Chapter

Diabetic Retinopathy and Blindness: An Epidemiological Overview

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Abstract

Prevalence of diabetes is rising worldwide. In the course of the last 20 years, blindness and low vision due to diabetic eye complications have increased in large regions in Eastern Europe, North Africa/Middle East, Asia, Latin America, and Oceania. The magnitude and trends of vision-threatening disease are presented. Systemic risk factors for progression to sight-threatening disease are reviewed. The impact of economic and cultural background on early diagnosis and adherence to treatment is highlighted. Current management of diabetic macular edema, proliferative diabetic retinopathy, neovascular glaucoma, and cataract surgery of diabetic patients is outlined, and its contribution to preventing vision loss is reviewed.

Keywords: diabetic retinopathy, trends, blindness, risk factors, treatment, visual outcome

1. Introduction

> *"It is a truism that each solution brings its own problems. Diabetic retinopathy in survivors of longstanding diabetes…represents the price paid for conquests that are not quite complete. The prolongation of life without corresponding prolongation of health, is loaded with intractable problems." commented Arnold Sorsby on the "striking increase" of blindness from diabetes for both men and women between 1948 and 1962. [1]*

The next six decades saw intensive research in the pathogenesis and epidemiology of diabetic eye disease and the introduction of laser photocoagulation in the early treatment of diabetic retinopathy, pars plana vitrectomy for traction, and rhegmatogenous retinal detachment and intravitreal pharmacotherapy in the management of diabetic macular edema (DME), all addressing prevention of vision loss in these patients.

2. Magnitude of blindness due to diabetic eye disease

Reports on the vision loss attributable to diabetes in the 1980s and 1990s vary greatly in their methodology—some have derived clinical information from hospital series, and others have reviewed the registry forms of certified disabled persons

from the records of societies of the blind; there are reviews on patients referred to low vision rehabilitation centers and finally some present data from population-based observational studies. Each source has its shortcomings. Definitions in registry databases depend on the national disability legislation and often differ from the categories for blindness and low vision in the International Classification of Diseases (ICD)—Ninth and Tenth Revisions—that were in use at that time. Many authors stress on the difficult task of identifying the onset and the main cause of vision loss in diabetic patients with multiple ophthalmic comorbidities, especially in their final stages. For a long period, well into the 1980s, non-ophthalmic professionals were allowed to certify blind persons for registration that raises reservations regarding the accuracy of the cause. A common concern is the inability to determine the number of underreported and unregistered diabetic persons with vision loss as registration is voluntary, and it depends on clinical, social, and cultural factors; many authors have noted a rise in the incidence rates of DR with the arrival of more consultants in the area, after upgrade in the financial benefits and social support for legally blind or following campaigns to improve public awareness and reduce stigmatization.

Hospital series analyze clinical data collected in specialized diabetic units over long periods in a consistent manner and provide reliable estimate on the severity and progression of vision loss; however, extrapolations of their findings for the population beyond their urban region are seldom possible.

Publications from the UK, Denmark, and Sweden demonstrate a decrease in the incidence of new blindness from DR in the 1980s and 1990s [2–5]; however it remained unchanged between 1967 and 1991 in Italy and Avon, UK [6, 7]. In their review on the trends in blindness in Singapore, See et al. [8] present a sharp increase in the prevalence of diabetes in the age between 15 and 69 from 1.99% in 1975 to 8.6% in 1992 and a rise in the proportion of blindness from diabetic complications from 5% in the 1950s to 47.3% in the 1980s.

Global data on blindness [9, 10], a review report of the WHO programme for prevention of blindness, summarized available information from population-based assessment of visual loss and its causes. DR was not among the four major causes for blindness and low vision globally and ranked between the first and fourth only in Western Europe, the former socialist economies of Europe, North America, Latin America, and Oceania. The authors note the lack of relevant epidemiological data for some specific causes of blindness; however they emphasize that this disease is "generally recognized to be the leading cause of blindness among those in working age in developed countries and rapidly emerging in urban areas of the developing world."

An update on the estimates of global and regional blindness and low vision was published in 2004 presenting results of new population-based studies and other sources of information. The proportion of DR rose to 4.8% globally, and it was ranked fifth as a cause of blindness, with significant regional variations reaching 17% for North America and Australia, 17–15% in Europe, and 3–7% in the rest of the world where the majority of vision loss was due to cataract, glaucoma, and corneal opacities as complications of trachoma [11].

A meta-analysis of all available population-based studies performed worldwide from 1990 to 2010 [12] estimated that 833,690 people were blind and 3.7 million were visually impaired globally in 2010 due to DR. The highest number of blind diabetic patients was in South Asia, 295,000; North Africa/Middle East, 108,000; Eastern sub-Saharan Africa, 50,000; and Western sub-Saharan Africa, 66,000. The age-standardized prevalence of blindness from diabetic retinopathy in people over the age of 50 years was 0.05% globally, reaching 0.19% in Western

sub-Saharan Africa, 0.16% in North Africa/Middle East, 0.14% in Eastern sub-Saharan Africa, and 0.12% in Southeast and East Asia. Moderate and severe vision impairment due to DR affected 3174 million, and the largest number of them were in South Asia, 1450 million, followed by North Africa/Middle East, 336,000; Eastern Asia, 279,000; Western Europe, 225,000; Western sub-Saharan Africa, 193,000; Eastern Europe, 166,000; Eastern sub-Saharan Africa, 128,000; and Central Latin America, 109,000. The age-standardized prevalence of moderate and severe vision impairment due to DR in people over the age of 50 years was 1.9% globally and was highest—0.51%—in South Asia, 0.50% in Western sub-Saharan Africa, 0.44% in North Africa/Middle East, 0.36% in Southern Latin America, 0.33% in Central sub-Saharan Africa, 0.32% in Andean Latin America, 0.31% in Eastern sub-Saharan Africa, and 0.26% in Oceania [13]. From 1990 to 2010, the number of blind diabetics had increased by 27% and those with visual impairment by 64% globally. Globally, age-standardized prevalence of blindness and vision impairment of diabetics over the age of 50 years was relatively unchanged in the course of these 20 years. It reduced by half in high-income Pacific Asia, Europe, Australasia, and North America; however it remained high in large, densely populated regions of Africa and Asia with rapidly increasing prevalence of diabetes.

A continuation of this systematic review and meta-analysis of data from 261 population-based studies published till 2014 [14] observed that while blindness to all causes reduced between 1990 and 2015, DR was the only one with prevalence that increased by 7.7% for blindness and by 28.6% for impairment. The proportion of vision loss attributable to diabetes ranked seventh in 2015 at 1.06% (0.15–2.38) globally and was highest in Eastern Europe, 4.91%, followed by Australasia, high-income North America, high-income Pacific Asia, and Central Asia. The contribution of DR to moderate and severe vision impairment was 1.30% (0.20–2.93) and reached 5.06% in Eastern Europe, followed by Australasia, high-income North America, high-income Pacific Asia, and Central Asia. The same regions were leading in the percentage of blindness and low vision due to DR for people over the age of 50 years. The age-standardized prevalence of blindness from DR across all ages was relatively low, in the range of 0.00–0.01 (0.00–0.02), and was considerably higher for vision impairment, 0.03% (0.00–0.13), with Eastern Europe ranking first at 0.11%, Central Asia, 0.09%; Southern Latin America, 0.08%; and North Africa/Middle East and Australasia, 0.07%. The age-standardized prevalence of blindness of diabetics over the age of 50 was 0.02% (0.00–0.07) and was highest in North Africa/Middle East, Eastern Europe, and Central Asia. The age-standardized prevalence of low vision in the same age group was 0.13% (0.01–0.48), and the same regions were most affected. For the first time, this report presented data on the gender differences in the cause and magnitude of vision loss and demonstrated that the relative risk of blindness and vision impairment in diabetic women as compared to men was 2.52. The number of people with blindness due to diabetic retinopathy was estimated at 400,000 (0–1.5 million) and low vision 2.6 million (0.2 million—9.9 million), both almost doubled since 1990. The projections for diabetic complications for 2020 are for further increase, and the largest number of people are expected to reside in North Africa/Middle East, 73,000 blind and 4,480,000 with low vision; Eastern Europe, 47,000 blind and 362,000 with low vision; Western Europe, 46,000 blind and 422,000 with low vision; East Asia, 41,000 blind and 400,000 with low vision; and Southeast Asia, 30,000 blind and 216,000 with low vision. The authors point out that the prevalence of any DR and sight-threatening DR was similar in men and women, whereas their analysis suggested female preponderance for

vision-impairing DR. They attribute this discrepancy to the use of aggregated data for both genders combined in some of the studies and highlight the need for further research into the gender differences. There are considerable regional variations in the blindness and low vision due to DR, and they are related to the prevalence of diabetes in the population and the life expectancy of the diabetic patients. In the Middle East, Kuwait, for example, the prevalence of diabetes has reached 20–25% of the whole population and over 50% after the age of 60 years. In some regions, in particular in South Asia, the life expectancy of diabetic individuals is reduced, they do not have the chance to develop retinopathy as sequela of the disease, and the prevalence of debilitating retinopathy is low despite the high proportion of diabetes.

A detailed meta-analysis of the trends in vision loss in high-income countries in Pacific Asia, Australasia, North and Latin America and Western Europe, as well as Central and Eastern Europe from 1990 to 2015 [15] presented a relatively low and stable prevalence of blindness due to DR for all ages in the range of 0.01–0.02% in the whole super-region; however the rates for moderate and severe visual impairment varied in the range from 0.6–0.7% in most of the high-income countries to 1.6% in Eastern Europe and Australasia. The crude prevalence of blindness among diabetics over 50 years was in the range of 0.02–0.03% in the high-income countries, 0.04% in Central Europe, and 0.06–0.07% in Eastern Europe, and visual impairment was lowest in Western and Central Europe and Pacific Asia, followed by North America and Australasia and highest in Eastern Europe. The projections for 2020 were for stable or slightly reduced prevalence of blindness and gradual increase of patients with visual impairment in the super-region.

Vision loss in the multiethnic population of Singapore over the age of 40 years was investigated in a series of population-based studies that demonstrated relatively high prevalence of diabetes in the sample—29.5%; DR was the second leading cause of vision impairment and blindness, and Indians and Malays were more affected than the Chinese. The authors point out that DR-related blindness in these three ethnicities in Singapore was less than the mainland Southern Indians, mainland Han Chinese, and peninsula Malays, and they attribute this to better access to qualified eye screening and care in Singapore. Diabetes was a significant contributing factor for visual impairment generally and increased the risk by 2.96 for people below the age of 60 years and 12.70 times for those over 60, particularly for females and patients with cognitive impairment and deafness, a tendency that was consistently observed across Malays, Indians, and Chinese. Diabetes in combination with other comorbidities, hypertension, hyperlipidemia, cardiovascular, or renal disease, was associated with higher risk of vision loss, up to 9.51 for people younger than 60 years and 26.56 for those older than 60, particularly for Indians, and an interaction effect for concomitant diabetes and renal diseases [16].

Vision-threatening DR (VTDR) is a compound term used in the literature for the presence of proliferative disease grading over level 60 by EDTRS scale and its modification and/or macular edema in its various stages [17, 18], and its magnitude is essential for planning the life-long management of these patients and prevention of blindness. The prevalence and risk factors of VTDR were estimated in a large meta-analysis of 38 population-based studies from Australia, the USA, Europe, and Asia involving 42,091 participants from 20 to 79 years with diabetes. There was no discernible sex difference in the age-standardized prevalence of VTDR, 11.7%; it was highest among African Americans, 16.89%; followed by Caucasians, 15.45%; and Hispanics, 10.35, and was lowest in South Asians—5.2%. Duration of diabetes (DM) was associated with rapidly increasing prevalence from 3.53% for DM less than 10 years to 17.78% for 10–20 years and up to 87% for more than 20 years.

Metabolic control, estimated by the levels of HbA1c, directly affected the extent of VTDR—the disease doubled in patients with levels between 7.1 and 8.0% and tripled among those with more than 9.0%. Elevated blood pressure over 140/90 and hypercholesterolemia over 4.0 mMol/L elevated the risk of VTDR twice, particularly for macular edema. Individuals with type 1 diabetes for more than 20 years were 15 times more likely to have proliferative diabetic retinopathy (PDR) (15.3 [11.3–20.8]), 5 times more likely to have DME (4.83 [3.71–6.30]), and 8.7 times more likely to have VTDR (8.69 [7.10–10.63]) than those with type 2 diabetes for less than 10 years. On a positive note, the prevalence of VTDR reduced from 15.62% in studies where the fundus photographs were taken before the year 2000 to 7.86% in the studies with assessment of the patients after 2000.

This pivotal work highlighted the importance and cutoff levels of the systemic factors associated with progression of DR to sight-threatening stage and the need for close collaboration with the treating diabetology team. It outlined the profile of the patients at risk of vision loss with their features—type and duration of diabetes, levels of metabolic control, hypertension, and hypercholesterolemia. The role of ethnicity was limited to the populations studied, and the authors note the absence of studies from Middle East, Africa, and South America that could affect the accuracy of their global estimates. The differences in the rates of VTDR in the various populations could be due to both genetic factors and access to health care. Ethnicity itself is multidimensional, and it may not be possible to differentiate its effect from the risk associated with remoteness, urbanization, lifestyle, education, health awareness, and individual income.

3. Social and economic risk factors

Social and economic factors have a fundamental impact on the visual prognosis of diabetic eye disease. A number of studies have investigated the negative influence of deprivation on the prevalence of diabetes, access to evaluation and care, level of metabolic control, and rate of complications and were reported in systematic reviews for type 1 [19] and type 2 diabetes [20]. Remoteness [odds ratio (OR) 2.02] and diabetes in combination with never having had an eye examination (OR 14.47) were among the main risk factors for vision loss in indigenous Australians, and blindness prevalence was 2.8 times higher among them than in non-indigenous Australians after age and gender adjustment [21]. The presence of PDR was associated with low income (OR = 3.6 for developing PDR if income was less than $20000) in the Proyecto VER Study in the USA involving 4774 Hispanics over the age of 40, after controlling for other factors [22]. Deprivation, as a comprehensive measure of income, employment, health and disability, education, crime, barriers to housing, services, and living environment at the level of small geographic areas, was developed in the UK as a numerical index per residential code and used in a large national database study of 79,775 diabetic patients to highlight its effect on visual acuity and need for early treatment at first hospital presentation [23]. The OR of presenting with "sight impairment" at first visit to the hospital eye service was gradually decreasing from 1.29 in the most deprived group to 0.77 in the least deprived one, and OR for "severely sight impaired" was 1.17 in the most deprived decile versus 0.88 in the least deprived one. The risk of sight-threatening maculopathy and vitreous hemorrhages showed little variations across the deprivation range, and tractional retinal detachment was less likely in the two least deprived deciles. The large scale of the study and use of "real-world" multicenter in-hospital dataset provided statistical strength to the conclusion that the impact of deprivation extends to late presentation of retinopathy, significant loss of vision at presentation,

and a pattern of advanced retinal complications that affect the treatment these patients receive. Financial factors are often self-reported by diabetic patients who are missing screening appointments and treatment sessions. However a study in Tanzania revealed that the reasons for poor compliance are more complicated. The clarity of referral process and ease of navigation through the unfamiliar hospital environment are essential, particularly for the elderly and less educated patients from remote areas [24]. Another formidable obstacle is the widespread complacency and fatalistic resignation with the notion that retinopathy will inevitably end up with blindness. Constant assurance and encouragement that diabetic eye disease is a treatable condition with good prognosis is a practical strategy to prevent delays in diagnosis of sight-threatening complications. Lack of education greatly affects the health awareness and adherence with retinopathy management. In Kuwait, 16% of the men and 46% of the women over 65 years are illiterate, and 20% of the men and 24% of the women in the same age group can only read and write [25]. This is a significant barrier to in-depth understanding and compliance with recommended treatment and lifestyle and eventually compromises the visual outcome despite the high economic standard of the Kuwaiti nationals and availability of services in the country. Family support greatly improves the continuum of care and is essential for the regular attendance of the patients, especially females from a more conservative background.

Progression of nonproliferative to proliferative disease was investigated in several large cohort studies [26, 27]. Disease severity was estimated by the EDTRS classification and taken separately for each eye or concatenated as the bilateral grade, and progression was defined as the increase of two or more steps in severity. The rate of progression to PDR varied greatly—it was from 4 to 9.9% in the first 4–5 years and 8–12% in the next 5 years and reached a cumulative level of 31% after 16 years and 42% after 25 years in type 1 and type 2 diabetics. There are differences between the populations and methodology applied in the hospital-based and community-based studies as more patients with severe disease that required active management were probably referred to tertiary care centers [28–32].

The diagnosis of diabetic macular edema has evolved with the introduction of stereoscopic photography of the posterior pole and optical coherence tomography (OCT). The presence of any edema and clinically significant edema (CSME) by the modified EDTRS classification has been investigated in multiple hospital series and population-based studies. Detection of DME in non-stereoscopic fundus photographs is less sensitive to milder forms with recent onset, and probably the reported prevalence covers the more severe chronic stage. The prevalence of CSME in type 1 patients was from 5.73% in Spain to 9.4% in Brazil [33, 34]. Among patients with type 2 diabetes, it was in the range from 1.4% in Portugal to 12.8% in Denmark [35, 36]. There are reports indicating that the prevalence of DME in Central and Eastern Europe [37], North Africa, and Middle East [38] is considerably higher, and further research on the magnitude of CSME and risk factors for its progression will contribute to the estimates of sight-threatening retinopathy globally.

4. Diabetic nephropathy

Diabetic nephropathy (DN), the primary cause of chronic kidney disease, is significantly associated with incidence and progression of diabetic retinopathy as demonstrated in Brazilian [39], Spanish [40], Korean [41], Taiwanese Chinese [42], and Australian [43] patients. The presence of chronic kidney impairment had adjusted a hazard ratio of 5.01 for nonproliferative and 9.7 for proliferative disease

as compared to patients without nephropathy. At 5-year follow-up, the hazard ratio of progression to PDR was 2.26 in patients with DN, and it was related to the levels of microalbuminuria and estimated glomerular filtration rate with cutoff below 60 mL/min/1.73 m^2 [44]. Hypertension and DN in patients with chronic kidney disease increased the risk of progression to proliferative disease; however diabetic nephropathy did not significantly affect the development or progression of DME. Among the Taiwanese Chinese patients, diabetic macular edema had high crude hazard ratio association with cerebrovascular accidents and lesser one for hypertension and use of statins; however the significance was lost after controlling for age, sex, comorbidities, and medications.

5. Pregnancy in diabetic patients

Diabetes affects 17% of pregnancies worldwide and can be pre-existing type 1, gestational, or type 2, in some of the patients—previously undiagnosed. The highest rate of diabetes in pregnancy is recorded in Southeast Asia, 25%, and the prevalence of pre-existing diabetes is highest among women from the Middle East and North Africa—3.1%. Australian mothers who were born in high diabetes risk areas such as Polynesia, Asia, and the Middle East are 1.4 times more likely to have type 2 diabetes during pregnancy [45]. Similarly, in the USA and UK, patients belonging to Black, Asian, Hispanic, and Pacific Island ethnic minorities had higher proportion of pre-existing diabetes and pre-existing type 2 DM. Progression of retinopathy during pregnancy is related to the level of diabetic retinopathy prior to conception and was noted in 58% of the patients with moderate or more severe DR at baseline. Duration of diabetes type 1 greater than 15 years and type 2 more than 6 years was significantly associated with higher rate of progression of retinopathy in patients with pre-existing proliferative disease. Poor glycemic control prior and during pregnancy was an independent risk factor for retinopathy progression; however tight control and rapid optimization of metabolic control in such patients were associated with worsening of retinopathy. As the long-term benefits of proper glycemic management outweigh the short-term risk of deteriorating retinopathy, optimal control is currently recommended prior to and as soon as possible after conception for the health of the mother and fetus. Progression of retinopathy during pregnancy was significantly higher in diabetic patients with preeclampsia, with sight-threatening complications in 50% of the diabetic women with preeclampsia compared to 8% without it [46]. Other risk factors for deteriorated retinopathy during pregnancy include young age of type 1 onset, insulin treatment in type 2 prior to pregnancy, low vision at baseline, and pre-existing macular edema at baseline [47].

6. Diabetic foot syndrome

Diabetic foot syndrome is one of the important consequences of long-term uncontrolled diabetes, which occurs due to a combination of peripheral neuropathy and microvasculopathy in the lower extremities. It may vary from a minor ulceration to necrosis of tissues, sometimes warranting amputation [48]. Several hospital series demonstrated the presence of retinopathy in 90–95% and proliferative disease and severe nonproliferative changes in 39–55% in such patients independent of the ulcer severity [49]. Diabetic foot syndrome in type 1 and type 2 diabetic patients with retinopathy was associated with higher levels of HbA1c, serum creatinine, older age, and lower hematocrit, particularly elevated in the subgroup

with proliferative disease—all characteristics of concomitant chronic kidney disease and neuropathy in poorly controlled, long-lasting diabetes. Despite the lack of data on macular edema, the presence of any stage of diabetic foot ulcer is emerging as a predictor for retinopathy deterioration [50, 51].

7. Depression and anxiety

The overall prevalence of depressive symptoms in diabetic patients with retinopathy is estimated in the range of 35% in China to 50% in African Americans and is more prevalent in type 2 [52, 53]. The association between depressive symptoms, diabetes, and diabetic retinopathy is likely to be bidirectional: the impairment and burden of diabetes and its complications can precipitate depression and vice versa, and depression can impair diabetes control through various biological and behavioral pathways [54, 55]. Depression aggregates negative attitudes toward treatment and often leads to poorer glycemic control, less adherence to treatment, higher risk for PDR, greater morbidity and mortality, and higher costs [56]. Low income has been implicated in some research from the USA; however it was not found significant in a large cross-sectional study from Australia. Patients with longer duration of diabetes, worse glycemic control, lower educational level, and severe vision impairment below 20/63 were associated with greater depression symptoms. Symptoms of anxiety were associated with type 1 diabetes, presence of myocardial infarction/angina, arrhythmia, stroke, asthma, anemia, arthritis or osteoporosis, younger age, and female gender [57]. Severe NPDR and PDR, but not macular edema, were independently associated with depressive symptoms, and the authors suggest that severity of retinopathy could be an indicator to prompt monitoring of depression in at-risk diabetic individuals. Antidepressant medications have been associated with slowing the progression of retinopathy in diabetic patients. However the outcome was limited to subjects with elevated C-reactive protein over 0.3 mg/dL. Selective serotonin reuptake inhibitor users had significantly lower risk of developing severe retinopathy than non-SSRI users [58]. The results of longitudinal studies show that the speed of cognitive decline in type 2 diabetic patients is up to twice as fast as that of normal aging individuals and diabetic patients have an increased risk of mild cognitive impairment (MCI). In addition, type 2 diabetic patients had an almost twofold higher risk of developing Alzheimer's disease than age-matched nondiabetic subjects. This increased risk was maintained even after adjusting for vascular risk factors. The annual conversion rate from MCI to dementia ranges between 10 and 30% in the general population, but this is much higher in the type 2 diabetic population. The impact of cognitive impairment on the compliance with lifelong retinopathy treatment and its outcome needs further evaluation; however clinical practice indicates the need for personalized multidisciplinary approach.

8. Progression to vision-threatening retinopathy

The variability in the rate of progression to vision-threatening retinopathy and particularly in the response to treatment was noted from the onset of clinical and epidemiological studies in diabetic patients and has been attributed to the effect of genetic predisposition together with systemic and socioeconomic factors. Single-nucleotide polymorphisms [58–60] and genome-wide associations [61–63] have been investigated in patients with proliferative disease and macular edema, and the results so far are inconclusive mainly due to the size of the samples and the

inclusion of cases with coexisting proliferations and edema in the cohorts. Detailed assessment in the polymorphisms of the VEGF gene revealed that some of them are related to higher susceptibility to severe retinopathy, but not to the outcome of ranibizumab intravitreal injections [64] in contrast to an earlier report on the response to bevacizumab [65]. In order to confirm the association of several novel genetic loci with severe retinopathy, replication studies and extension in additional cohorts and ethnic groups have been recommended [66]. Research of systemic and retinal inflammation as risk factors for DR and DME [67, 68], upregulated leptin [69, 70] and adiponectin [71], oxidative stress [72], and vitamin D deficiency [73] has provided significant associations. Reliable and accessible markers of these factors can be important predictors of the disease severity and progression and thus provide early guidance in personalizing the monitoring and treatment of the patients at risk of vision loss.

9. Management of DME

The introduction of intravitreal anti-VEGF drugs and corticosteroid implants revolutionized the management of DME. Prospective randomized clinical trials have addressed the efficacy and safety of different types of agents and administration regimens and have shown wide variations in terms of visual acuity gain. In the DRCR.net trial, after 2 years of treatment, approximately 98% of the patients maintained their visual acuity and attained visual gain in 37% of the patients on ranibizumab, 35% of those on bevacizumab, and 39% of those on aflibercept [74]. Stratified analysis of RESTORE in DME, RETAIN, and Protocol I demonstrated that the most significant gain in number of EDTRS letters after 12–36 months was in patients with baseline BCVA 60 and less letters in the range of 8.6–10.36 letters, versus the gain for patients with baseline BCVA 61–71 letters who achieved 7.96–4.36 letters, and the least gain of 5.42–4.2 letters was in the group with baseline BCVA better that 73 letters [75]. Thus, the patients with most severe vision deterioration and baseline BCVA in the range of 20/320–20/63 who responded favorably to 2 years of intensive therapy improved to BCVA from 20/160 to 20/40. High visual acuity in the range of 20/40–20/32 was achieved only in patients with baseline BCVA over 20/30 despite the small number of gained EDTRS letters. The range and stability of this visual improvement depended on increasing age, level of glycemic control, and previous panretinal photocoagulation [76]. OCT markers of better functional outcome after anti-VEGF treatment were the presence of intact ellipsoid zone and lack of hyperreflective spots or disruption of the inner retinal layers, which are seen in patients with more recent onset of the edema and no previous macular grid laser [77]. Patients with chronic macular edema had considerably better functional and structural results after treatment with steroid implants. Visual gain of more than 15 letters was achieved in 22% after 3 years on intravitreal dexamethasone [78] and in 34% after 3 years on fluocinolone acetonide [79]. Eyes with submacular fluid, no hyperreflective foci, and a continuous IS-OS layer responded better to dexamethasone implants with gain of 10 or more letters after 2 and 4 months [80]. The adverse effects of both implants included the formation of cataract, 13–50% after 1 year on dexamethasone and 82% after 3 years on fluocinolone acetonide, and intraocular pressure rise over 25 mmHg in 42% of the eyes with dexamethasone and 38% with fluocinolone acetonide; however a small percentage required glaucoma surgery—0.5% of the eyes with dexamethasone and 4.8% with fluocinolone acetonide. Patients with poorly controlled diabetes and DME, severe nonproliferative or proliferative disease,

epimacular membranes, myopia, glaucoma, and various degrees of cataract are excluded from the randomized clinical trials; however such cases are predominant in real-world practice and add new dimensions to the challenge of visual rehabilitation. Analysis of large electronic medical record databases from the USA [81] and Korea [82] demonstrated visual outcomes that are meaningfully inferior to those in the clinical trials and were attributed to undertreatment and lack of close monitoring. A sizable group of DME patients were lost to follow-up in the initial stages of anti-VEGF treatment—25% were reported from a single retina practice in the USA and the main risk factors were being Hispanic, Black, or a Pacific islander; low income, AGI less than $50,000; and decreasing baseline visual acuity [83]. In a study of European DME patients, 46% had at least one break-off in their anti-VEGF treatment for more than 100 days, and the most common reason for poor compliance was comorbidity. In 60% of these cases, the visual acuity deteriorated significantly after the break [84]. Prevention of vision loss from diabetic macular edema is achievable with the current therapeutic modalities; however it requires very early identification at stages with relatively high visual acuity and needs the introduction of best-corrected visual acuity and OCT in the screening protocol. As shown in the Protocol G—Subclinical DME study of the DRCR.net that involved a longitudinal assessment of eyes that had retinal thickening on OCT without thickening on clinical exam, a progression to clinically apparent DME was seen in 23–58% of eyes within 2 years.

10. Management of proliferative disease

Vision loss in approximately 25% of patient with diabetic retinopathy is associated with complications of proliferative disease. An estimated 17 million diabetic people worldwide have PDR [17], and without treatment more than half of the patients with high-risk PDR will be blind within 5 years. Panretinal photocoagulation was established as an effective treatment to reduce by 50% the incidence of severe vision loss, if performed prior to the development of vitreous hemorrhages and tractional retinal detachment [85]. Still, the EDTRS has shown that 5% of patients with PDR will require vitreous surgery despite having received adequate PRP [86]. The Diabetic Retinopathy Vitrectomy Study validated the superiority of vitrectomy over observation; however despite the fact that the trial did not include patients with macula, involving traction, the visual outcome was low. Subsequent studies on vitrectomy for PDR reported that between 10 and 20% of the patients did not improve their visual acuity above hand motion or less [87]. Favorable factors for visual rehabilitation after vitrectomy for macula-involving tractional retinal detachment included short duration of detachment, previous panretinal photocoagulation, and lack of severe neovascularization and vitreous hemorrhage. Predictors of poor visual results were iris neovascularization and neovascular glaucoma, papillo-vitreal traction, baseline visual acuity below 20/200, initial macular detachment, intraoperative iatrogenic break, or use of heavy silicone oil [88–90]. Functional outcome was significantly affected in patients with postoperative macular ischemia, recurrent vitreous hemorrhage, optic atrophy, epiretinal membranes, and recurrent retinal detachment [91, 92]. The introduction of small-gauge vitrectomy instruments and trans-scleral cannulas enabled the fast and effective removal of most fibrovascular membranes with the vitrectomy probe applying the lift and shave technique [93]. Visual outcomes were poorer in older age group, tractional retinal detachments involving macula and eyes with extensive membranes and with silicone oil as tamponade; however both 23-gauge and 25-gauge groups were comparable in relation to visual improvement, anatomical success, and intraoperative

and postoperative complications [94]. The integration of swept-source optical coherence tomography and digital displays can provide important guidance during surgery for PDR complications and facilitate decision-making [95]; however further research will show whether these technological advances will translate into better postoperative visual outcome.

Medical treatment for PDR has had minimal advancement over the past 40 years since the wide acceptance of panretinal photocoagulation in the early management of the disease. Regression of proliferative activity was noted in eyes treated with anti-VEGF for concomitant macular edema [96] and that lead to a series of trials on aflibercept and ranibizumab versus panretinal photocoagulation in the management of PDR. Both drugs were superior to PRP in 1 [97] and 2 years [98] in terms of visual acuity and visual field sensitivity. Assessment of the peripapillary retinal nerve fiver layer thickness in patients treated with ranibizumab revealed reduction that was due to decreased edema rather than loss of axons [99]. Patients with mild and moderate vitreous hemorrhages treated with ranibizumab had significantly less need for vitrectomy, less recurrences of hemorrhage, and better visual acuity on all follow-up visits than the patient under observation or operated for non-resolving or aggravated hemorrhages [100]. However, despite the improvement in retinopathy severity on color photographs, the retinal perfusion did not improve on wide-field fluorescein angiography that revealed no reperfusion of small vessels in areas of previous capillary non-perfusion [101]. Diabetic patients are prone to significant loss to follow up due to illness, financial hardship, and lack of compliance. The rate of complications and loss of vision after unintentional interruptions for more than 6 months in PDR patients treated only on anti-VEGF was considerably higher than the eyes that received PRP, with a significantly higher number of eyes with tractional retinal detachment and neovascularization of the iris [102]. In a retrospective review of 13 eyes treated exclusively with anti-VEGF for PDR with or without macular edema or severe NPDR with macular edema, with hiatus of 12 months, 9 presented with vitreous hemorrhage, 5 with neovascular glaucoma, and 4 with tractional retinal detachment. Despite the aggressive treatment of the complications, 10 eyes lost more than 3 lines of vision, and 2 had final vision hand motions [103]. So, while anti-VEGF proved to be effective for PDR in the clinical trials, in real-world the unclear long-term advantages of pharmacological monotherapy over PRP, the increased cost, and treatment burden are not optimal for many diabetic patients.

Neovascular glaucoma is a late complication of proliferative disease with chronic ischemia in the posterior segment and development of a fibrovascular membrane on the anterior surface of the iris and iridocorneal angle of anterior chamber, and usually its onset correlates with poor glycemic control. In the early stages, iris neovascularization can be found without elevated IOP. Panretinal photocoagulation remains the mainstay in controlling the neovascular drive and should be considered in all cases of neovascularization of the anterior segment when retinal ischemia is present. After panretinal photocoagulation, complete regression of retinal neovascularization can be reached in 67–77% of cases, visual loss can be prevented in 59–73%, and IOP reduction can be achieved in 42% [104]. Anti-VEGF injections can lead to regression of both iris and angle neovascularization and improve intraocular pressure control when the angle remains open. However, the effects of anti-VEGF agents seemed to induce only a temporary regression of new vessels in the anterior chamber angle and IOP reduction, generally lasting between 4 and 6 weeks [105]. Glaucoma drainage devices are usually considered the first treatment option for refractory glaucoma. Neovascular glaucoma patients are at greater risk for surgical failure after glaucoma valve surgery compared with non-neovascular glaucoma controls. A recent retrospective, comparative, case series of 163 eyes of 151 patients with neovascular glaucoma included 99 treated without and 64 treated

with intravitreal bevacizumab. IOP decreased to 18.3 ± 13.8 mmHg in the non-bevacizumab group and 15.3 ± 8.0 mmHg in the bevacizumab group. Panretinal photocoagulation substantially reduced the need for glaucoma surgery ($P < 0.001$) in bevacizumab-treated eyes. Therefore, although bevacizumab delayed the need for glaucoma surgery, panretinal photocoagulation was the most important factor that reduced the need for surgery. Vision and IOP in eyes with neovascular glaucoma treated with bevacizumab showed no long-term differences when compared with eyes that were not treated with bevacizumab. Thus, intravitreal anti-VEGF drugs serve as an effective temporizing treatment but are not a replacement for close monitoring and definitive treatment of neovascular glaucoma [106, 107].

Impairment of vision in diabetic patients is not limited to retinopathy—the leading causes of deteriorated vision and progression of vision loss in a cohort from South India were cataracts and uncorrected refractive errors [108]. The introduction of phacoemulsification significantly reduced the surgical trauma and leads to a growing tendency toward earlier cataract surgery in diabetic patients [109]. This approach facilitates panretinal photocoagulation and allows for the identification and adequate treatment of diabetic macular edema before and after cataract surgery. Preexisting macular edema can increase the risk of edema progression by 20–50%, and intravitreal anti-VEGF agents are recommended perioperatively [110]. Steroids, on the other hand, have been shown to be effective for persistent or refractory diabetic macular edema prior to and after cataract procedures. Dexamethasone implants and fluocinolone implants resulted in significant improvement in clinically significant macular edema and visual outcomes [111]. Despite the advancement in phacoemulsification technology, poor visual acuity following cataract extraction is still common in patients with diabetes. Posterior capsule opacification, postoperative cystoid macular edema, diabetic macular edema [112], and worsening of the DR are the main complications seen in diabetic patients. According to the Early Treatment of Diabetic Retinopathy Study, the presence of clinically significant diabetic macular edema at the time of cataract surgery was significantly associated with poor visual acuity and was a predictor of final visual acuity worse than 20/200 following uncomplicated phacoemulsification [113]. The severity of DR at the time of cataract surgery is also a significant determinant of postoperative VA; more severe retinopathy seems to be associated with an increased prevalence of macular ischemia or edema and a reduced tendency for spontaneous resolution of postoperative macular edema with associated poor postoperative VA. Treatment-naïve PDR before cataract surgery may progress to vitreous hemorrhage and tractional retinal detachment following phacoemulsification, thus threatening good visual outcome [114].

In conclusion, vision loss due to diabetic complications in the eye is growing worldwide despite availability of screening programs, advanced diagnostic tools, pharmacotherapy, and rapidly evolving surgical technology. Prevention requires:

- Identification of the social groups and individuals at high risk of vision-threatening diabetic complications
- Coverage with diabetic retinopathy screening with introduction of AI tools, wide-field retinal assessment, telemedicine, and OCT of the posterior segment
- Outreach of qualified management closer to the diabetic patients' communities
- Early, intensive management before significant vision loss
- Lifetime, highly qualified monitoring and early management of complications

- Close, continuous collaboration with the treating diabetology team
- Involvement of the family, community, diabetic patients' organizations, and social media in patient care, adherence to treatment, prevention of physical and mental disability, and improvement of quality of life

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