THE CHANGING ROLE OF THE ENDOCRINOLOGIST IN THE CARE OF PATIENTS WITH DIABETIC RETINOPATHY.

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Abstract

Diabetic Retinopathy (DR) is the most common microvascular complication of diabetes and still represents a leading cause of visual impairment in working age in industrialized countries. It develops following non proliferative (mild, moderate or severe) and proliferative stages, the earliest being often asymptomatic and with diabetic macular edema potentially developing at any of these. The prevalence and incidence of DR increase with diabetes duration and worsening of metabolic and blood pressure control. Current approaches to prevent and/or treat DR include optimized control of blood glucose and blood pressure and screening for early identification of high risk, though still asymptomatic retinal lesions. Results from recent clinical trials suggest a role for blockers of the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and for fenofibrate in reducing progression and/or inducing regression of mild to moderate non proliferative DR. Intra-vitreal administration of anti-VEGF agents was shown to reduce visual loss in more advanced stages of DR, especially in macular edema.

Key words: Diabetes mellitus, diabetic retinopathy, renin-angiotensin system, serum lipids, Vascular Endothelial Growth Factor.

Epidemiology and Classification

According to World Health Organisation Report [1] in January 2011, over 220 million people worldwide had diabetes and the prevalence will rise to 366 million by 2030 [2]. Type 2 diabetes is spreading due to a combination of longevity and a rapid increase in obesity and this rise in the incidence of diabetes represents a major public health concern [3] because it is likely to be followed by a rise in its associated complications. DR is the most common microvascular complication of diabetes [4] and is the leading cause of visual impairment in working age in industrialized countries. Moreover, it can reach its more advanced stages in the almost total absence of symptoms. DR prevalence is about 70% in patients with type 1 diabetes and 40% among those with type 2, with no differences by gender [5]. The prevalence increases with disease duration and practically all patients with type 1 diabetes develop retinopathy, proliferative in half the cases, within 20 years of the diagnosis. However, remarkable in management of diabetes over the last 30 years have been associated with significant decreases in the prevalence and incidence of DR and

visual impairment in type 1 diabetics [6]. The most serious forms of retinopathy, proliferative and macular edema, occur in 23% and 14% of patients with type 1 and type 2 diabetes, respectively. At our screening center in Turin, out of 6,857 consecutive patients screened in 1992 - 2003, the prevalence of retinopathy was 39%, of which 19% mild, 11% moderate, and more severe in the remaining cases.

Alterations of retinal capillaries are present in all forms of DR and include multiple occlusions, increased permeability of the vessel wall and, in the proliferative form, growth of newly-formed vessels. Occlusions cause areas of ischemia and focal (*microaneurysms*) or generalized dilatation of the capillaries. Dilated, fragile and hyperpermeable vessels result in *microhaemorrhages* and leakage of serum and lipoproteins in the neuroretina, with formation of edema and the so-called "hard exudates". Occlusion of vessels may result in focal retinal ischemia, which may be manifested as white-grayish areas with blurred margins, or *cotton wool spots*. The presence of these lesions defines non proliferative retinopathy, which can be mild, moderate or severe and can develop into two forms at high risk of visual loss: diabetic macular edema (DME) and proliferative retinopathy (PDR) [7].

When the lesions of DR involve the macula lutea, the part of the retina responsible for vision of colors and details, severe functional impairment may result. DME affects primarily patients with type 2 diabetes and, as these represent more than 90% of the diabetic population, it is now the main cause of visual impairment in diabetes. Progressive ischemia of the peripheral retina can cause PDR, with growth of new vessels which may invade the vitreous and give rise to *vitreous haemorrhages* and development of fibro-glial tissue. The latter, by contracting, may cause retinal detachment. Severe ischaemia may proceed to the anterior chamber with development of iris neo-vascularization (*rubeosis iridis*), causing the terminal condition of *neo-vascular glaucoma*.

Although DR is considered predominantly a pathology of microvessels, increasing evidence points at degeneration of the neuroretina (mainly apoptosis of ganglion cells and glial activation) as an early event which may predate and perhaps contribute to microcirculatory abnormalities [8-12]. Damage of the neuroretina may result in loss of colour discrimination and contrast sensitivity, as detectable by electrophysiological studies in patients with short diabetes duration [13-15] and delayed multifocal electroretinographic implicit time may predict the development of early microangiopathy [16-18]. Metabolic and signalling pathways involved in retinal neurodegeneration

may be shared with, and/or activate mechanisms involved in, the pathogenesis of microangiopathy [19].

Pathophysiology

Possible mechanisms of glucose-induced vascular damage have been investigated, some of them acting as potential targets for therapy. Four major hypotheses have been conceived: 1. increased flux through the polyol pathway; 2. increased formation of advanced glycation end-products (AGE); 3. protein-kinase C (PKC) activation; 4. increased flux through the hexosamine pathway.

Aldose reductase (AR) is the main enzyme of polyol pathway. Its role consists in reducing toxic aldehydes to inactive alcohols and excess intracellular glucose to sorbitol while consuming NADPH with consequent hyperglycaemic pseudohypoxia [20] and increased susceptibility to intracellular oxidative stress [21]. However, a clinical trial showed that sorbinil, an AR inhibitor, did not modify the course of DR [22].

Advanced glycation end products contribute to vascular damage as explained hereinafter. Intracellular high glucose reacts with proteins, amino acids and nucleic acids via Schiff base condensation with amino groups, followed by irreversible rearrangement into Amadori products. Further Maillard reactions slowly produce AGE, which can also derive from earlier glycation products through glycoxidation or reactive dicarbonyl fragments generated from free glucose. AGE, in turn, can modify intracellular proteins [23], extracellular matrix [24] and circulating proteins, leading to activation of AGE receptors and production of inflammatory cytokines and growth factors. Aminoguanidina has been shown to inhibit AGE and prevent structural changes in experimental diabetic retinopathy [25], but its toxicity hinders experimentation in humans.

De novo synthesis of the lipid second messenger diacylglycerol is enhanced by intracellular high glucose and it in turn activates PKC [26], causing a number of effects, such as decreased synthesis of endothelial nitric oxide synthase and increased synthesis of endothelin-1, transforming growth factor ß, plasminogen activator inhibitor-1[27] and NF-κB [28]. Ruboxistaurin, a specific inhibitor for the β-1 and -2 isoforms of PKC that are mostly activated in the diabetic retina was developed and subjected to clinical trials. Although its use was associated with better visual acuity than placebo in patients with DME, and although there were remarkably few side effects, this interesting agent was not registered with an indication for treatment of DR [29].

Finally, excess fructose-6-phosphate derived from high availability of intracellular glucose can be transformed to glucosamine-6-phosphate and then to UDP *N*-acetyl-glucosamine, which acts on serine and threonine residues of transcription factors, resulting in pathological changes in gene expression [30]. Moreover, this pathway seems to be active mostly in the pathogenesis of diabetic nephropathy.

Brownlee and co-workers have hypothesized that the possible common denominator ("unifying mechanism") of these apparently independent biochemical pathways is high-glucose-induced excess production of reactive oxygen species (ROS) by the mitochondrial electron transport chain inside the endothelium, as a result of increased flux through the Krebs' cycle [21,28]. ROS, by causing strand breaks in nuclear DNA, activate poly-(ADP-ribose)-polymerase (PARP) which in turn inhibit glyceraldehyde phosphate dehydrogenase (GAPDH) activity [31], therefore pushing metabolites from glycolysis in the upstream pathways mentioned above. Benfotiamine a thiamine derivative which can be administered orally, blocks all the above major pathways implicated in the pathogenesis of DR, and has been shown effective in preventing experimental DR [32]. However, clinical trials demonstrating its effectiveness in humans are still lacking.

It is a common clinical observation that patients with good metabolic control still develop retinopathy, sometimes severe, while others do not show retinal changes even after many years in very poor control, suggesting that genetic factors may play a major role in the pathogenesis of this complication. However, despite many studies addressing the possible associations with a number of genes, with special emphasis on those coding for VEGF, aldose reductase and AGE receptors, no consistent linkage has been established so far [33].

Current treatment options

Several standardized grading systems have been proposed, the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales being one of the most clinically relevant and facilitating communication between practitioners [34]. Nevertheless, they don't provide enough advice on clinical management of patients with the different levels of retinopathy. Adherence to an annual ophthalmologic examination, as recommended in American Diabetes Association guidelines, is poor [33] therefore rising attention on improving early detection and treatment of DR. Moreover, standardized screening programs are likely to be beneficial.

The main aims of systemic therapy in DR are to reduce the risk of diabetic patients developing these conditions in the first place and to reduce the risk of progression of existing

retinopathy or maculopathy to more severe, sight-threatening forms. Systemic therapies are designed to target the key modifiable risk factors, which in the case of both DR and DME are metabolic and blood pressure control [35].

Improving glycemic control and lowering the level of glycosylated hemoglobin (HbA1c) is, at present, the most effective medical treatment to slow the progression of DR as demonstrated by two main clinical trials presented below [35].

The Diabetes Control and Complications Trial (DCCT) showed in patients with type 1 diabetes that optimized insulin treatment reduces the incidence of retinopathy by 76%, progression of mild to moderate non-proliferative DR by 54% and the need for photocoagulation by 56% [36]. In patients with type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) showed that, over 12 years, optimized metabolic control reduces progression of DR by 21%, and need for cataract surgery in 24% of cases [37]. Follow up of the patients involved in these studies showed that the beneficial effects of glycaemic control carry over in time in a sort of metabolic "memory" [38], so that any period of life spent in good glycaemic control is "accounted for" in the later prevention of retinopathy and other complications. However, a recent metanalysis carried out on most relevant clinical trials concerning type 2 diabetes, concludes that, although optimal glycemic control is effective in reducing new-onset diabetic retinopathy and progression of mild forms, it doesn't prevent neither use of photocoagulation nor the development of severe visual impairment and blindness. On the other hand, intensive treatment to strictly reach glycemic control, more than doubles the onset of severe hypoglycemia episodes [39].

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study an extremely tight glycemic control reached with insulin and multiple oral agents was associated with increased all-cause mortality [40], thus leading the study to be stopped. Even if only mortality showed an adverse trend, and this was inconsistent with other outcomes and if chance is a likely explanation, a real effect cannot be excluded [41].

Hypertension is known to be a major risk factor for DR and DME. In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) progression of retinopathy was associated with higher diastolic blood pressure at baseline and an increase in diastolic blood pressure over a 4-year follow-up period [42]. Thus, blood pressure control could concur to prevent and slow down DR development.

The UKPDS [43] showed that reducing blood pressure (from 154/87 to 144/82 mmHg throughout 8 years) reduces the progression of DR by 34% and the overall risk of worsening of visual acuity by 47%, possibly by reducing DME. Until recently, the only intervention study to support a role for intensive hypertension control in the prevention of DR was the UKPDS. However, the ADVANCE [44] and ACCORD [45] trials could not confirm an influence of blood pressure lowering on progression of DR. However, patients in the UKPDS had larger reductions from higher blood pressure values than those in ADVANCE (-5.6 mmHg systolic and -2.2 diastolic blood pressure from 145/81 mmHg, follow up 4.3 years) [44] or in ACCORD, starting from 135/75 down to 128/68 with a median follow up of 3.7 years [45], suggesting either that blood pressure lowering is more effective in poorly controlled hypertension or that longer follow-up is necessary to observe an effect on DR progression. No legacy effect was observed for blood pressure control in the UKPDS patients [39].

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial compared the effects of intensive and moderate blood pressure control in hypertensive type 2 diabetic subjects [46]. Nisoldipine, a calcium-channel antagonist, was compared with enalapril, an angiotensin-converting enzyme (ACE) inhibitor, resulting that nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions. However, there was no difference between moderate and intensive treatment groups with regard to the progression of diabetic retinopathy.

Current guidelines recommend to maintain HbA1c below 7.0% and blood pressure below 130/80. However, achieving these targets is far from easy outside of clinical trials in the general diabetic population and data collected in the US [47], France [48], UK [49], Italy [50] and other countries show that less than half, often less than one third, of patients do stay within those targets. Patients on insulin therapy have worse control than those treated with oral hypoglycemic agents and, in turn, the latter fare worse than those on diet alone [49], presumably reflecting the levels of residual endogenous insulin secretion. Possible reasons for this high level of therapeutic failure include medical inertia, reduced patient adherence to prescriptions and the inadequacy of current pharmacological options and lifestyle measures. New approaches to lowering HbA1c has been described by Trento and colleagues [51]: in their multicenter Rethink Organization to iMprove Education and Outcomes (ROMEO) trial they demonstrated that seeing and educating type 2 diabetic patients in groups of 9 or 10 every 3 months has a statistically significant beneficial effect on their metabolic control.

Doctors often are poorly proactive in correcting high levels of glycated hemoglobin and blood pressure, as shown by a survey of practice in 30 American academic clinics [47]. That however may not be the only reason. In a 2-year clinical intervention study conducted in Liverpool on 200 patients with inadequate metabolic control, the best efforts of doctors went unrewarded and the only patients who obtained a drop in HbA1c were those treated with diet only [49]. The situation is particularly worrying in children and adolescents among whom, according to a recent report, less than 5% have an HbA1c lower than 7.0% and more than 80% are above 8.0% [52]. It may be that therapeutic goals are too ambitious, at least for younger and older age groups, as suggested for the latter by an increase in mortality observed when trying to push the HbA1c target below 6.5% [40]. It is also possible that individual patients are somehow set on different levels of diabetes severity, manifested by their values of glycated hemoglobin, in different stages of their life. Of course, this is a point of view that can be perceived as pragmatic or utilitarian, perhaps politically incorrect and certainly not supported by scientific evidence. However, if one considers goal focusing and personal motivation as contributors to improve metabolic control, then it stands out that only in exceptional circumstances of limited duration, such as pregnancy, are levels of HbA1c below 6.5% reached in more than 80% of patients [53], often to drift back upwards after delivery.

In any case, the overall outcomes of diabetes care seem to be improving gradually worldwide, thanks to increasing awareness and availability of materials for self-monitoring and therapy. Data from the National Health and Nutrition Examining Survey (NHANES) 1999-2004 show a slow but steady increase in the percentage of U.S. patients with HbA1c less than 7.0% [54]. Probably in connection with this positive trend, the epidemiological data collected in Scandinavia and Wisconsin show a lower cumulative incidence of proliferative retinopathy in patients who contracted type 1 diabetes in more recent years [55,56]. In the DCCT/EDIC cohort, in 30 years of follow up, the cumulative incidence of PDR was 21% in the patients originally randomized to optimized therapy during the DCCT, compared to 50% in those who remained all their life on conventional treatment [38].

There are however different approaches to interpreting these data. Progression of DR might be delayed rather than reduced in absolute terms, and the prolongation of life expectancy in patients may result in PDR appearing later rather than never at all. Data extrapolated from the DCCT dataset

suggest that optimized insulin treatment would prolong life free of PDR by 14.7 years, of macular edema by 8.2 years and life free of blindness by 7.7 years [57], all weighted against a 2-3 times higher risk of severe hypoglycemia and increase in body weight. In addition, other predisposing factors not yet identified may play a role, as suggested by daily clinical experience and also quantified in the DCCT series. In fact, a post-hoc analysis of all patients who participated in the trial showed that 10% of those who remained in the lowest HbA1c quintile (< 6.87%) still developed DR, and 43% of those who remained in the worst quintile (HbA1c > 9.49%) did not develop retinal lesions during the study [58]. The search for genetic markers that make patients susceptible to, or protected by, microangiopathy remains an open field that has so far produced few generalizable results.

Currently, the main therapeutic tool at our disposal to prevent visual impairment consequent to DR is laser photocoagulation, which reduces the incidence of blindness from PDR by 95% and loss of visual acuity due to DME by 50% [59]. When laser is not sufficient, because retinopathy is too advanced and/or aggressive, vitreo-retinal surgery (vitrectomy) becomes an option [60].

Since blood glucose and blood pressure levels recommended by the guidelines cannot be reached in all patients, and since retinopathy may still develop in patients who are well controlled, it is paramount to organize systematic population screening programs. Screening is a simple diagnostic procedure applied to an entire population at risk aimed at identifying severe lesions that can be subjected to appropriate treatment before they have caused symptoms and functional damage. Screening does not represent a complete diagnostic workup but a method to identify patients who require further investigation. The efficacy of screening for high-risk DR has been demonstrated in places such as Iceland or Sweden, where it has led to reduction of diabetes-related blindness [61]. A countrywide screening programme has been established in the UK [62], and the results will become available in the coming years.

New therapeutic perspectives

Lack of therapies targeting specific pathogenetic mechanisms remains a serious limitation to the prevention of diabetes-related blindness. Experimental evidence suggests involvement of the

renin-angiotensin system (RAS) in that a physiologically active RAS is present in the eye, where angiotensin-2 appears to promote retinal expression of VEGF, through AT-1 receptors, and endothelial cell proliferation.

The EUCLID study [63] reported that lisinopril, an angiotensin-converting enzyme inhibitor (ACEi), may reduce the progression of DR and the incidence of PDR in normotensive patients with type 1 diabetes. Whether this effect was due to RAS blockade or a benefit from incremental lowering of blood pressure in normotensive subjects remains unknown [4]. Moreover, retinopathy was not a primary outcome of the study, which was also undersized from the statistical power point of view.

The more recent ADVANCE/ADREM [64] appeared to show some protective effect, though not statistically significant, on progression of retinopathy of another ACEi, perindopril, associated with indapamide, a diuretic, in 1241 patients with type 2 diabetes. DIRECT (Diabetic Retinopathy Candesartan Trials) was a group of 3 multicenter, randomized, placebo-controlled studies designed to determine if pharmacological blockade of the RAS by candesartan 32 mg is able to prevent the onset of DR in patients with type 1 diabetes (DIRECT-Prevent 1) and to prevent progression or promote regression of DR in patients with type 1 (DIRECT-Protect 1) and 2 (DIRECT-Protect 2) diabetes [65,66]. A total of 5231 patients with normoalbuminuria were randomized. All patients with type 1 diabetes and 27% of those with type 2 diabetes were normotensive while the remainder were taking non RAS blockers for hypertension. The average follow-up was 4.7 years. Prevent-1 showed that candesartan reduces the risk of onset of retinopathy in type 1 diabetes by 35%, with a NNT of 18 patients treated to prevent one event. The severity of retinopathy at the end of the study was significantly more favorable in patients treated with candesartan in Prevent-1, Protect-1 (539 patients treated) [65], and Protect-2 (539 patients treated) [66]. The latter study showed a 13% reduction, not statistically significant, in the risk of progression of DR and a highly significant 34% increase in the probability of DR regression in type 2 diabetes, with an NNT of 21 patients treated to achieve an event. The results of DIRECT-Protect 2 represent the first description in the literature of regression of DR induced by a drug. The favourable effect of RAS blockade was confirmed by the RASS study [67], conducted on 285 normotensive patients treated with enalapril 20 mg/day, losartan 100 mg/day or placebo. Enalapril and losartan reduced the likelihood of DR progression by 65% and 70%, respectively, in patients with type 1 diabetes. Although the results of the previous studies are strongly indicative of a beneficial effect of RAS blockade in the early stages of DR, none of them was sufficient to grant registration for this specific indication. Hence, their use cannot

be formally recommended in patients with DR who do not also have hypertension and/or microalbuminuria.

Lipid –lowering agents may decrease the risk of vision loss in patients with DR, according to previous studies as the one led by Gordon et al. [68] in 1991 that found that lipid-lowering therapy reduced hard exudates and microaneurysms in DR.

The FIELD study showed a reduction by approximately 30% in the need for laser treatment for DME and PDR in patients treated with fenofibrate 200 mg/day. The drug prevented progression and requirement for first laser therapy of existing retinopathy, regardless of its metabolic effects, but was not effective in terms of primary prevention [69]. However, the retinopathy endpoint was a tertiary objective, measured in 1012 of 9795 patients enrolled in the study. Moreover, the conclusions from this study were limited by uneven statin use [70].

Another clinical trial, ACCORD-Eye [45] confirmed reduced progression of DR in patients with type 2 diabetes treated with fenofibrate and statins, compared to patients treated with statins alone. The reduction was similar to that observed intensifying blood glucose control, but with a good safety profile and without increasing the risk of hypoglycemia [71]. The possible mechanisms for this unexpected action of fenofibrate remain to be elucidated.

Increased tendency to platelet aggregation in diabetes has long been suspected to play a role in determining capillary occlusions which characterize the intermediate stages of non-proliferative DR. Antiplatelet drugs such as aspirin, dipyridamole and ticlopidine underwent clinical trials in the '70s and '80s, demonstrating modest efficacy in slowing the formation of new microaneurysms in early non proliferative DR [72,73] and no effects on evolution once DR reaches the pre-proliferative and proliferative stages [74]. Aspirin, however, does not increase the risk of bleeding from new vessels, so that proliferative retinopathy is not a contraindication to its use for other indications [74].

The only example of an effective mechanism-targeting treatment in DR is the use of anti-vascular endothelial growth factor (VEGF) agents in DME. VEGF is upregulated in eyes with DME [75] and may be a major mediator of increased retinal permeability [76]. Anti-VEGF agents have to be injected directly into the vitreous body at regular intervals. Those under more advanced investigation include bevacizumab, ranibizumab, pegaptanib and VEGF Trap-Eye. While laser treatment permits at best to preserve visual acuity, clinical trials indicate that vision can improve

with repeated injections of bevacizumab 1.25 mg [77], ranibizumab 0.5 mg [78] and pegaptanib 0.3 mg [79]. Mean best-corrected visual acuity improvements of 4.7 letters are obtained with a mean of five injection over 36 weeks with pegaptanib 0.3 mg and 5.6 letters with a median of nine injections over 1 year with bevacizumab 1.25 mg VEGF Trap-Eye has also shown promising short-term results in a phase II study [80].

Also intravitreal triamcinolone has been widely used to treat DME and PDR in view of the inflammatory components in the pathogenesis of these sight-threatening stages of DR [81]. However, its benefits are short-lived, accompanied by high rates of cataract, glaucoma and infections, and the 3-year visual acuity is worse than obtained with grid laser treatment alone [82]. Visual acuity benefits of steroids are comparable to those of anti-VEGF in aphakic patients only [83]. Moreover, several clinical trials are investigating the effectiveness of intraocular implants of slow-release corticosteroids, that, although having the same side effects of triamcinolone, would allow less repeated injections, limitating procedure-related risks.

Conclusions

Overall, the results of the trials reported above suggest that interventions targeted at potential pathogenic mechanisms may be effective in early or mild, rather than moderate or more advanced stages of retinopathy in which damage to the capillary wall and the neuroretina may already be too advanced. Here the question arises of whether a "point of no return" exists in the natural history of DR. Anti-platelet agents appeared to slow down retinopathy at a very early stage characterized by the presence of microaneurysms alone [72,73], but not later when capillary occlusion becomes the prevailing feature [74]. Similarly, in DIRECT-Protect 2 [66] administration of candesartan was associated with regression of minimal to mild retinopathy (occasional microaneurysms, micro-haemorrhages, hard exudates and/or cotton wool spots) whereas non proliferative stages, though classified as moderate, proved non responsive, suggesting that also blockade of the RAS could be effective earlier than originally envisaged, again when damage of the capillary wall is minimal. This suggests that overactivation of the intraocular RAS may exert its pathogenic effects through mechanisms different from VEGF activation, or that VEGF might have pathogenic effects independent of its ability to increase vessel wall permeability and angiogenesis, possibly involving its neuroprotective characteristics. However, data from FIELD [69] and ACCORD [45] appear to show that the progression of retinopathy can be stopped by fenofibrate at

more advanced stages, moderate and severe non-proliferative, suggesting that different pathogenic mechanisms, responsive to different pharmacological agents, may intervene in various stages of this complication.

Progress in medical treatment of DR remains incomplete, just like our understanding of the mechanisms underlying this complication. More is achieved in the advanced stages, using VEGF inhibitors, than early in the evolution of DR but we are still far from the day when retinopathy will be treated aiming directly at a cause (as we do, for example, with iron for iron-deficient anemia) or a mechanism (as with proton pump inhibitors for peptic ulcers). Causes for failure so far to identify a *primum movens* for retinopathy and, more generally, diabetic microangiopathy involve a series of good reasons: lack of funding and researchers dedicated to the specific problem, a presumably multifactorial pathogenesis, the undoubted complexity of the phenomena involved. It is hoped that, as diabetes and its complications rise worldwide, the mere health and economic size of its consequences will stimulate further research into this field of human disease.

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