Nova Acta Leopoldina NF *119*, Nr. 401, 21–28 (2014)

Diabetic Retinopathy: Past, Present and Future

Paul A. Sieving (Bethesda, MD, USA)

With 4 Figures

Abstract

Diabetes and diabetic retinopathy cause major morbidity in the human population. Diabetes was described as long ago as 1552 B. C. in the *Papyrus Ebers*, and it affects many organ systems of the body, including the eye where it leads to vascular leakage and haemorrhage and results in blurred vision and ultimately total vision loss from proliferative retinopathy. Diabetic retinopathy was reported for perhaps the first time by Appolinaire Bouchardat in 1846. Three major stages of understanding this disease have occurred since then. The first phase began with the first description in 1846 and continued into the middle of the 20th century when various clinical aspects of the conditions were described. The second stage began in the 1970s with a series of interventional treatments that began with pan-retinal photocoagulation, developed through the National Eye Institute (NEI) Diabetic Retinopathy Study. This remains the mainstay of medical treatment for the ocular component of advanced diabetes. We have now entered a third phase, which portends the future based on biologic intervention at the molecular level. This work has been pioneered through the Diabetic Retinopathy Clinical Research Network (DRCR.net), established in 2002, which recently demonstrated that intraocular anti-vascular endothelial growth factor (VEGF) treatment was effective for diabetic macular edema. Success of this molecular approach will gather speed in the years ahead as we begin to understand the pathology at a cellular and system biology level.

Zusammenfassung

Diabetes mellitus wurde bereits im *Papyrus Ebers* im Jahr 1552 v. Chr. dokumentiert. Die Erkrankung betrifft das gesamte Nerven- und Gefäßsystem des Körpers und damit auch das Auge. Diabetische Retinopathie ist eine häufige Folgeerkrankung von Diabetes mellitus und stellt die häufigste Ursache der Erblindung in den westlichen Industriestaaten dar. Die pathologischen Veränderungen am Auge führen zu Wasseraustritt, Blutungen und Gefäßverschlüssen, die eine Sehverschlechterung und bei der proliferativen Form Sehverlust verursachen. Zum ersten Mal wurde die diabetische Retinopathie im Jahre 1846 von Appolinaire Bouchardat beschrieben. Seitdem unterscheidet man drei verschiedene Zeitabschnitte, die dem Verstehen der Erkrankung dienten. Der erste Zeitabschnitt begann bereits mit der ersten Beschreibung 1846 und hat sich mit den klinischen Aspekten der Retinopathie befasst. Diese Phase dauerte bis zur Mitte des 20. Jahrhunderts an. Erst ab 1970 hat ein neuer Zeitabschnitt begonnen, in dem die interventionellen Strategien, inklusive panretinaler Photokoagulation (Diabetische Retinopathie-Studie, *National Eye Institute*), entwickelt wurden. Die dritte Phase weist auf biologische Interventionen auf Molekularebene hin. Das im Jahr 2002 etablierte Netzwerk *Diabetic Retinopathy Clinical Research Network* hat den Weg für die molekularbiologischen Ansätze gebahnt, indem es die positiven Effekte von intraokulärem VEGF (*anti-vascular endothelial growth factor*) auf das Makulaödem nachgewiesen hat.

1. Introduction: Setting the Stage: Diabetes and Diabetic Retinopathy

In discussing diabetic retinopathy, one must first understand something of the history of diabetes mellitus. The term has a Greek origin meaning “syphon”, or copious urination, and “honey”, characterizing the loss of sugars in the urine. The historical record of diabetes traces back to 1552 B. C. when Hesa-Ra, an Egyptian physician, described a disease involving

urination and emaciation, as recorded in the *Papyrus Ebers*. Over the subsequent 2000 years, this condition was further described, and by 500 A. D. it had been differentiated into type 1 disease, which becomes apparent in young individuals, and type 2 disease, which affects adults and is related to weight. Worldwide, increasing economic success, first of industrialized countries and now extending even to developing countries, has led to a weight-related explosion of individuals affected. Current estimates indicate that approximately 300 million individuals are affected worldwide (Danaei et al. 2011). This presents a tremendous burden and cost to society, estimated at $245 billion in the U. S. alone in 2012 (*American Diabetes Association* 2013). As the world population increases, one can fully expect that millions more will be affected in the coming years.

Diabetes mellitus affects the health of many organ systems, including the eyes. Effect on the retinal vasculature causes microvascular angiopathy and leads to vascular leakage of serum and blood and, ultimately, proliferation of microvasculature in the late stage of diabetic retinopathy. It is estimated that 10 % of individuals have severe vision impairment, and 2 % are legally blind after 15 years of diabetes. According to a 2006 survey by Lions Club International, patients with diabetes are concerned by the potential for ocular disease, which they score as their top concern for the sequel of diabetes to cause impaired vision and to go blind.

2. Diabetic Retinopathy: Developing an Understanding

The first seminal event in developing a medical and clinical understanding of diabetic retinopathy came with the invention of the ophthalmoscope by Hermann von Helmholtz in 1851. This instrument allowed physicians to directly view the ocular fundus to observe the integrity of the blood vessels. By the turn of the 20th century, vascular problems were clearly known to be associated with longer-duration diabetes and ultimately these changes were associated with capillary micro-aneurisms seen in post-mortem retinal tissue from affected individuals.

Gerhard Meyer-Schwickerath, a German ophthalmologist, made a seminal observation in 1950 when he observed spots of retinal damage in individuals who had viewed a solar eclipse without appropriate visual screening of the intense light. He then looked for ways to apply light deliberately to destroy lesions in the retina by photocoagulating retinal tissue in a controlled fashion. Ultimately, he used high-intensity focused light from a xenon-arc lamp to photo-cauterize retinal tissue and blood vessels. In the 1960s, the development of concentrated light from the ruby laser was applied to the retina, and William P. Beetham and Lloyd M. Aiello recognized that photocoagulation seemed to be effective in treating neovascular diabetic retinopathy. This led to the pioneering large-scale ophthalmic clinical trial, termed the Diabetic Retinopathy Study (DRS), initiated in the 1970s. This randomized controlled trial enrolled approximately 1700 patients with advanced proliferative retinopathy at 15 participating centres. Eyes were randomized to receive photocoagulation, and the fellow control eyes were followed but not treated. A large reduction of risk for progression to severe vision loss was found for photocoagulated eyes, with a greater than 50 % risk reduction by pan-retinal photocoagulation (Figs. 1 and 2, *The Diabetic Retinopathy Study Research Group* 1978). This success spawned additional randomized controlled trials for diabetic retinopathy, the Diabetic Retinopathy Vitrectomy Study in 1976 and the Early Treatment Diabetic Retinopathy Study of 1979. The outcomes of these three studies have made a major impact on ameliorating risk of blindness from diabetic retinopathy and are still the mainstay of current treatment.

Question

- Does photocoagulation prevent severe vision loss from proliferative retinopathy?

Trial Description

- The randomized, controlled trial included more than 1700 patients at 15 centres.
- Eyes were randomized to immediate argon laser or xenon arc photocoagulation.
- The control fellow eye was not treated.
- Visual acuity was measured at four-month intervals for more than five years.

Results

- Argon laser and xenon photocoagulation conferred greater than 50 % risk reduction of severe visual loss.
- Photocoagulation benefit outweighs the risk for high-risk proliferative retinopathy.

Fig. 1 Diabetic Retinopathy Study

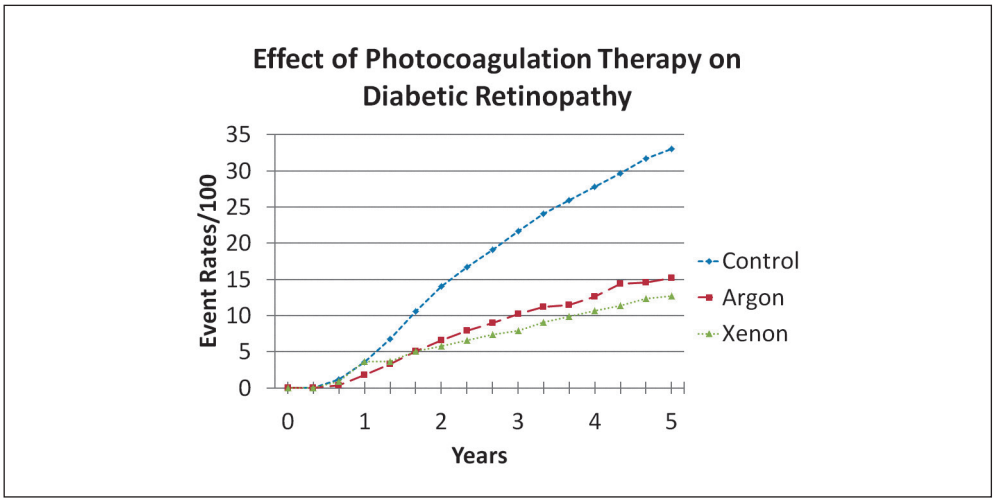

Fig. 2 The NEI Diabetic Retinopathy Study Research Group showed that photocoagulation therapy significantly reduced the cumulative event rate (oddurence of vision loss). A greater than 50 % risk reduction for progression to severe vision loss was found for eyes treated with pan-retinal argon laser or xenon arc phocoagulation (*The Diabetic Retinopathy Study Research Group* 1978).

Clinical trials for diabetic retinopathy then moved into a new phase in which attention shifted to controlling the underlying diabetes to learn whether this lessened the risk of vision impairment from diabetic retinopathy. The first of these trials was launched in 1983: the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetes Intervention and Complications Trial, and the United Kingdom Prospective Diabetes Study. These demonstrated that tight control of glucose reduced diabetic complications, particularly when stratified by maintaining a hemoglobin A1c value of 7 % or less. This was as-

sociated with substantial reduction in progression of retinopathy. Variations on this theme were conducted.

These series of trials included the Diabetes Prevention Program Outcome Study of 1996, which found that lifestyle modification was more powerful at reducing the conversion rate from a pre-diabetes to type 2 diabetes when compared with metformin, a standard oral medication taken to normalize systemic glucose levels and reduce hyperglycaemia. This trial was stopped before it ran the full course because of the power observed in risk reduction by exercise and weight loss. It is interesting to consider that this trial in the second millennium A. D. confirmed the apostolate of Indian physicians Sushruta and Charaka, identified between 400–500 A. D., that type 2 adult diabetes had an overt connection with overweight individuals. The strong environmental and lifestyle components of diabetes and diabetic retinopathy become confounding factors when considering a purely pharmaceutical intervention for this condition and when attempting to elucidate underlying causative factors.

3. Diabetic Retinopathy: The Present

The current era of diabetic retinopathy treatment entered a new phase with the formation of the Diabetic Retinopathy Clinical Research Network (DRCR.net). This multi-centre clinical research network was initiated in 2002 by the National Eye Institute with support from the National Institute of Diabetes, Digestive and Kidney Diseases at NIH. By 2012, it had 868 investigators at 249 sites. DRCR.net seeks to identify clinical opportunities to design and implement trial protocols for successful intervention in diabetic retinopathy. A key component of this effort is a set of standardized key study procedures that allow accurate data pooling across a large number of participating physicians. Without this standardization, the intrinsic noise in uncoordinated data would prevent successful study.

The modern era of treatments for diabetic retinopathy involves intervention at the molecular and cellular level, and major success has been achieved by attention to the microvascular angiopathy, which causes the diabetic macular edema that reduces visual acuity due to vascular leakage as serum collects in the macular retinal tissues. Recently, new compounds have been developed and received FDA certification for clinical use evaluation to treat angiopathy in solid tumour cancers (bevacizumab). Subsequently, this approach was also used for vasculopathy from age related macular degeneration (ranibizumab). Through the DRCR.net, this quickly led to consideration of anti-VEGF treatment for diabetic macular edema, and a study was begun, which ran from 2007–2010. The study design competed ranibizumab treatment, with or without immediate laser, *versus* laser retinal photocoagulation, with or without concomitant intraocular steroid (Triamcinolone). The anti-VEGF treatment provided clear benefit compared to laser treatment, with improvement in visual acuity compared to laser treatment and also the benefit that fewer eyes suffered visual acuity impairment compared to laser treatment. This work sets the stage for recognition that hypotheses-driven therapeutic interventions based on knowledge of underlying biology is a powerful approach for treatment in diabetic retinopathy and presumably as a generalizable strategy for medical disease.

4. Diabetic Retinopathy: The Future

As demonstrated by the DRCR.net, anti-VEGF treatment for diabetic macular edema provides clear benefit to patients. In addition, there is an equally important lesson to understand that treatments that focus on the underlying pathophysiology of disease hold great promise for the future. However, one must first reach a critical level of understanding the cellular pathways involved in disease ideology and progression. And this will be difficult because of the complexities of the underlying pathophysiology, in this case of diabetes and the inciting of factors that trigger diabetic retinopathy. Not all individuals with long-standing diabetes progress to developing diabetic retinopathy. A recent meta-analysis of 35 population-based studies of diabetics worldwide indicates that about one third of diabetic individuals have some degree of diabetic retinopathy, and fewer than 10 % have either diabetic macular edema or proliferative diabetic retinopathy (Fig. 3, Yau et al. 2012). This means that a substantial number of individuals with underlying diabetes do not progress to overt diabetic retinopathy. Consequently, one of the important facets of research for the future must come to understand the triggering events that lead to developing retinopathy. One pathway is through the use of molecular genetics to identify factors that contribute risks for conversion from diabetes to diabetic retinopathy.

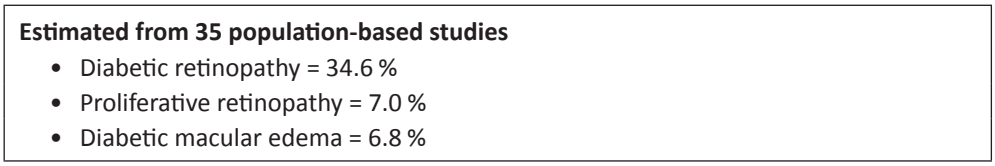

Fig. 3 Global prevalence of diabetic retinopathy among people with diabetes. Data from Yau et al. 2012

5. Diabetic Retinopathy: Genetics of Common Complex Diseases

The possibility of underlying genetic susceptibility is intimated from observing high risk populations, such as the Pima Indians in the U. S., who have high rates of diabetic retinopathy. Pima Indians are an isolated population of about 11,000 individuals residing on the Gila River Indian Reservation in Arizona, U. S. They have high rates of diabetes: about 50 % of Pima Indian youth have type 2 diabetes, which most commonly affects adults. The cumulative incident of proliferative retinopathy after 20 years is 14 % (Looker et al. 2003). Studies of 103 affected sib-pairs showed genetic linkage to chromosomes 3 and 9 in a study published in 1998 (Fig. 4, Imperatore et al. 1998). However, subsequent work has been unable to refine these loci. A potentially complicating factor is the recognition that diabetes prevalence of the youth of this tribe has increased two-fold since 1967, indicating that any underlying susceptibility will be compounded by environmental and lifestyle factors in studying individuals in this tribe.

A second example of a potential underlying genetic susceptibility for diabetic retinopathy comes from the Mexican-Americans in Starr County, Texas (Fu et al. 2010). This was a Genome Wide Association Study (GWAS) screen of 286 Mexican-Americans with type 2 diabetes. Two genetic markers showed strong association with advanced diabetic retinopathy, one mapping to chromosome 5 at an intron of calcium/calmodulin-dependent protein kinase 4 gene and a second at chromosomal location 15q13 within the formin 1 gene.

High Rate of Diabetic Retinopathy

- 11,000 members of the Gila River Indian Reservation in Arizona were studied for 30 years.
- 50 % of Pima Indians, including children, has type 2 diabetes.
- Pima Indians have a 14 % cumulative incidence of proliferative retinopathy after 20 years with diabetes.
- The prevalence of diabetes among Pima youth has increased twofold since 1967.

A 1998 study of 103 affected sib-pairs showed genetic linkage to chromosomes 3 and 9.

Fig. 4 Pima Indians in the U. S.

Despite these promising early indications of genetic association, identifying genes strongly associated with diabetic retinopathy has proven difficult. This may stem from several factors. Perhaps each gene makes only a small contribution that segments the risks and thereby requires a large number of cases for genetic analysis. Thus far, population sizes for retinopathy gene searches have been in the hundreds, *versus* the thousands of cases that have been employed for gene searches in diabetes and other systemic conditions. Other factors complicating the gene search would include diverse clinical features at different stages of disease progression. Or perhaps the environmental component is actually so large that it swamps the genetic determinants. And any role for epigenetics has not yet been studied.

Despite the lack of conclusive genetic etiologic factors, the preliminary analysis of GWAS studies indicates that a number of pathways and gene families may be involved in conversion to diabetic retinopathy and in its progression, including the glycemic pathway UDP-glucuronosyltranferases, *Wnt* signalling pathway, and crystallins, among others. This is the current state of future-directed genomic analysis of disease: searching for cellular ties into disease biology and thereby providing the next powerful development in epidemiology.

There are certainly other approaches to understanding the cellular basis of disease as it will develop in the future. Animal models exist for diabetes. Even though they do not perfectly recapitulate all facets of human disease, they nevertheless warrant careful biologic dissection and attention. They may provide clues as to which cells are affected early during disease progression.

The triggers for vascular changes clearly warrant attention. Throughout the decades and centuries and millennia of observing diabetes mellitus, vascular changes clearly are involved front and centre, as they also are in diabetic retinopathy. Hence, attention to human biomarkers for vasculopathy need further study. Inflammatory signals, both systemic and possibly those with a local retinal origin are warranted, given the treatment benefit of intravitreal steroid application in modifying transient diabetic retinopathy. And, attention to the remarkable biological tools that have been developed just in the decade since 2000 warrant consideration, such as silencing and micro RNAs.

6. Diabetic Retinopathy: Continuing Medical Needs and Opportunities

Meanwhile, as physicians, we still have the task of treating our patients with diabetic retinopathy to preserve vision. How can physicians best help patients? Clear management guidelines

exist for treating diabetic retinopathy (*American Academy of Ophthalmology Retina Panel* 2008). The outcomes developed from the DCCT provide clear indication that patients benefit from managing hyperglycaemia, hypertension, and serum lipids. Further, all patients with diabetes should seek regular ophthalmic clinical care to monitor early signs of development and progression of retinopathy. Much has been learned in managing life-threatening diabetes and vision-threatening diabetic retinopathy over the past half century. As physicians, we need to provide such care routinely to diabetic individuals.

And, what of the future? How can physicians help research? Beyond the care of individual patients, we still need to study disease manifestations and interventions. Ophthalmic physicians might well consider participating in large consortia to study diabetic retinopathy as a disease. For instance, the DRCR.net in the U. S. and comparable clinical networks outside the U. S. provide critical organizational resources and structure to make progress in treating this disease. Ultimately, these large-scale consortia will need to move into biologically-based hypothesis-driven therapeutic trials, and one way to identify cellular mechanisms is through participation in large-scale genetics initiatives.

7. Summary

Viewing diabetes and diabetic retinopathy across several millennia provides a perspective of our current unique position in biologic history. Medicine has clearly begun to study disease pathophysiology at the cellular level and to intervene with knowledge of how the biological system is failing at a systems level. Many of these techniques and biologic insights come only with years of scientific training and years of carefully developed research methodologies. At the other end of the spectrum, human disease develops in human patients and requires careful investigation by clinical research physicians. The future will require increased collaborative interactions between basic scientists and clinical investigators to build a strong platform that supports clinical research. Collaboration across the spectrum from disease biology to disease medicine can only come when scientists and clinical practitioners have opportunity to communicate. We must continue to foster such interactions to ameliorate vision loss and to restore and preserve health in diabetic retinopathy and diabetes.

References

American Academy of Ophthalmology Retina Panel: Preferred Practice Pattern Guidelines: Diabetic Retinopathy. San Francisco: American Academy of Ophthalmology 2008

American Diabetes Association, *A. D.*: Economic costs of diabetes in the U. S. in 2012. Diabetes Care. *36*/4, 1033–1046 (2013)

Danaei, G., Finucane, M. M., Lu, Y., Singh, G. M., Cowan, M. J., Paciorek, C. J., and Ezzati, M.: National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet *378*/9785, 31–40 (2011)

Fu, Y. P., Hallman, D. M., Gonzalez, V. H., Klein, B. E., Klein, R., Hayes, M. G., and Hanis, C. L.: Identification of diabetic retinopathy genes through a genome-wide association study among Mexican-Americans from Starr County, Texas. J. Ophthalmol. *pii*, 86129 (2010)

Imperatore, G., Hanson, R. L., Pettitt, D. J., Kobes, S., Bennett, P. H., Knowler, W. C., and *Pima Diabetes Genes Group*: Sib-pair linkage analysis for susceptibility genes for microvascular complications among pima indians with type 2 diabetes. Diabetes *47*/5, 821–830 (1998)

Looker, H. C., Krakoff, J., Knowler, W. C., Bennett, P. H., Klein, R., and Hanson, R. L.: Longitudinal studies of incidence and progression of diabetic retinopathy assessed by retinal photography in pima indians. Diabetes Care *26*/2, 320–326 (2003)

The Diabetic Retinopathy Study Research Group: Photocoagulation treatment of proliferative diabetic retinopathy: The second report from the Diabetic Retinopathy Study. Ophthalmology *85*, 81–106 (1978)

Yau, J. W., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., and Wong, T. Y.: Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care *35*/3, 556–564 (2012)

Paul A. Sieving, M.D., Ph.D.
Director
National Eye Institute, NIH
Bethesda, Maryland
31 Center Drive MSC 2510
Bethesda, MD 20892-2510
USA
Phone: +301 4965248
Fax: +301 4803246
E-Mail: PAS@NEI.NIH.GOV
PaulSieving@Gmail.com