ACCORD composite	HR per category change: 1.38 (1.10-1.74)	<0.05
Rajala ⁷⁴ T1DM & T2DM	Prospective (107)	DR	CVD mortality	OR = 5.6 (2.6-19.0)	<0.05
Juutilainen ⁷⁵ T2DM	Prospective (824)	Background DR PDR	CVD mortality CHD mortality CVD mortality CHD mortality	HR = 1.52 (1.15-1.99) HR = 1.47 (1.06-2.02) HR = 3.43 (2.01-5.85) HR = 3.45 (1.87-6.36)	0.003 0.020 <0.001 <0.001
Kramer 2011 ⁷⁶ T1DM & T2DM	Meta-analysis (19234)	DR	All-cause mortality	T1DM: OR = 3.65 (1.05-12.66) T2DM: OR = 2.41 (1.87-3.10)	NR

Abbreviations: ABI, ankle-brachial index; β , β coefficient; CI, confidence interval; cIMT, carotid intima-media thickness; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; DR, diabetic retinopathy; HR, hazard ratio; ICA-IMT, internal carotid artery intima-media thickness; NPDR, non-proliferative diabetic retinopathy; NR, not reported; OR, odds ratio; PDR, proliferative diabetic retinopathy; RR, relative risk; STDR, sight-threatening diabetic retinopathy (defined as clinically significant macular oedema and/or severe non-proliferative DR, or clinically significant macular oedema and/or PDR); T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VTDR, vision-threatening diabetic retinopathy (defined as clinically significant macular oedema or PDR).

^a Adjusted for nephropathy.

TABLE 5 Studies describing the association between DR and peripheral complications

Reference Study population	Study design (n)	Independent variable	Dependent variable	OR/HR/RR (95% CI)	P value
Baba ⁷⁷ T2DM	Longitudinal (1296)	DR	Hospitalization with ulcer	HR = 3.86 (2.26-6.59)	<0.001
Leymarie ⁷⁸ T1DM and T2DM	Cross-sectional (555)	DR	Ulcer	OR = 4.2 (2.4-7.4)	<0.05
Bruun ⁷⁹ T2DM	Registry (1381)	DR	Ulcer at diabetes diagnosis Amputation	OR = 6.21 (2.13-18.10) OR = 6.43 (2.59-15.90)	<0.001 <0.001
Paris ⁸⁰ T1DM & T2DM	Cross-sectional (1455)	DR	Ulcer	OR = 1.68 (1.08-2.62)	0.022
Tomita ⁸¹ T2DM	Retrospective (1305)	DR + microalbuminuria	Ulcer	HR = 6.84 (3.48-13.41)	<0.001
Harris Nwanyanwu ⁸² T1DM & T2DM	Retrospective (4617)	Non-healing ulcers	PDR	HR = 1.54 (1.15-2.07)	<0.05
Chaturvedi ⁸³ T1DM & T2DM	Prospective (3443)	DR	Amputation	T1DM: RR = 2.4 (1.0-5.9) T2DM: RR = 3.6 (1.8-7.2)	NR
Hämäläinen ⁸⁴ T1DM & T2DM	Prospective (733)	DR	Amputation	OR = 6.1 (1.9-19.6)	0.0024
Lai ⁸⁵ T2DM	Retrospective (1588)	DR	Amputation	HR = 2.07 (1.12-3.82)	<0.05
Rodrigues ⁸⁶ T1DM & T2DM	Retrospective (129)	DR	Amputation	OR = 5.20 (2.15-12.75)	0.00
Saltoglu ⁸⁷ T1DM & T2DM	Retrospective (455)	DR	Amputation	OR = 2.25 (1.19-4.25)	0.012
Tsai ⁸⁸ T2DM	Registry (2011)	Amputation	DR	HR = 2.24 (1.79-2.80)	<0.0001
Mohammedi ⁸⁹ T2DM	Prospective (11140)	Chronic ulceration or amputation	DR	HR = 1.53 (1.01-2.30)	0.04
X. Li ⁹⁰ T2DM	Cross-sectional (3924)	DR	Low ABI	OR = 1.83 (1.14-2.93)	0.004
S. C. Chen ⁹¹ T2DM	Cross-sectional (2001)	PDR	Abnormal ABI	OR = 1.72 (1.15-2.56)	0.008
Y. W. Chen ⁹² T2DM	Cross-sectional (1544)	PDR	Abnormal ABI Abnormal TBI Abnormal duplex Critical limb ischaemia	OR = 3.61 (1.15-11.26) OR = 2.84 (1.19-6.74) OR = 3.28 (1.00-10.71) OR = 5.52 (2.14-14.26)	0.027 0.018 0.049 <0.001
Roy 2008 ⁹³ T1DM	Prospective (483)	Severe DR	LEAD	OR = 4.93 (1.13-21.55)	0.0002
Yan ⁹⁴ T2DM	Cross-sectional (12772)	Borderline ABI	DR	OR = 1.19 (1.04-1.37)	<0.05

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; DR, diabetic retinopathy; HR, hazard ratio; LEAD, lower extremity arterial disease; NR, not reported; OR, odds ratio; PDR, proliferative diabetic retinopathy; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TBI, toe-brachial index.

had diabetes with DR in comparison to patients who had diabetes without DR was 11.7 (95% CI, 3.7-37).⁹⁵

Overall, the above findings are consistent with those from other prospective studies, indicating that DR, particularly advanced DR, is an independent risk factor for CVD in patients with diabetes.^{65,70-72} Furthermore, Torffvit et al. demonstrated that the presence of VTDR in patients with T1DM increases the risk of incident CHD by 4.4 times, compared with no DR presence.⁷³ Notably, the association did not remain after adjusting for the presence of macroalbuminuria.⁷³ However, this contrasts with results from the Atherosclerosis Risk in Communities (ARIC) Study in T2DM, in which adjusting for nephropathy had minimal impact on the association between DR and CHD.⁹⁶ In this study, the risk of incident CHD increased with DR severity, and severe DR was also a significant independent risk factor for fatal CHD.⁹⁶

In the ACCORD Eye Study, DR severity and progression were associated with the composite outcome of first occurrence of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death

in patients with T2DM.¹⁸ Analyses revealed that the risk of this primary outcome increased by 38% for every category of change in DR severity.¹⁸ Elsewhere, retinopathy and PDR have been shown to increase the risk of cardiovascular or all-cause mortality in patients with T1DM and patients with T2DM.⁷⁴⁻⁷⁶

3.3.3 | Peripheral complications

Neuropathic and vascular complications caused by diabetes can lead to the development of diabetic foot ulcers and infections, and cause amputations. Several studies have shown that DR is an independent risk factor for foot ulceration in individuals with diabetes.⁷⁷⁻⁸⁰ However, a retrospective analysis of patients with T2DM by Tomita et al. found retinopathy to significantly increase the risk of developing ulcers only in the presence of microalbuminuria after adjusting for neuropathy and macroangiopathy.⁸¹ Furthermore, it has been shown that, among individuals with newly diagnosed NPDR, those with non-healing foot ulcers have an increased risk of progressing to

PDR.⁸² A number of papers have also identified DR as a key risk factor for lower extremity amputation in both patients with T1DM and patients with T2DM.^{79,83–87}

Notably, patients who have T2DM and undergo lower extremity amputation (LEAs) have been found to be at higher risk of developing DR than those without LEAs.⁸⁸ This was also observed in the ADVANCE-ON post-trial observational study in T2DM, which demonstrated that lower extremity ulceration or amputation, as a major presentation of PAD, increased the risk of retinal photocoagulation or blindness.⁸⁹ PAD is diagnosed using the ABI, with values less than 0.9 indicative of the disease.⁹⁷ Li et al. demonstrated that DR was independently associated with a low ABI in patients with T2DM, irrespective of age.⁹⁰ However, Chen et al. found PDR, but not NPDR, to be correlated with an abnormal ABI in patients with T2DM after adjustment for HbA1c.⁹¹ This result was replicated in another study, in which PDR was found to be independently associated with other measures of PAD, such as the toe-brachial index, Doppler ultrasound and critical limb ischaemia.⁹² In addition, a prospective study in African-Americans with T1DM found that DR severity at baseline was a significant independent risk factor for the incidence of lower extremity arterial disease, defined as present if a patient has had an amputation or angioplasty for poor circulation, or if there is an absence of major arterial pulse in the legs.⁹³ However, in patients with T2DM, a borderline ABI (0.90–0.99) has been identified as an independent predictor of DR and other microvascular and macrovascular complications.⁹⁴

4 | DISCUSSION

The present structured analysis has provided clear evidence supporting relationships between DR and complications of diabetes, including micro- and macrovascular conditions and events. Although many of these associations have been identified in cross-sectional and retrospective studies, several have been confirmed in prospective investigations, based on multivariate analyses that controlled for the influence of traditional or other known risk factors.

With regard to microvascular outcomes, DR was found to increase the likelihood of nephropathy^{15,25,26} and to be a significant and independent predictor of progression to micro- or macroalbuminuria,¹⁵ but it remains unclear whether albuminuria increases the risk of retinopathy.^{29,30,37} In this regard, Kotlarsky et al. concluded that renal injury precedes retinal damage, but they stated that prospective studies are required to confirm this conclusion.³⁷ Additionally, the reviewed evidence indicates that DR correlates with declining GFR^{34,48} and, specifically, that retinopathy severity at baseline is a predictor of the rate of decline of eGFR.⁴⁸ An important implication of the above findings is that close monitoring of individuals with DR for the presence of other microvascular complications, particularly albuminuria and impaired glomerular function, may help prevent progression to more serious kidney disease.^{34,98} Furthermore, as evidence suggests that DR severity parallels the severity of nephropathy, a key area of further research is whether systemic interventions to prevent the progression of one might influence the progression of the other. A strong association was also observed

between DR and CAN, with prospective studies indicating that the risk of developing the latter increases in the presence of retinopathy and that, in individuals with T2DM, DR stage is independently correlated with CAN.^{16,45} As both CAN and DR have been identified as predictors of cardiovascular morbidity and mortality in several prospective studies of individuals with diabetes,^{65,70–72,99} it may be interesting to investigate whether both conditions in conjunction is associated with a greater risk of cardiovascular complications, compared with the presence of either complication alone. If this were the case, screening for CAN in patients who have diabetes with DR could help identify high-risk groups, for monitoring and early detection of clinical progression to CVD. Outcomes from the reviewed studies also demonstrate that DR is a significant risk factor for DPN,^{38,40,41,51} and that the risk of developing this complication is greater in the presence of PDR than with early-stage retinopathy.⁴¹

As for the relationship between DR and the macrovascular complications of diabetes, risk estimates from several large prospective studies indicate that DR is a strong predictor of stroke, and that progression of DR significantly increases the risk of this complication.^{22,52,53} Severe DR was found to independently increase the risk of cerebral infarction and cerebral haemorrhage in patients with T1DM,²² and was associated with small-artery ischaemic stroke in patients with T2DM.²³ Evidence presented here also demonstrates that DR is associated with subclinical atherosclerosis,^{61–63} and that the presence of this complication is independently correlated with cIMT and carotid plaques in T2DM populations.^{17,61,65} Two studies showed that DR is associated with increased risk of CHD-related events and mortality^{53,55} and, overall, DR was found to be an independent risk factor for CVD.^{65,70–72} Similarly, outcomes from the reviewed studies demonstrate that DR, and particularly PDR, is a strong risk factor for PAD, which carries a risk of lower extremity ulceration and amputation.^{90–92} Therefore, worsening DR could prove useful as a marker for individuals at increased risk of these serious macrovascular complications. Specifically, the evidence indicates that patients with diabetes who have PDR are more likely than those with NPDR to have an abnormal ABI.⁹¹ Furthermore, DR was identified as an independent risk factor for foot ulceration and a key risk factor for lower extremity amputation.^{77–79} Interestingly, two studies found that patients with diabetes who have non-healing foot ulcers or who have undergone lower extremity amputation are at risk of DR development and progression.^{82,89}

We performed a comprehensive search of the literature that resulted in the inclusion of 71 studies, with a total of over 400 000 patients, and the approach taken to review was objective and systematic, complying with several of the key items included in the PRISMA checklist for systematic reviews and meta-analyses. One limitation of our study was that only the PubMed literature database was searched. Despite this, our findings are an important contribution to the understanding of the relationship between DR and the micro- and macrovascular complications of diabetes and, as such, provide valuable information to support the wider multidisciplinary team that is involved in the care of individuals with diabetes. In particular, the findings underscore the need for prompt screening and referral for DR, which can both reduce vision loss and, potentially, identify patients at increased risk of other complications of diabetes. This highlights the

need for a coordinated and collaborative approach to patient management on the part of all the healthcare professionals involved in diabetes care in order to optimize clinical outcomes. A risk assessment model that incorporates DR presence as an input factor, rather than an outcome, may provide a powerful tool for identifying individuals at high risk of potentially life-threatening complications of diabetes. Indeed, a study has demonstrated that incorporation of microvascular complications into cardiovascular risk algorithms improves CVD risk prediction in T2DM.¹⁰⁰ The ability to identify the individuals most at risk of developing complications could improve the targeting of preventive treatments, potentially reducing morbidity and mortality among patients with diabetes. Further exploration in this area is warranted.

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CONFLICT OF INTEREST

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Author contributions

All authors contributed to the concept development, determining the search strategy and evaluating the results for inclusion, and provided critical review of the manuscript.

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