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Diagnosis and treatment of diabetic retinopathy — historical overview

ABSTRACT

Before the discovery of insulin, diabetes had been a fatal disease. Insulin extended lifespan of diabetic patients, yet it also gave rise to a number of chronic vascular complications, including diabetic retinopathy. Ophthalmic lesions were first observed in 1798 by John Rollo. Precise assessment of the eye fundus became possible following the construction of ophthalmoscope, which later made it possible to propose a classification of diabetic eye disease. The history of diabetic retinopathy encompasses not only the discovery of diagnostic methods such as fluorescein angiography, ultrasound examination or optical coherence tomography, but also the history of its treatment.

Both initially as well as at present, clinical nutrition constitutes the most important aspect of treatment. DCCT and UKPDS have shown that good metabolic balance plays a significant role in preventing and treating DR. Further studies proved that pharmacological treatment based on fibrates and angiotensin-converting-enzyme inhibitors. A turning point in the history of DR treatment appeared when laser photocoagulation was introduced in 1959. The discovery of epidermal growth factor in 1982 led to the use of anti-VEGF medications in treating maculopathy. Surgical treat-

ment of DR primarily consisted of vitrectomy whose procedures are continually improved. (Clin Diabetol 2017; 6, 5: 182–188)

Key words: diabetes, complication, diabetic retinopathy

Introduction

The history of diabetes reaches as far as ancient times. The first reports date back to 3500 years ago and come from the ancient Egypt. The first clinical description of diabetes was presented in the Ebers Papyrus from 1530 BC. Then a lot of attention was paid to patients' urine, which — as Characa, a doctor living in India in 800–200 BC, noticed — “attracted ants and flies”. Hippocrates (466–377 BC) described diabetes as a disease with polyuria which led to emaciation. The word “diabetes” from the Greek “syphon”, as “the flow of water through the body” was first used by Aretaeus of Cappadocia (30–90 AD). He was also first to present a full clinical description of a patient with diabetes [1, 2]. In turn, the term “diabetes mellitus” was first used by John Rollo in 1797 [3]. In 1889, Minkowski and von Mering proved a correlation between diabetes and islets of Langerhans [4]. However, it was the discovery of insulin in 1922 by Banting, Macleod, Best and Collip that constituted a breakthrough. For their work the scientists received a Nobel Prize in physiology [5, 6]. Introducing insulin, and in the subsequent years also other antiglycemic medications, into the treatment of diabetes resulted in extending the lifespan of diabetic patients, yet it also started an era of chronic vascular complications, including those of the eye [7] (Fig. 1).

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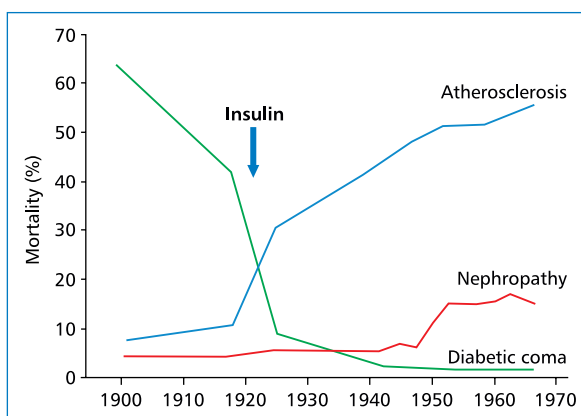


Figure 1. The mortality of patients with diabetes before and after the discovery of insulin [7]

Diagnosing diabetic retinopathy

Although diabetes has been known since 3000 BC, its ocular complications came into focus only 200 years ago, while their treatment started 100 years ago. Ophthalmic lesions co-occurring in diabetes were first described in 1798 by John Rollo in a monograph devoted to eye lesions in diabetes, which also referred to a connection between diabetes and cataract. When in 1851 Helmholtz constructed an ophthalmoscope, he made it possible to diagnose and follow lesions in the fundus of the eye in diabetic patients. For the first time such lesions were described by a Viennese ophthalmologist Eduard von Jaeger, in a paper "Beiträge zum Pathologie des Auges" published in 1855. He called lesions in the fundus "retinitis diabetic" [8, 9]. Von Jaeger was the first to notice lesions perceived as diabetic maculopathy, yet his reports were back then criticised by some authors, such as Albrecht von Graefe, who denounced any connection between diabetes and changes observed in the retina [10]. Correlations between diabetes and lesions within the macula were unequivocally determined in 1969 by Henry Noyes, and confirmed three years later by Edward Nettleship, who presented them in his paper on histopathological changes in the macula in diabetic patients. Thus he provided the foundations for the current definition of diabetic maculopathy [11, 12].

The knowledge on the topic of ocular lesions in diabetes was publicised in 1876 by Wilhelm Manz in a richly illustrated work entitled *Retinitis proliferans* [13]. A year later, on the basis of post mortem examinations, Mackenzie was first to determine the presence of micro-aneurisms in the retina as lesions typical only of diabetes; he also observed bleeding into the retina and the vitreous body in diabetic patients [8]. Nine

years later Nettleship reported venous beading in the retina in diabetic patients, and undertook description of proliferative retinopathy [14]. The natural history of diabetic retinopathy, including its division into four types, was presented by Julius Hirschberg in 1890, yet the full description of DR was published only in 1944 by Ballantyne and Lowenstein. They enumerated five stages of DR, which provided the basis for the current classification [15, 16]. In turn, in 1954 Lundbaek introduced the term "diabetic angiopathy", which referred to the diabetic disease of small blood vessels [17].

All the discoveries presented above contributed to outlining the classification of retinopathy proposed by the Royal College of Ophthalmology (RCO) and based on the lesions in the fundus, starting from non-proliferative retinopathy, to pre-proliferative retinopathy, to proliferative retinopathy. This division did not, however, account for maculopathy, which can co-occur with retinopathy at each of its stages. At present, there is a number of DR classifications proposed by diabetology and ophthalmology societies such as: American Academy of Ophthalmology (AAO), International Council of Ophthalmology (ICO), the RCO. There are also classifications proposed for the purpose of scientific research, for instance Early Treatment Diabetic Retinopathy Study (ETDRS). It needs emphasising that all of them make it possible to specify lesions characteristic for retinopathy as well as maculopathy [18–21]. In 1842, Christian Doppler described a phenomenon which consists in a difference of frequencies sent by a wave source and registered by an observer who moves relative to the source [22]. This discovery led to the development of Doppler ultrasonography, and thanks to Erickson and Hendrix it found its applications also in ophthalmology. In the 1990s, 3D diagnostic methods were introduced in ocular ultrasonography [23, 24]. In the following years, optical coherence tomography (OCT) started to be employed, which allows the doctor to assess cross-sections of the cornea, vitreous body and retina, as well as optic nerve head [25, 26]. The discovery of fluorescence and Stokes' law made it possible — already 50 years ago — to retrieve images of the retina in fluorescein angiography. Maurice pioneered analysing layers of the cornea, yet it was thanks to Nipokov's research that a confocal microscope was introduced to the diagnostics of ocular lesions, and its first version was constructed by Minsky in 1955 [27–30]. Subsequent studies were conducted by Svishcher in 1969, while Masters and Paddock analysed the cells of corneal epithelium in a confocal laser scanning microscope [28].

Over the years diagnostics employed to assess diabetic retinopathy has become more and more precise. What is more, now it reaches more and more patients

thanks to screening programmes and development of telemedicine. The first screening tests for DR were conducted in 1980 in Iceland [31, 32]. Another mass screening programme commenced in 1991 in Singapore. It employed non-mydratic 45-degree Topcon Polaroid fundus cameras which were operated by technicians and optometrists. The results were then assessed by ophthalmologists [33]. Currently, programmes for early detection of diabetic retinopathy are conducted in many countries in the world and unequivocally confirm their medical as well as economic effectiveness [34].

Treatment of diabetic retinopathy

Treatment of diabetic retinopathy initially meant only treating hyperglycaemia and introducing low-fat clinical nutrition in order to limit the number of hard exudates.

In 1953 Poulsen observed slower development of DR in women with postpartum pituitary necrosis. This discovery led to attempts to treat patients with proliferative DR with resection of the pituitary gland, yet the procedure proved effective only in 30% of cases. The method was abandoned because the treatment was so radical and with a risk accompanying the operation, as well as the need to implement hormonal replacement therapy subsequently [35].

The 1990s saw introduction of medications improving mechanical resistance of capillary walls and decreasing their permeability, such as calcium dobesilate or vinpocetine, yet in the subsequent years their biological impact on DR was not confirmed [36]. Drugs which failed to produce the expected effects included also: aldose reductase inhibitors, acetylsalicylic acid, sulodexide, ticlopidine, antioxidants (vitamin C, E) and rutin derivatives [37–40].

At present it is known that the most important method to prevent the occurrence and development of diabetic retinopathy consists in achieving optimal glycaemia [41]. This is based on the results of Diabetes Control and Complications Trial (DCCT) which was started in 1986. It was shown that in DM1 patients who underwent intensive treatment the risk of developing retinopathy was reduced by 76%, and its progression was slowed by 54% [42]. In DM2 patients the results of United Kingdom Prospective Diabetes Study (UKPDS) which started in 1977 also confirmed a beneficial effect of intensive diabetes type 2 treatment on limiting the risk of developing retinopathy. In the UKPDS it was shown that reducing HbA_{1c} by 1% led to the reduction of DR progression by 21% and to a 30% reduction of the need for laser therapy. In the same study reducing systolic pressure by 10 mm Hg reduced the risk of microangiopathy, including retinopathy, by 13% [43].

Similar results confirming the effect of good metabolic control on the risk of developing retinopathy were shown in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) conducted in 1979, and in the later Kumamoto Study (1995) as well as ACCORD-Eye (2001) [44–46].

In the 1980, studies aimed at improving lipid parameters as one of the methods to reduce diabetic retinopathy were initiated [47, 48]. 1990s is the time when a number of studies showing a beneficial effect of improved lipid metabolism on retinopathy were published, while in 2005 the results of Fenofibrate Interventions and Event Lowering in Diabetes (FIELD) unequivocally showed that fenofibrate treatment reduced the need for laser photocoagulation in diabetic patients by 30% [49, 50].

Another group of substances which exert positive impact in diabetes are statins; the first of them — mevastatin — was isolated from the mold *Penicillium citrinum* in 1976 by Japanese researchers Akiro Endo and Masudo Kuroda. Pravastatin and simvastatin were isolated from *Aspergillus terreus* in 1991 [51–54].

In ETDRS it was shown that every 10% increase in cholesterol levels increased the number of hard exudates in the retina, while their number lowered not after photocoagulation but after the statin therapy [47, 55].

Another turning point in hypertension and diabetic retinopathy treatment consisted in the discovery of angiotensin-converting-enzyme inhibitors. It would not have been possible if it had not been for Finnish researchers Tigersted and Bergman, who 100 years ago discovered renin, a proteolytic enzyme which increased blood pressure in rabbits [56]. In 1939, American researchers Page and Helmer described angiotonin, which was later renamed to angiotensin [57]. In turn in 1950–1956 a Cleveland-based team of Leonard Skeggs isolated angiotensin-converting enzyme and subsequently its inhibitor [58]. In 1970, Ondetti and Cushman isolated a substance from viper's venom whose activity was similar to ACE inhibitor, and five years later the same researchers synthesised captopril, which was implemented in regular treatment in 1981 [59, 60]. In DR treatment ACE inhibitors maintain a stable position and their effectiveness was proved for instance in EURODIAB Controlles Trial of Lisinopril in insulin dependent diabetes (EUCLID). Lisinopril treatment reduced the incidence of diabetic retinopathy by 30% and by 50% progression of already diagnosed DR [61]. Also a 5-year RAAS study showed reduced progression of DR by 60% in patients treated with enalapril [62].

In the recent years some hopes have been invested in application of steroids into the vitreous body or ocu-

lar area [63]. Although most recent reports question the effectiveness of triamcynolon treatment, anecortave acetate and dexametazone are still applied [64, 65].

In the recent years there has also been a considerable improvement in diabetic maculopathy treatment. It was made possible thanks to discovering the VEGF (vascular endothelial growth factor) in 1982. Its participation in DR development was confirmed in 1994, showing its increased concentration in the vitreous body in PDR patients [66, 67]. The first synthesised inhibitor of this factor was pegaptanib, administered in an injection into the vitreous body, then VEGF-A antibodies ranibizumab and bevacizumab were obtained; they showed better effectiveness than pegaptanib [68]. Their first application was age-related macular degeneration (AMD) treatment. After subsequent studies, at the beginning of 2011, ranibizumab was registered in the therapy of diabetic macular oedema [68, 69]. At present, anti-VEGF treatment constitutes the basis for this therapy. In diabetic maculopathy also infliximab, a monoclonal antibody acting like human TNF α , is also used. In other studies, it was shown that hyaluronidase and microplasmin reduce the risk of intraocular bleeding. Moreover, positive results of implementing protein kinase C inhibitors were observed impeding the development of diabetic retinopathy [70–73].

In line with better pharmacological treatment, another milestone in DR treatment consisted in laser photocoagulation of the retina. In 1959, Gerhard Meyer-Schwickerath undertook the first attempts to implement this treatment in diabetic patients [74]. The first large scale studies were conducted in 1963 by Paul Wetzling; however, it was Beetham and Aiello who fully proved the effectiveness of photocoagulation in DR treatment [75, 76]. Patz also proved that argon laser was effective in stabilisation and improvement in diabetic maculopathy treatment [77]. In 1979, Diabetic Retinopathy Study Research Group announced that both argon as well as xenon laser reduces the risk of blindness, and a similar view was taken in 1995 by ETDRS (Early Treatment Diabetic Retinopathy study Research Group) [78, 79].

Surgical treatment in the course of ophthalmological complications is represented mainly by vitrectomy, a procedure introduced in 1971. These operations, first performed by Robert Mecherer, are mainly indicated for patients with bleeding in the vitreous body; at present they are more and more common and safe thanks to advances in microsurgery [80].

Cataract is diagnosed more often in DM2 patients, and in almost 50% of cases diabetic retinopathy is a coexisting condition. Poor metabolic control increases progression of cataract. In DM1 cataract can occur as

a result of sudden fluctuations in glucose levels, which leads to changes in lens hydration. Restoring proper metabolic balance can cause almost complete regression of cataract [81–83].

Surgical cataract treatment has been practiced since thousands of years BC and initially consisted in pushing the lens into the vitreous body. Only in 1747 Jacques Daviel incised the cornea and extracted the lens [84, 85]. In 1753 Samuel Sharp removed the lens with no harm to its capsule [86]. The subsequent years saw development of the aspirational cataract removal method. One of its pioneers, Laugier, in 1847 performed aspiration through a sclerotic puncture. More than 100 years later, Scheie performed aspiration-irrigation procedure [87]. In 1949, Sir Harold Ridley was first to implant artificial lens. Although his success was only partial and caused many protests it was a huge step forward in treating cataract. In 1967 another breakthrough took place — it was phacoemulsification pioneered by Charles Kelman, a procedure which made it possible to perform “small incision surgery” [88]. At present, foldable lens are used, and they are implanted through an incision 1.8–3.2 mm, or even 1.0–1.5 mm long, and the procedure apart from removing the cataract corrects astigmatism and presbyopia [89–91].

At present we witness a shift in the pathogenesis of diabetic retinopathy, as it is no longer a purely microvascular complication, but also a neurovascular one [92]. This turn in our thinking about retinopathy has become possible thanks to a discovery made in 1960 by Wolter and Bloodworth, who observed degeneration of neurons in the postmortem examination of the retina in diabetic patients [93]. Modern researchers claim that neurodegeneration of the retina may precede microvascular lesions typical of diabetic retinopathy. However, neurodegeneration is not a dominant pathogenic factor in all patients. What is more, diabetic retinopathy develops in diabetic patients in various manners, and its three phenotypes have been differentiated depending on progression and risk of vision loss [94, 95]. Following the revolution in pathogenesis, there appear new possibilities in treatment of diabetic retinopathy. There are promising results of studies into somatostatins and brimonidine applied locally, which increased survival and limited apoptosis of photoreceptor cells in the retina [96]. Endothelin receptor antagonists decrease apoptosis of pericytes and reduce angiogenesis [97]. It has been confirmed that lixisenatide, a GLP-1 agonist, has a protective effect on the neurovascular unit in diabetic retinopathy [98]. Local application of DPP-IV inhibitor prevented neurodegeneration in experimental diabetes [99]. A neuroprotective effect was also confirmed for rosiglitazone and fenofibrate [100, 101]. One

should hope that research into other new compounds will also bring positive results.

Summary

Having presented all the above facts, it is necessary to emphasise tremendous knowledge, work and courage of researchers diagnosing and treating diabetes and its complications throughout the history. Physicians owe them respect and gratitude, hoping that modern scientists will live up to the expectations and provide diabetologists with tools to stop the epidemics of diabetes and its complications.

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