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REVIEW

Epidemiology of diabetic retinopathy and macular oedema: a systematic review

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Abstract

Aims **To systematically review the literature on the prevalence and incidence of diabetic retinopathy (DR) and macular oedema (MO).**
Methods **A search of the bibliographic databases (Medline, Embase, CINAHL) was conducted up to October 2001. Selected relevant studies were scrutinized and included in the review.**
Results **A total of 359 studies were included. The studies were reported in nearly 100 different journals and in over 50 countries. The majority of the studies were US-based, with large studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy dominating the literature. The studies were quite dated and highly heterogeneous in nature in terms of patient selection with variable inclusion criteria (age range, gender, diabetes duration and type, ethnicity, comorbidity, and DR status, assessment, and classification).**
Conclusions **There are inconsistencies between epidemiological studies, and differences in study methods may contribute to conflicting reports of prevalence and incidence of DR and MO in diabetic populations. As new therapies for DR and its associated complications emerge, the need to capture and monitor new epidemiological data becomes increasingly important to be able to assess the impact and effectiveness of these therapies. Robust, longitudinal capture of patient data is, therefore, essential to evaluate the impact of current practice on the epidemiology of diabetic eye complications.**

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Introduction

Diabetes mellitus results in considerable morbidity and mortality, affecting about 180 million people worldwide.[1] The disease is classified according to two distinct groups of patients: type I diabetes (previously known as 'insulin dependent' or 'juvenile onset') is characterized by destruction of the insulin secretory pancreatic β-cells of the islets of Langerhans caused by an autoimmune process, usually leading to absolute insulin deficiency; type II diabetes (noninsulin dependent, adult-onset) is characterized by insulin resistance in peripheral tissues and an insulin secretory defect of the β-cell.[2] Between 70 and 90% of diabetic patients have type II diabetes.[3] However, current statistics suggest that an estimated 50% of diabetes sufferers remain undiagnosed.[4–6]

The total number of people with diabetes is expected to rise to an estimated 300 million cases by the year 2025, with the most significant increases in developing countries, thought to be the result of population growth, ageing, obesity, and sedentary lifestyles.[7] Proportionally, the global population is predicted to increase by 64% between the years 1995 and 2025, compared with the prevalence of diabetes mellitus among adults, which is expected to rise by over 120%.[7] Indeed, by 2010, the number of people suffering from type II diabetes, which constitutes 90–95% of diabetic patients,[8] is set to double.[9]

The development of diabetes immediately increases a patient's propensity for developing a broad spectrum of irreversible complications.[10] Complications of diabetes can be largely divided into macrovascular and microvascular complications. The macrovascular complications include cerebrovascular disease, coronary heart disease, and peripheral vascular

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disease. The microvascular complications include diabetic retinopathy (DR), diabetic neuropathy, and diabetic nephropathy. The prevalence of these complications is strongly related to the prevalence, type, and duration of diabetes; therefore, the increasing global population, changing age demographics, and predicted rise in the proportion of adults suffering from diabetes will inevitably be accompanied by an increase in the frequency of diabetic complications.

Diabetes has many manifestations in the eye, of which cataracts and DR are the most significant cause of visual impairment and blindness, and people with diabetes are 25 times more likely than the general population to become blind.[11] In developed countries, diabetic eye disease represents the leading cause of blindness in adults under 75 years.[12] DR is the most common complication in type I diabetes and nearly all patients will have some degree of retinopathy 15–20 years after diagnosis.[13–16] Similarly, more than 60% of type II diabetes sufferers will have evidence of DR during this period.[14,17] Visual impairment as a result of DR has a significant impact on patients' quality of life,[18] and can compromise their ability to manage successfully their disease, which can in turn have a negative impact on the incidence of other diabetic complications and overall life expectancy.

DR is a progressive disease predominantly affecting the integrity of the microscopic vessels found in the retina. DR can be broadly divided into two clinical stages: nonproliferative and proliferative diabetic retinopathy (PDR). During nonproliferative DR, the earliest visible sign of retinal damage results from abnormal permeability and/or nonperfusion of capillaries, leading to the formation of microaneurysms.[19,20] Abnormal capillary permeability results in the leaking of fluid and solutes into the surrounding retinal tissue, which collects around the macula; this is referred to as macular oedema (MO) and it threatens visual acuity. PDR develops following the occlusion of retinal capillaries leading to retinal ischaemia, which promotes the development of neovascularization, a process by which new blood vessels proliferate on the surface of the retina. However, these vessels are fragile and haemorrhage easily. The resulting accumulation of blood in the vitreous cavity from these haemorrhaging vessels seriously impairs vision. This may be permanent due to further complications such as traction retinal detachment leading to registered blindness. It has been estimated that without treatment for PDR, 50% of all patients will become blind within 5 years following diagnosis.[21]

The aim of this systematic review is to provide a comprehensive overview of the published literature pertaining to the epidemiology of DR and MO.

Methods

Literature search

Three electronic bibliographic databases of medical literature (Medline, Embase, and CINAHL) were interrogated using customized searches developed by one of the authors (MA) in conjunction with a Cochrane Collaboration trained Trials Co-ordinator. The searches were limited to reported studies on humans published in English language papers. The Publication Type filter was applied to exclude comments, letters, and editorial citations. Medline was searched, initially, from January 1966 to July 2001, Embase from January 1980 to July 2001, and CINAHL from January 1982 to July 2001. In addition, the 38 most productive journals in terms of articles identified from pilot electronic searches were hand-searched from January 2001 to identify articles incorrectly indexed and those awaiting indexing. A rerun of the electronic searches up to and including October 2001 provided the final reference list for data abstraction.

Indexing terms differ between databases; therefore, a different search strategy was developed for each database searched (Table 1). The three search strategies were constructed in two sections:

- MeSH subject headings and free-text terms relating to DR and ME. Free-text terms used to describe the staging of diabetic retinopathy were also included.
- Epidemiological studies and relevant study designs. This section consisted of MeSH subject headings covering the scope of incidence and prevalence of disease in a population and the associated issue of risk factors and staging and screening for the disease.

Results

The original Medline search generated 4720 citations. After a review of the publication abstracts by the Cochrane Trials Co-ordinator, 361 publications were considered relevant. Relevant articles were original reports of studies designed to describe specifically incidence and/or prevalence or DR or MO. Editorials, letters, and reviews, as well as original papers describing biochemical and pathogenic mechanisms and treatment trials identified by the electronic search were excluded. The Embase search generated 1570 citations, and these were merged with the results of the Medline search, and duplicate publications discarded. This search identified an additional 35 articles on Embase that had not been identified on Medline. The CINAHL search generated 88 citations, which were merged with the results from the Medline and Embase searches. This did not generate any additional, relevant citations. Altogether, a total of 396 citations were identified as potentially relevant at this

Table 1 Customized literature search strategies

Medline (1966–2001)	*Embase (1980–2001)*	*CINAHL (1982–2001)*
1. Diabetic retinopathy/ or 'diabetic retinopathy'.mp.	1. Diabetic retinopathy/ or 'diabetic retinopathy'.mp.	1. Diabetic retinopathy/or 'diabetic retinopathy'.mp.
2. (diabet$ adj3 retinopath$).tw.	2. (diabet$ adj3 retinopath$).tw.	2. (diabet$ adj3 retinopath$).tw.
3. (background adj3 diabetic adj3 retinopathy).tw.	3. (background adj3 diabet$ adj3 retinopath$).tw.	3. (background adj3 diabetic adj3 retinopathy).tw.
4. (preproliferative adj3 diabetic adj3 retinopathy).tw.	4. (preproliferative adj3 diabet$ adj3 retinopath$).tw.	4. (preproliferative adj3 diabetic adj3 retinopathy).tw.
5. PPDR.tw.	5. PPDR.tw.	5. PPDR.tw.
6. (proliferative adj3 diabetic adj3 retinopathy).tw.	6. (proliferative adj3 diabet$ adj3 retinopath$).tw.	6. (proliferative adj3 diabetic adj3 retinopathy).tw.
7. exp macular edema/	7. Retina macula edema/ or 'retinal macula edema'.mp.	7. exp macular edema/
8. (macul$ adj3 edema).tw.	8. (macul$ adj3 edema).tw.	8. (macul$ adj3 edema).tw.
9. (macul$ adj3 oedema).tw.	9. (macul$ adj3 oedema).tw.	9. (macul$ adj3 oedema).tw.
10. or/1–9	10. or/1–9	10. or/1–9
11. exp prevalence/	11. exp incidence/	11. exp prevalence/
12. exp incidence/	12. exp prevalence/	12. exp incidence/
13. exp mass screening/	13. Mass screening/	13. exp vision screening/
14. exp vision screening/	14. exp vision screening/	14. exp practice guidelines/
15. exp visual acuity/	15. exp visual acuity/	15. exp risk factors/
16. exp practice guidelines/	16. exp practice guidelines/	16. exp time factors/
17. exp risk factors/	17. exp risk factors/	17. exp severity of illness indices/
18. exp time factors/	18. exp time factors/	18. exp epidemiological research/
19. exp severity of illness index/	19. exp severity of illness index/	19. or/11–18
20. exp epidemiological studies/	20. exp health survey/	20. 10 and 19
21. exp population surveillance/	21. exp geographic ophthalmology/	21. limit 20 to English
22. or/11–21	22. or/11–21	22. limit 21 to (editorial or letter)
23. 10 and 22	23. 22 and 10	23. 21 not 22
24. limit 23 to human	24. limit 23 to (human and English language)	
25. limit 24 to English language	25. limit 24 to (editorial or letter or note)	
26. limit 25 to (comment or editorial or letter)	26. 24 not 25	
27. 25 not 26		

stage. The hand search identified a further 16 citations for consideration, and the rerun search up to October 2001, unfiltered by the trials coordinator, added a further 309 potential articles. All the resulting abstracts were then independently assessed by three of the authors (MA, HB, RW), and following review of full articles, a total of 359 articles were included in the literature review.

Citations—overall commentary

The 359 articles were reported in nearly 100 different journals and included studies carried out in over 50 countries. The majority of the reports were relatively recent, with only 70 studies pre-1990. Studies were principally US-based, with the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) accounting for a significant number of articles. Some of the US-based studies included Native American populations, and several studies examined differences in DR incidence, prevalence, and associated risk factors in those of Hispanic and black American origin. Studies from the UK, Sweden, Japan, Australia, Denmark, Finland, Germany, and India accounted for 129 reports. A number of UK studies report on DR rates among British South Asian populations.

DR incidence and prevalence

Approximately one-third of studies were reports of people with type I diabetes, one-third reported type II diabetes and the remaining third reported mixed populations including both type I and type II. Just under one-half of the reports involved studies of population-based (as opposed to clinic-based) cohorts; however, this figure is partly a reflection of the large output from a few large longitudinal population studies such as the WESDR.

The publications pertaining to prevalence and incidence of DR were found to be highly heterogeneous in terms of subject selection with variable inclusion criteria, such as age range, gender, diabetes duration and type, ethnicity, comorbidity and DR status, assessment

and classification. A large number of studies were of clinical attendees. Published data cover a wide range of countries (European, American, African, Asian, Australasian) and population groups (controls, type I diabetes, type II diabetes treated by diet, type II diabetes treated with oral hypoglycaemic agents, type II diabetes treated with insulin); however, studies are limited in scope and the literature is dominated by a few large studies (eg WESDR).

Prevalence studies

Point prevalence can be defined as the proportion of cases of a disorder or disease in a particular population at a particular point in time, whereas lifetime prevalence is the proportion of the population who have a history of a given condition at a particular point in time.

A total of 153 references provided prevalence data for DR (including PDR) or MO (including clinically significantly MO; CSMO) in type I, type II, or mixed populations. The range of prevalence data was wide, and a summary of the data is given in Table 2.[9,13,15–17,22–169] Those studies that specifically report the prevalence of retinopathy at diagnosis (rather than pooled prevalence data from patients who may have had varied exposure to the disease) suggest that the prevalence of DR of any severity in people with newly diagnosed diabetes is dependent upon the type of diabetes (type I or type II). Generally, the prevalence of retinopathy at diagnosis of type I diabetes is reportedly low, between 0 and 3%,[45,59,101,160] while a higher proportion of those with newly diagnosed type II diabetes have evidence of DR (6.7–30.2%).[14,32,39,79,98,104,160,166,170]

Studies not confined to newly diagnosed diabetes show that the prevalence of DR in type I and type II diabetes is strongly correlated with duration of disease. Type I and type II patients enrolled into the WESDR, which began in 1979 and included 2990 patients across 11 counties in southern Wisconsin, USA, were more likely to have evidence of DR or PDR the longer the duration of their disease (Table 3).[171] The WESDR also identified an association between insulin treatment and the prevalence of DR or PDR in type II patients (Figure 1). Of the type II patients who had evidence of DR, 62% were treated with insulin and 36% were treated without insulin.[95] Similarly, 25 and 5% of patients showed evidence of PDR with and without insulin treatment, respectively. This effect is also evident in a Swedish study where noninsulin-treated type II patients were categorized into those treated with oral hypoglycaemic agents or by diet alone and compared with type I patients. DR was identified in a similar proportion of type I and type II patients treated with insulin (68.3 *vs* 65.9%) compared with 30 and 6.7% of type II patients treated with oral hypoglycaemic agents or diet, respectively.[144]

In contrast to the results in newly diagnosed type I diabetes cited above, the Diabetes Control and Complications Trial (DCCT) was a clinical study conducted from 1983 to 1993 by the National Institute of Diabetes and Digestive and Kidney Diseases involving volunteers with type I diabetes from 29 medical centres in Canada and the USA. The trial reports fundal photographic evidence of DR in 44.4% of patients with diabetes of less than 5 years duration and retinopathic changes on fluorescein angiography in 22% of patients, which were not evident from fundal photography.[172] Thus, 54.2% of patients had DR at baseline and 67.1% had DR within 5 years of diabetes duration.

The United Kingdom Prospective Diabetes Study (UKPDS) was a 20-year study involving 23 centres in the UK with more than 5000 patients with type II diabetes. This study also found a higher prevalence of DR in newly diagnosed type II diabetes than have other studies. In a subset of 2964 white, newly referred patients, DR (defined as microaneurysms or worse in one eye) was present in 39 and 35% of men and women, respectively; 'cotton wool' spots and neovascularization were also present in 8% of men and 4% of women.[104] Other findings from the UK are summarized in Table 4.

The prevalence of MO has also been found to be related to the duration of the disease. In 919 type I and 1121 type II patients enrolled into the WESDR, 0% of type I patients with less than 5 years' disease duration showed evidence of MO, compared with 29% after 20 years duration. Similarly, within 5 years of diagnosis, only 3% of type II patients had MO, compared with 28% after 20 years' duration.[96] Similar prevalence data have been reported in other studies in type II patients (8,[77] 5.4,[42] 3.7,[136] 8.2,[149] 4.7–8.2,[64] 2%[98]). The effect of insulin treatment on MO prevalence has also been investigated in type II patients; in 902 type I patients, 674 insulin-treated type II patients, and 696 noninsulin-treated patients from the WESDR, MO was present in 18, 20, and 12% of patients, respectively, after 15 years' disease duration[95,96] In a study in Sweden, MO prevalence rates of patients undergoing three-field stereo fundal photography were 16, 26.1, 8.6, and 0.6% in type I patients and type II patients treated with insulin, oral hypoglycaemic agents, or diet alone, respectively.[144] The prevalence of clinically significant MO (ie MO that threatens central visual function; CSMO) is reportedly low in patients with type I diabetes (5%)[96,173] and type II diabetes (2%)[118] in the first years following diagnosis. However, this increases to more than 20% in people who have had type I diabetes for 25 years.[96] While these studies are valuable, it is important to recognize that the definition of CSMO is based on subjective criteria, and

Table 2 Summary of the range of global prevalence estimates in type I, type II and mixed cohort diabetic patients[9,13,15,16,17,22–169]

Population	*Retinopathy grade*	*Type I (IDDM)*	*Type II (NIDDM)*	*Mixed cohort*
Caucasian				
USA	Any DR	0–84% (97.5% >15 years DM duration)	7–55%	37–61.1%
	PDR	3.8–25% (70% >30 years DM duration)	0.9–5%	
	CSMO	6%	2–4%	
UK	Any DR	33.6–36.7%	21–52%	16.5–41%
	PDR	1.1–2.0%	1.1–4%	1.1–8%
	CSMO	2.3–6.4%		6.4–6.8%
Australian	Any DR	42%	13–59.7%	29.1% (10% at 5 years and 80% >35 years DM duration)
	PDR			1.6–7%
	CSMO			4.3–10%
European	Any DR	16.6–76.5%	32.6–61.8%	26.2%
	PDR	7.3–17%	3.1–15.9%	1.8%
	CSMO		5.4%	
Scandinavian	Any DR	10.8–68.3% (90% >20 years DM duration)	18.8–65.9%	13.8–75.1%
	PDR	2.6–28.4%	4.2–14.5%	1.7–2.4%
	CSMO	16%	0.6–26.1%	8%
	Blindness	1.4%		
African American	Any DR	63.9%	26.5–31.4%	28.5%
	PDR	18.9%	0.9–1.5%	0.9%
	CSMO		8.6%	8.6%
	Blindness	3.1%		
Hispanic American	Any DR		33.4–45%	48%
	PDR		5.6–6.0%	
	CSMO			
American Indian	Any DR	19.7– 20.9%	19–49.3%	1.7% (total population)
	PDR		5.1–7%	
	CSMO			
South Asian				
South Asia	Any DR	13.6%	6.7–34.1%	
	PDR	1.9%	0.7–10.3%	
	CSMO		6.4–13.3%	
	Blindness		4.1%	
UK	Any DR		11.6%	
	PDR			
	CSMO			
Japanese	Any DR		31.6–38%	
	PDR		2.8–10%	
	CSMO			
	Blindness		2.9%	
Chinese	Any DR		19–42%	28–45.2%
	PDR		0.4–12.7%	2.2%
	CSMO		2.7%	
	Blindness		0.3%	
African	Any DR	26–43%	30.5–43%	12.7–42.4%
	PDR			12.8%
	CSMO			
South American	Any DR		54–51.2%	
	PDR		3.4–5.5%	
	CSMO		4.7–8.2%	

CSMO, clinically significant macula oedema; DM, diabetes mellitus, DR, diabetic retinopathy; IDDM, noninsulin-dependent diabetes mellitus; NIDDM, insulin-dependent diabetes mellitus; PDR, proliferative DR.

the degree of interstudy differences based on application of methodology is unknown at this time. Clearly, the most reliable data are derived from longitudinal studies from within the same patient population such as the WESDR and the UKPDS, where rigid clinical criteria were applied; however, even between these two studies,

Table 3 Prevalence of DR and PDR in patients enrolled in the WESDR[171]

	Type I		Type II	
	Duration of DM (years)	*Prevalence (%)*	*Duration of DM (years)*	*Prevalence (%)*
DR	<2	2	<2	23 (insulin[a]), 20 (no insulin[b])
	⩾15	98	⩾15	85 (insulin), 58 (no insulin)
PDR	<5	0	<4 y	4 (insulin), 3 (no insulin)
	9–10	4	⩾15	
	15–16	26		20 (insulin), 4 (no insulin)
	>20	56		

DR, diabetic retinopathy; PDR, proliferative. DR; DM, diabetes mellitus.
[a]Type II diabetic patients on insulin treatment.
[b]Type II diabetic patients not treated with insulin.

methodological differences apply. There is undoubtedly a need for a more objective method for determination of CSMO that can be universally applied.

A number of other studies have been conducted in Australia, Denmark, Finland, Sweden, Germany, India, Italy, Japan, and other European, Asian, and African countries (see Table 2). A few of these studies looked at large numbers of patients (between 2631 and 10 709 patients);[61,88,91,104,112,114,116,118,121,139,143,158,164] however, the majority of the remaining studies recruited smaller numbers of patients.

In Australia, 29% of 4744 older patients (>40 years old) enrolled in the Visual Impairment Project had DR, 2.8% of whom had untreated sight-threatening retinopathy.[116] Another large Australian study yielded similar prevalence rates (32.4%) in 3654 people aged 49 years or older undergoing eye examinations.[118] Of the patients studied, 21% had evidence of DR within 1 year of diagnosis, while DR was present in 68% of patients after 20 years of disease.

The European Diabetes Study (EURODIAB) investigated patients from 31 centres in 16 European countries. The overall mean prevalence of DR in type I patients ($n=3250$) for all the participating centres was found to be 35.9% (range 18.9–68.8%), while the mean prevalence rate for PDR was 10.8% (range 3–19.8%).[158] In the UK, in a population-based study of 10 709 diabetes patients identified through health district audit and data linkage, 16.5% had DR.[121] DR prevalence was found to be slightly higher in Sweden following a population-based study; of 4127 patients identified in a health district, 27% were identified from their medical records as having DR.[114]

Two large studies in India screened type II patients. In 6792 patients, the prevalence of any DR was 34.1%, with 3.4% having PDR and 6.4% MO.[143] In the second slightly smaller study ($n=3010$), DR was present in fewer patients (20%), although the prevalence of PDR was virtually identical (3.7%).[139] A large population-based study in Libya ($n=8922$) found that just under one-third (30.5%) of type II patients had DR.[88] In Barbados, DR was present in 28.5% of black/mixed race (almost entirely type II) patients.[112] Of these patients, under 1% were found to have PDR, and CSMO was found in 8.6% of patients.

Ethnic variation

Several studies in the USA investigate the prevalence of DR in the Hispanic, Mexican, African American, and Native Americans (Pima, Sioux, Hopi, and Navajo).[25,45,52,60,61,65–67,69,70,124,126,141,146,164] Of these, only five were comparative studies between ethnic groups.[52,65,67,69,70] One study reported a similar prevalence in Hispanics and non-Hispanic whites,[52] whereas the remaining four reported differences between blacks, whites, Mexicans, and Hispanics. In the third National Health and Nutrition Examination Survey in the USA, the prevalence of DR was 46% higher in blacks and 84% higher in Mexican Americans than whites with diabetes (Table 5).[70]

Outside of the US, the prevalence of DR in Fiji has been reported to be 52.6% (47% in Fijians and 53% in Indians) *vs* 13.3% in Australians (21% in Indians and 13% in Europeans).[29] In the Fijian population, significantly more people had evidence of moderate-to-severe DR or PDR compared with Australians. Three other studies have examined ethnic differences in DR prevalence. The studies in South Africa and the UK report a similar prevalence between people of African, European, and Indian origin with type II diabetes,[92] Asian and Europeans,[38] and black West Indians, Jamaicans, and Caucasians.[35]

Incidence studies

Disease incidence can be defined as the number of new cases of a particular disease occurring over a defined

Table 4 Summary of prevalence studies in the UK

Reference	*Setting*	*Participant characteristics*	*Prevalence*	*Comments*
Kohner *et al*[104] (UKPDS)	Clinic	2964 white, newly diagnosed NIDDM undergoing fundal photography	DR defined as microaneurysms or worse in one eye present in 39% men and 35% women. Cotton wool spots and neovascularization present in 8% men and 4% women	DR common in newly diagnosed NIDDM. Severity associated with higher FPG and BP, lower insulin levels and B-cell function. In men related to higher alcohol intake and in women lower BMI
Davis *et al*[39] (UKPDS)	Clinic	3027 newly diagnosed NIDDM followed for 6 years	Prevalence of DR 21% at baseline	Subsequent risk of DR increased significantly with age at diagnosis
Broadbent *et al*[28]	Population	357 patients identified from GP registers: 49 type I (group 1), 40 type II insulin treated (group 2), and 268 type II noninsulin treated (group 3). Screened using slit lamp and fundal photography and Wisconsin grading	Prevalences of any DR: 33.6, 36.7, 45.0, and 31.3%; for PDR/ advanced DR 1.1, 2.0, 0, and 1.1%; and for CSMO 6.4, 2.3, 16.2, and 5.7% for all DM patients, group 1, group 2, and group 3 patients, respectively. Sight-threatening diabetic eye disease was found in 13.4%	Prevalence appears to have declined in type I but remains high in type II, especially in those requiring insulin
Morgan *et al*[121]	Population	10709 DM patients identified through health district audit and data linkage	DR registered in 16.5% of patients	All diabetic complications related to age and duration but duration particularly apparent for microvascular complication such as DR and nephropathy
Das *et al*[38]	Population	337 people randomly sampled from GP practices screened for any eye disease	Main finding is that prevalence of cataract in Asians is significantly higher than in Europeans (30 *vs* 3%, respectively, <60 years of age and 78 *vs* 54%, respectively, >60 years of age). No ethnic differences in the presence of DR	Asian/European comparison
Sparrow *et al*[153]	Population	215 noninsulin-treated DM patients, 74% with follow-up seven-field stereo fundal photography. DR graded using the Wisconsin method and maculopathy by the ETDRS criteria	Prevalence of any DR or PDR was 52 and 4%, respectively. Maculopathy requiring treatment present in 10%	DM duration, female sex, higher BP, antihypertensive therapy, and smoking are risk factors

Table 4 *Continued*

Reference	*Setting*	*Participant characteristics*	*Prevalence*	*Comments*
Leese *et al*[111]	Clinic	961 DM patients in rural Tayside and 1225 in urban Tayside presenting for screening for eye disease through a mobile unit	DM patients in rural area more likely to have advanced DR (MO or PDR) than those in urban areas (DR: 13 *vs* 7%; $p<0.001$) and require urgent laser treatment for previously unrecognized DR (1.4 *vs* 0.5%; $p<0.02$).	Current screening in rural areas appears to be less effective than in urban areas
Samanta *et al*[147]	Clinic	907 consecutive patients (456 Asian, 451 Caucasian) assessed according to WHO multicentre criteria	Prevalence of DR less in patients of Asian origin compared to Caucasian origin (11.6 *vs* 32.3%; $P<0.01$). Also, lower prevalence of PVD, same IHD and higher renal disease. These differences remained significant after correcting for age at diagnosis, duration, hypertension, smoking, and insulin treatment	Marked heterogeneity in complications of diabetes between Asian and Caucasians
McLeod *et al*[117]	Population	Population-based survey of insulin-requiring DM	41% prevalence of any DR. Background DR in 33% and PDR in 8%. Maculopathy was found in 6.8%	Significant risk factors for DR identified as duration of DM and elevated diastolic BP, and for maculopathy were increasing age at onset and elevated systolic BP
Cruickshank and Alleyne[35]	Clinic	77 black West Indians matched with 74 Caucasians from the UK and 131 Jamaicans with DM examined with undilated ophthalmoscope	No difference between groups in the total level of background DR	Study suggests ethnic variation in large-vessel disease rather than small-vessel disease
Donovan[44]	Clinic	704 DM patients undergoing mydriatic ophthalmoscopic examination	22.7% had evidence of DR	

BMI, body mass index; BP, blood pressure; CSMO, clinically significant macular oedema; DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment of Diabeteic Retinopathy Study; FBG, fasting blood glucose; IHD, ischaemic heart disease; NIDDM, noninsulin-dependent DM; MO, macular oedema; PDR, proliferative DR; PVD, peripheral vascular disease; WHO, World Health Organization.

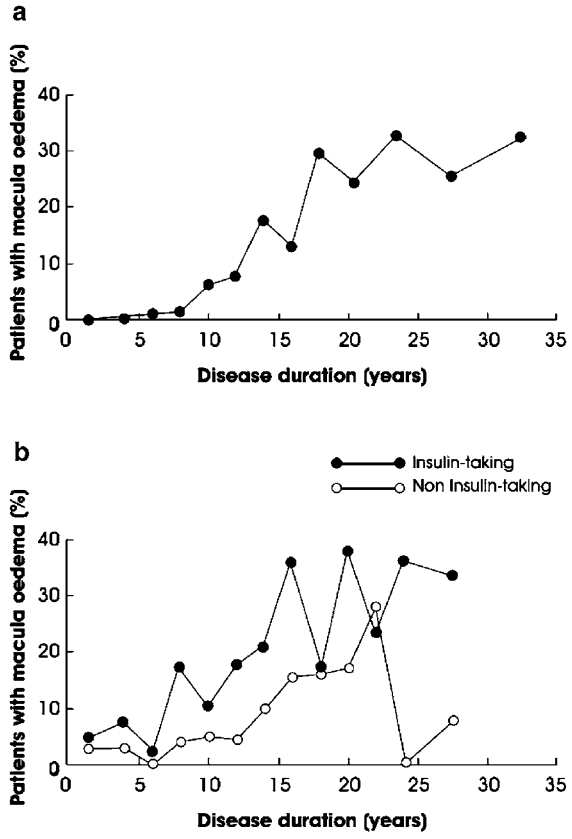

Figure 1 Frequency of MO by duration of diabetes in insulin-treated patients with young-onset diabetes (a) and patients with insulin- and noninsulin-treated older-onset diabetes (b). Reprinted from Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy IV. Diabetic macular edema. *Ophthalmology* 1984; **91**: 1464–1474, copyright (1984), with permission from Elsevier Science.[96]

Table 5 Prevalence of DR in white, African American, and Mexican Americans[70]

	Prevalence of DR (%)		
	White	*African American*	*Mexican American*
Any DR	18.2	26.5	33.4
Mild non-PDR	12.3	15.5	15.4
Moderate non-PDR	5.2	9.2	12.4
PDR	0.9	1.5	5.6
Any DR undiagnosed patients	7.7	1.5	9.9

time period. Incidence data can also be presented on the percentage of cases progressing to the next stage of a disease over a defined time period.

A total of 70 references provided incidence data for DR, PDR, or MO in type I, type II, or mixed cohorts. The range of incidence data for these studies is given in Table 6.[101,174–241] The spread of countries and populations covered in the studies pertaining to DR incidence was more limited than those for prevalence, and dominated by the WESDR.

The 4-year incidence of any DR in 891 people with type I diabetes enrolled in the WESDR was estimated to be 59%.[213] In the same study, 987 type II patients were split into two groups: those treated with insulin and those not treated with insulin. The 4-year incidence of any DR in these two groups of type II patients was 47.4 and 34.4%, respectively. Progression of DR and progression to PDR was observed in 41.2 and 10.5% of type I patients during the 4-year study. DR progression was seen in just over one-third (34%) of insulin-treated type II patients and 24.9% of noninsulin-treated type II patients. Progression to PDR was seen in 7.4 and 2.3% of these patients, respectively. In the three patient groups (type I, insulin-treated type II, and non-insulin-treated type II), the 4-year incidence of CSMO was 4.3, 5.1, and 1.3%, respectively, whereas the incidence of legal blindness was found to be 1.5, 3.2, and 2.7%, respectively.[213] In another group of 1075 patients in the WESDR, 4.7% developed PDR and 2.8% developed CSMO after 4 years.[209] In these patients, those experiencing one or more steps of progression (on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale) after 4 years were calculated to be 5.85 times more likely to develop PDR in the next 6 years compared with those with no progression.

The 10-year incidence of any DR, MO, or visual loss in patients enrolled in the WESDR was 89.3, 20.1, and 9.2% in type I diabetes ($n=996$), 79.2, 25.4, and 32.8% in insulin-treated type II diabetes ($n=674$), and 66.9, 13.9, and 21.4% in noninsulin-treated type II diabetes ($n=696$), respectively.[211] The 10-year incidence of visual loss was also investigated as part of the WESDR in 891 type I, 485 insulin-treated type II, and 502 noninsulin-treated type II patients.[226] At 10 years, blindness (visual acuity of 20/200 or less) was 1.8, 4.0, and 4.8% in type I, insulin-treated type II, and noninsulin-treated type II patients, respectively.[226] In these three groups of patients, the 10-year incidence of doubling of the visual angle (visual acuity of 20/40 or less) was 9.2, 32.8, and 21.4%, respectively, while visual impairment (measured as a loss of 15 letters on a scale of 0–70 letters) was 9.4, 37.2, and 23.9%, respectively.[226] Subjects have since been followed up for 14 years, and the 14-year rate of progression of DR was 86% in 634 type I diabetes patients, as measured by stereo fundal photography (grade Airlie House).[173] Regression occurred in 17% of these patients and 37% had progression to PDR, whereas the incidence of MO was 26%. In 880 type I patients, the cumulative 14-year incidence rate of blindness, doubling of the visual angle,

Table 6 Summary of the range of global incidence estimates in type I, type II, and mixed cohort diabetic patients[101,174–241]

Population	*Retinopathy grade*	*Type I (IDDM)*	*Type II (NIDDM)*	*Mixed cohort*
Caucasian				
USA	No DR to DR	33% over 2 years[a], 89.3% over 10 years	76.1/1000 PY, 66.9% over 10 years	17.4/1000 PY
	DR to PDR	37% over 4 years	53–69% over 10 years	1.6/1000 PY
	Two-step progression	76% over 10 years	10–24% over 10 years	
	CSMO	20.1% over 10 years	13.9% over 10 years	
	Blindness	1.8% over 10 years, 2.4% over 14 years	4.8% over 10 years	
UK	No DR to DR		60/1000 PY, 22% over 6 years	
	No DR to PDR		7/1000 PY	15.0/1000 PY
	Non-PDR to PDR			42.1/1000 PY
	Two-step progression		29% over 6 years	
	CSMO			
	Blindness			64/100 000 PY
Australian	No DR to DR			8% per year
	DR to PDR			7% per year
	CSMO			7% per year
European	No DR to DR	56% over 7 years, 47% over 5 years		
	DR to PDR	9% over 5 years		
	CSMO			
	Blindness	60.5/100 000/year for DM population		
Scandinavian	No DR to DR	85% over 15 years, 38% over 4 years		
	No DR to PDR	13% over 10 years, 16% over 20 years		
	CSMO	3.4% over 4 years		
	Blindness	0.23–1.1/10 000 years, 0.5% over 5 years	0.6% over 5 years	
African American	No DR to DR			
	DR to PDR	2% over 4 years		
	Two-step progression	19% over 4 years		
	CSMO			
Hispanic American	No DR to DR		58.3/1000 PY	
	DR to PDR			
	Two-step progression	24.1% over 4 years		
	CSMO			
American Indian	No DR to DR		72.3% over 12.8 years	
	No DR to PDR		12/1000 PY	
	CSMO			
South Asian				
South Asia	No DR to DR			
	DR to PDR			
	CSMO			
UK	No DR to DR			
	DR to PDR			
	CSMO			

Table 6 *Continued*

Population	*Retinopathy grade*	*Type I (IDDM)*	*Type II (NIDDM)*	*Mixed cohort*
Japanese	No DR to DR	70% at 29 years	39.8/1000 PY, 48.1/1000 PY	FPG <125 mg/dl: 3/1000 PY
	DR to PDR		57.7/1000 PY	FPG 126–139 mg/dl: 6.9/1000 PY FPG >140 mg/dl: 13.9/1000 PY
Chinese	No DR to DR		19.2% over 4 years, 44.4/1000 PY	
	DR to PDR		5.8% over 4 years, 37.5/1000 PY	
	CSMO			
African	No DR to DR DR to PDR CSMO			
South American	No DR to DR DR to PDR CSMO	6.6/100 PY		

[a]Diabetes duration.CSMO; clinically significant macular oedema; DR, diabetic retinopathy; FPG, fasting plasma glucose; IDDM, insulin-dependent diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; PDR, proliferative DR; PY, person–years.

and visual impairment (classified as above) were 2.4, 14.2, and 12.7%, respectively.[227]

The ETDRS enrolled 3711 patients with mild-to-severe non-PDR or early PDR in both eyes. One eye of each patient was assigned randomly to early photocoagulation and the other to deferral photocoagulation. Follow-up examinations were scheduled at least every 4 months. The study showed that focal photocoagulation of CSMO, but not scatter photocoagulation, is effective in reducing the risk of moderate visual loss.[242] The chance of developing high-risk PDR in 1 year ranged from 1% with mild DR at baseline to 3–8% for moderate, 15% for severe, and 45% for very severe DR. The incidence rose to 16, 27–39, 56, and 71% after 5 years in the respective groups.[14]

In 1919 patients with newly diagnosed type II diabetes in the UKPDS, 22% of those with no sign of DR at baseline developed DR at 6 years, and in 29% of patients with baseline DR, DR progressed two or more steps on the ETDRS scale after 6 years' disease duration.[237] The risk of photocoagulation in relation to baseline DR severity was also examined in the UKPDS. Over 60% of newly diagnosed type II patients ($n=3709$) were free of DR at baseline: 0.2% required photocoagulation at 3 years, 1.1% at 6 years, and 2.6% at 9 years.[217] This compares with those patients with more severe retinopathy features at entry (14% of patients enrolled), of which 15.3% received photocoagulation at 3 years and 31.9% after 9 years. In those patients with microaneurysms in one eye at baseline, 0, 1.8, and 4.7% needed treatment at 3, 6, and 9 years, respectively (Table 7).

Table 7 Prevalence of DR in type II diabetic patients in relation to 10-year mean HbA1c level[125]

HbA1c value (10-year mean) (%)	*Prevalence of retinopathy (%)*
<6.0	0
6.0–6.9	17.2
7.0–7.9	14.3
8.0–8.9	41.9
⩾9.0	54.8
χ^2 test for trend	$P<0.005$

There are also a number of studies from Europe, Africa, Australia, and Asia in both type I and type II diabetes. In Japan, the incidence rate of DR in 394 type II patients was 48.1/1000 person-years (PY) and progression to PDR in those patients with baseline DR was 57.7/1000 PY.[232] In type I diabetes, the cumulative incidence of PDR has been estimated to be 20% at 15 years, 40% at 19 years, and rising to 70% at 29 years of diabetes duration.[241]

Discussion

This systematic review of the literature has described studies examining the prevalence and incidence for the development of DR and its associated retinal complications. The methodological approach used to identify articles for inclusion in the literature review is based upon the ideals of the Cochrane Collaboration. The search strategies are systematic, sensitive, and transparent. The Cochrane Collaboration is principally concerned with the comparison of treatments using randomized controlled trials, and therefore the key terms or MESH headings from those studies are becoming increasingly effective as authors become aware of the importance of accurately key wording their publications. However, the epidemiological studies described here are of varying designs, thereby necessitating the complex searching strategies employed to identify them. In addition, the key diabetes, ophthalmological, and general medicine journals were searched manually for the final 6-month period covered by the electronic searches to reduce the likelihood of nonidentification of studies due to a time delay in cataloguing the electronic bibliographic databases used. While no methodological strategy can guarantee complete incorporation of all relevant citations, the approach taken in this review is considered robust.

The literature is dominated by a few large studies such as the WESDR, UKPDS, DCCT, and ETDRS trials. These trials are regarded by many as the 'gold standard', and patients have since been followed up for a number of years, providing excellent information on the incidence of disease progression. However, the large studies—important as they are—are now dated, and in some cases may reflect treatment from a previous era. The smaller studies are often limited in scope and may uncover confounding or conflicting results due to their small sample size. In addition, a number of studies are also clinic-based as opposed to population-based. While these studies are valuable, the data they produce may not be generalized and the frequency and severity of a disease may be overestimated. For example, people with long-standing diabetes who have difficulty managing their disease may be referred more frequently for eye examination to specialists, rather than being treated in the community. For this reason, population-based studies may more accurately reflect the true situation. The heterogeneous nature of studies (eg patient selection criteria, diabetes type) and the disparity between study methods (eg eight-field colour fundal photography *vs* two-field retinal imagery *vs* ophthalmoscopy *vs* slit-lamp examination) may contribute to conflicting reports of prevalence and incidence—sometimes even within the same country—making direct comparison of studies difficult. This highlights the need for consistent data capture within and between countries.

Recently, computerized diagnostic testing screening has been evaluated and compared with other established means of testing, that is, ophthalmologist *vs* physician *vs* optometrist.[243] The automated computer-based method was shown to be as effective as the 'gold standard' screening by an ophthalmologist for the detection of any retinopathy. This screening process is instantly translatable across studies and does not 'fatigue', making it an attractive possibility for the detection of retinopathy in diabetic patients. Automated detection may provide a useful role by identifying retinal images worthy of closer inspection or by eliminating up to 50% or more of the screening population who have no retinopathy.[243]

Diabetic retinopathy: the problem

Studies that are of sufficient size to stratify for age and duration of eye disease clearly show an increase in the prevalence of DR in older age groups with long-standing disease. As many as 100% of type I diabetic patients have been observed to develop some degree of retinopathy after 20–30 years,[16,84,85] peaking at about 10–15 years after diagnosis. Although some studies document a decline in retinopathy prevalence after this time, it is likely linked to differential survival during the later stages of the disease. Nevertheless, the prevalence of blindness and visual impairment is declining over time, despite no evidence of a reduction in the incidence of DR. This is likely due to better glycaemic, blood pressure, and lipid control. It is further helped by improved screening practices, recent advances in laser treatment, and increased disease awareness. The timely and appropriate care for diabetic patients can significantly reduce visual loss over time, not only improving patients' quality of life, but reducing the financial burden associated with the complications of visual impairment. However, as DR can progress irreversibly with relatively few visual symptoms,[187] the importance of early and adequate ophthalmological screening and subsequent treatment for all patients with diabetes is imperative.[218,244] It is also known that, despite adequate glycaemic and blood pressure control, DR can progress and once the disease process reaches a certain stage, its effects become irreversible. This phenomenon of 'retinopathic momentum' was defined in the DCCT and suggests that once DR progresses far enough down the line, then the momentum carries it forward, and that any form of intervention would not affect its relentless progress.[245] Nevertheless, screening and treatment have been predicted to prevent approximately three-quarters of expected cases of blindness in areas of the UK.[246] Despite this, studies suggest that over one-third of diabetic

patients do not adhere to screening guidelines,[247–249] endangering their visual acuity and long-term health. In addition, the provision of treatment guidelines for DR was found to have little impact on the healthcare management of the community, suggesting that mere dissemination of these guidelines is not adequate to change referral or treatment behaviours of physicians.[250]

Future directions

The phenomenon of retinopathic momentum needs to be further investigated with large studies looking at the different stages of DR and their progression rates, and it is postulated that different therapies may have different 'windows' of therapeutic effect in the overall DR disease process. Despite evidence suggesting that intensive glycaemic therapy is effective in controlling diabetic complications, maintaining strict blood glucose levels (and blood pressure) has proven difficult for many patients with diabetes, and the risk of hypoglycaemia is increased under this treatment regimen.[187,245] Consequently, this therapy is not suited to all individuals, and even strict blood glucose regimens do not completely eliminate the threat of retinopathy.[251] Unfortunately, some patients will also become visually impaired or blind and will require photocoagulation or surgical vitrectomy as a result of their underlying disease.[252,253] Thus, microvascular complications may be regarded as a partially preventable but inevitable outcome of diabetes,[254] suggesting that biochemical mechanisms other than hyperglycaemia alone are involved in the pathogenesis of DR.[74,255] This inevitability of the development of DR in many patients —in some cases leading to visual impairment and even blindness—despite intensive glycaemic control signals the need to capitalize on current screening programmes and treatment options while developing novel, improved treatments for the underlying condition. Evaluation of current screening programmes largely supports the view that they are effective in the identification of early DR and MO.[175] However, they must be widely, reliably, and economically applied, and they clearly have to be supported by effective treatment programmes consisting, at present, of laser photocoagulation for the treatment of advanced retinopathy including PDR and sight-threatening MO. Present literature is limited in terms of the acceptability of different approaches to screening, methods of maximizing uptake, and the effects of less than optimal uptake on the sensitivity of *programmes* (as opposed to the sensitivity of screening *methods*). This is an avenue that should be further explored.

Development of new compounds for the treatment of neovascularization represents a significant advance in the ability to treat diabetic patients, with the hope of preventing visual impairment and blindness in significant proportions of patients. These compounds are being developed to target the underlying cellular mechanisms of retinal complications. Vascular endothelial growth factor (VEGF) is a well-described mediator of ocular angiogenesis and permeability—indeed, it was first identified as a permeability factor—as is protein kinase-C-beta (PKC-β), a regulatory enzyme involved downstream of the VEGF receptor.[256] PKC-β is present in high levels in the retina, and increased activation of this enzyme leads to increased production of VEGF.[256] Therefore, targeting PKC-β with inhibitors or antagonists may arrest the development and/or progression of DR.[256] Indeed, clinical trials with an orally administered PKC-β inhibitor have demonstrated a significant beneficial effect on abnormal retinal haemodynamics.[257] Two Phase III randomized controlled trials are currently underway with such an inhibitor and hold much promise for the future.[256] In addition, other potential treatments such as the use of statins and anti-adhesion molecules are clinical concepts and currently under experimental development, bringing hope for the future treatment and prevention of diabetic retinal complications.

As new therapies become available, the need to capture and monitor new epidemiological data becomes ever more important to help determine the size of the economic burden and also how progression of DR relates to novel treatments. Additionally, a general consensus is developing among ophthalmologists, which suggests there is a 'low-risk' category of DR patients, where intervention can have a significant impact, and a 'high-risk' group of DR patients where intervention is not so effective. Further research is needed in order to establish whether such a distinction exists. With these points in mind, epidemiological studies in the future need to make use of standard criteria and apply consistent terminology for the definition and identification of stages of DR and MO. The studies should, whenever possible, include samples that are representative of the communities from which they are drawn.

Robust longitudinal collection of patient data will be essential to be able to identify the true extent of diagnosed retinal complications of diabetes, in turn providing healthcare planners with essential information to aid future decision-making.

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