GLP-1R as a Target for the Treatment of Diabetic Retinopathy: Friend or Foe?

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Glucagon-like peptide 1 receptor (GLP-1R) agonists are increasingly being used as treatment for type 2 diabetes. Since the U.S. Food and Drug Administration published recommendations about the cardiovascular safety of new antidiabetes therapies for treating type 2 diabetes in 2008, the results of two outstanding clinical trials using GLP-1R agonists addressing this issue (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation [LEADER] and Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6]) have been published. Both studies found beneficial effects in terms of reducing the rates of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. However, their results regarding the progression of diabetic retinopathy (DR) were neutral with liraglutide (LEADER) or worse when compared with placebo in the case of semaglutide (SUSTAIN-6). These results are surprising because of the beneficial effects of GLP-1R analogs reported in experimental models of DR. In this Perspective, an overview of the mechanisms by which GLP-1R activation exerts its effects in preventing or arresting experimental DR is given. In addition, we consider the possible reasons for the negative results regarding the progression of DR in the SUSTAIN-6 study, as well as the gaps that still need to be covered to further clarify this important issue in the management of type 2 diabetes.

Diabetic retinopathy (DR) is the most common complication of diabetes and remains the leading cause of blindness among working-age individuals in developed countries (1–3). DR prevalence in the diabetic population is approximately one-third, and 10% have vision-threatening states such as diabetic macular edema or proliferative DR (3). In addition, the presence and progression of DR is associated with significant increases in health care costs (4). Since DR is the most common complication of diabetes and is expected to increase from 415 million in 2015 to 642 million by 2040, DR will become an even more serious problem in the future (5).

In recent years, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have emerged as effective and safe treatments for type 2 diabetes and have been incorporated into the clinical guidelines of the American Diabetes Association and the European Association for the Study of Diabetes. In addition, a myriad of preclinical studies have shown that GLP-1RAs exhibit potent pleiotropic protective effects on diabetic vascular complications, including DR. However, the recent results of two seminal clinical trials using liraglutide (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation [LEADER]) (6) and semaglutide (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6]) (7) have questioned the beneficial results obtained in experimental studies. In the LEADER study, liraglutide reduced the rate of cardiovascular morbidity and mortality in patients with type 2 diabetes with high cardiovascular risk. However, there was a higher but not significant rate of DR events with liraglutide than with placebo (hazard ratio 1.15 [95% CI 0.87–1.52]; P = 0.33) (6). The SUSTAIN-6 study also demonstrated beneficial results in cardiovascular outcomes of semaglutide (a long-acting GLP-1 analog with an extended half-life of ~1 week) but found that it significantly increased the rate of severe DR complications in

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comparison with placebo (hazard ratio 1.76 [95% CI 1.11–2.78]; $P = 0.002$) (7).

In this Perspective, an overview of the current treatment of DR and the mechanisms by which GLP-1R activation exerts its positive effect in preventing or arresting experimental DR will be given. In addition, we will consider the possible reasons for the negative results regarding the progression of DR in the SUSTAIN-6 study, as well as the gaps that should be covered to further clarify this important issue in the management of type 2 diabetes.

CURRENT TREATMENT OF DR AND THE POTENTIAL ROLE OF TARGETING GLP-1R

The tight control of both blood glucose levels and blood pressure are essential in preventing DR development or in arresting its progression. Other treatments such as laser photocoagulation, intravitreal injections of corticosteroids or anti–vascular endothelial growth factor (VEGF) agents, and vitreoretinal surgery are not implemented until very advanced stages of DR. All these treatments are expensive, require a vitreoretinal specialist, and have a significant number of secondary effects. Therefore, new treatments for the early stages of DR are needed (8,9).

The strong relationship between the reduction of HbA_{1c} and the beneficial effects on DR has obscured the necessity of performing clinical trials to investigate the specific effect of hypoglycemia drugs on DR per se, independently of their effectiveness in lowering blood glucose levels. The reported pleiotropic actions of GLP-1RA in experimental models of DR, apart from their capacity in lowering blood glucose levels (see below), confers on these drugs a potential extra value in preventing the development of or arresting the progression of DR.

Although there is no doubt regarding the relationship between glycemic control and the long-term development and progression of DR, initial worsening of DR has been reported as a consequence of rapid improvement of hyperglycemia. An early worsening was observed in 13.1% of 711 patients with type 1 diabetes assigned to intensive treatment in the Diabetes Control and Complications Trial (DCCT) at 6 and/or 12 months in comparison with 7.6% of 728 patients assigned to conventional treatment (odds ratio 2.06; $P < 0$ 0.001) (10). The most important risk factors for early worsening were a higher HbA_{1c} level at screening, a large reduction of HbA_{1c} (<2%), and the severity of DR at baseline (10–12). A similar phenomenon was reported in patients with type 2 diabetes after a rapid improvement of blood glucose levels when they were changed from oral agents or diet alone to insulin therapy (13,14) and, more recently, after bariatric surgery (15). As reported in patients with type 1 diabetes, the magnitude of the reduction of HbA_{1c} and the presence of preexisting DR were the main factors involved in the risk of this transient or permanent progression of DR.

Interestingly, the initial worsening of DR observed in the early period of intensive glycemic control is manifested by the increase of soft exudates, a typical feature of the ischemic retina. Hypoglycemia exacerbates ischemic retinal injury (16), and, therefore, antidiabetes drugs such GLP-1RA with very low capacity if any to provoke hypoglycemia might theoretically be more appropriate for initiating intensive treatment in those patients with DR.

GLP-1R Activation and Retinal Neuroprotection

Although DR has been classically considered a microcirculatory disease of the retina, there is emerging evidence suggesting that retinal neurodegeneration is an early event in the pathogenesis of DR that could participate in the development of microvascular abnormalities (1,8,9,17–19).

GLP-1 exerts neuroprotective effects in both the central and peripheral nervous system (20,21). In fact, there are ongoing pilot studies of GLP-1 analogs for preventing Alzheimer disease (20). Given that the retina is ontogenetically a brain-derived tissue, it is reasonable to expect that GLP-1 would also be useful in preventing or arresting retinal neurodegeneration in the setting of DR. Recently, we have found abundant expression of the GLP-1R in human retinas (22). Therefore, it could be hypothesized that GLP-1RAs could provide neuroprotection to the diabetic eye.

In addition, both GLP-1 and exendin-4 (a long-acting GLP-1RA) are able to completely protect cultured rat hippocampal neurons against glutamate-induced apoptosis (23). This is important because glutamate excitotoxicity is also a major mediator of neurodegeneration in DR (24). Furthermore, it has been shown that intravitreal injections of exendin-4 prevent electroretinograpical abnormalities and morphological features related to neurodegeneration in rats with streptozotocin (STZ)-induced diabetes (25,26) and in Goto-Kakizaki rats (27). However, in these early stages of DR, intravitreous injections are inappropriately invasive. In this regard, we have recently found that the topical administration of GLP-1RAs is able to prevent the neurodegenerative process (reactive gliosis and apoptosis) in the retina of a spontaneous diabetic model (*db/db* mouse) (22). The beneficial morphological effects observed using intravitreous injections of exendin-4 or eye drops containing native GLP-1 or its analogs ran in parallel with an improvement in functional abnormalities assessed by electroretinography (22,25–28). Since intravitreous or topical administration of GLP-1RA does not influence blood glucose levels, the beneficial effects should be attributed to a direct effect of GLP-1RA in the retina. Interestingly, similar results were obtained by using liraglutide administered by the systemic route (22), but in this case it was impossible to elucidate whether neuroprotection was due to the reduction of blood glucose levels or to the direct effect of liraglutide at the retinal level.

The main mechanisms by which GLP-1R activations induce neuroprotection in the diabetic retina are displayed in Fig. 1.

GLP-1R activation is able to inhibit glutamate accumulation in the extracellular space, thus preventing excitotoxicity and neuron death (22,25,26). This can be attributed to the

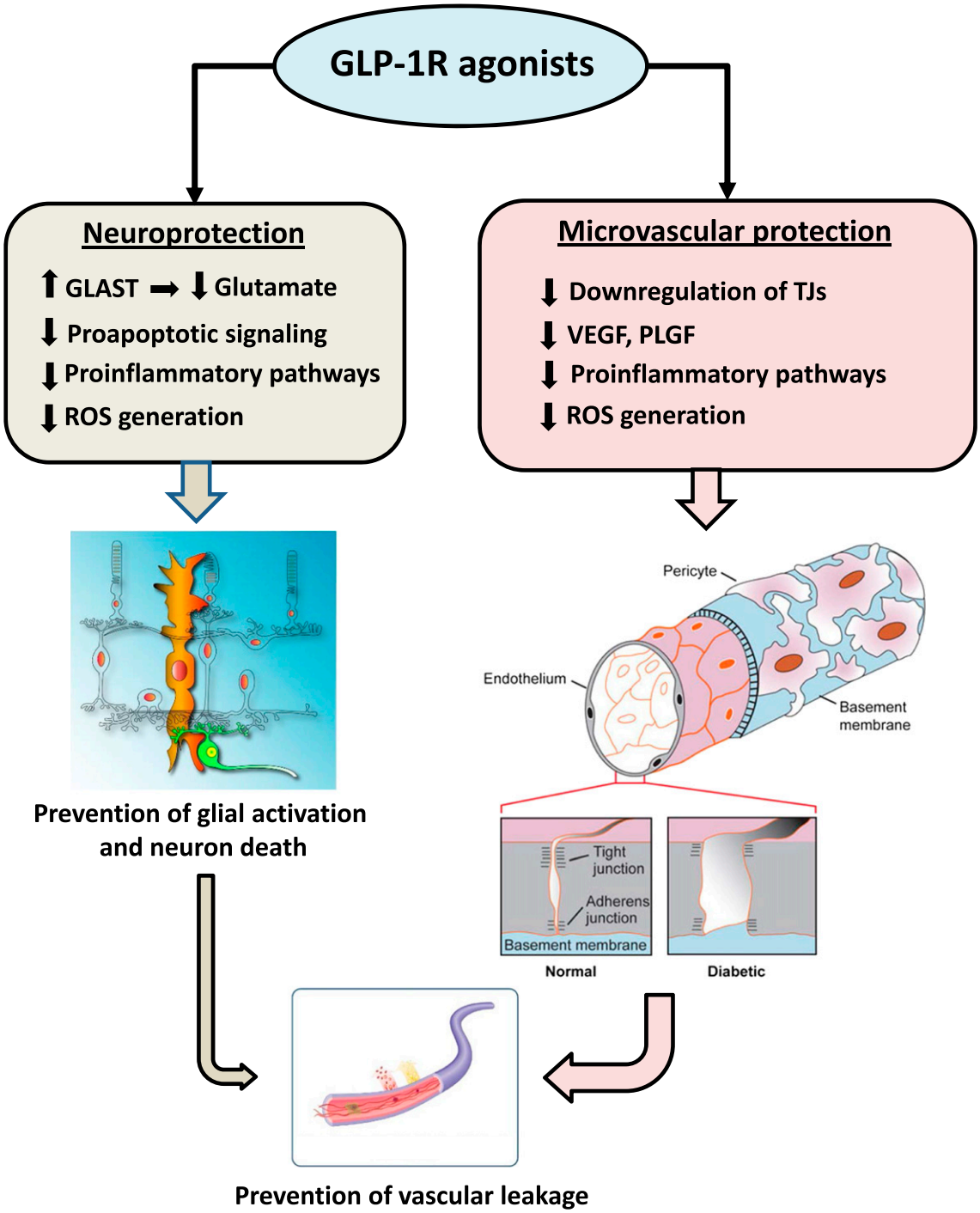

Figure 1—Dual beneficial effects of GLP-1R at the retinal level demonstrated in experimental research. GLP-1R exerts both a neuroprotective and vasculotropic effect by means of several pathways, leading to the prevention of vascular leakage, an early event in the pathogenesis of DR. PLGF, placental growth factor; TJs, tight junctions.

inhibition by GLP-1RAs of the downregulation of glutamate-aspartate transporter (GLAST) induced by diabetes (22,26). GLAST is an essential molecule for the clearance of glutamate and, therefore, the higher the levels of GLAST, the lower the excitotoxicity and neural apoptosis. In addition, we have recently found that retinal receptors of glutamate are downregulated by GLP-1 (R.S., C.H., unpublished observations).

Another significant effect of GLP-1R activation is to prevent the upregulation of proapoptotic/proinflammatory markers (iNOS, FasL, caspase 8, P53/p-P53, Bax) and the downregulation of survival pathways (Bcl-xL, Bcl-2) induced by diabetes in the neuroretina (22,28,29). In addition, a significant increase in the ratio p-AKT/AKT has been observed, which is essential for the survival of the neurons (22).

Finally, it has recently been reported that the intravitreal injection of exendin-4 reduces retinal cell death and reactive oxygen species (ROS) generation by upregulating Sirt1 and Sirt3 expressions in the retina (30).

Although it seems reasonable that the effects of GLP-1 and GLP-1 agonists are mediated by GLP-1R activation, the participation of other pathways unrelated to GLP-1R activation cannot be ruled out. The use of experimental knockout models for GLP-1R would be very useful in order to further clarify this issue. In addition, it has been reported that GLP-1(9-36)amide, originally considered to be an inactive degradation product of GLP-1, has important physiological effects, distinct from those of its precursor, that appear not to be mediated by GLP-1R (31,32). In this regard, Giacco et al. (33) have shown that GLP-1(9-36)amide normalizes ROS production and its pathophysiological consequences in cultured endothelial cells and in mice after transient hyperglycemia.

GLP-1R Activation and Vasculotropic Action

Preclinical studies have demonstrated the beneficial effects of GLP-1RA on the myocardium and vascular endothelium independently of their capacity to lower blood glucose levels (34), and many clinical studies evaluating changes in surrogate markers of cardiovascular disease have suggested the potential benefits of the use of GLP-1RAs (35,36). In this regard, the effects in lowering blood pressure and lipids can also be considered beneficial in preventing or arresting DR. However, little is known about the direct effects of GLP-1RA on the microvasculature of the retina.

Fan et al. (27) have shown that intravitreal injections of exendin-4 in Goto-Kakizaki rats protect the blood-retinal barrier (BRB) from diabetes-induced vascular leakage by preventing the downregulation of tight junction proteins (i.e., claudin-5 and occludin). These effects are associated with a decrease of placental growth factor and VEGF via the ERK and AKT/PKB pathways. In addition, we have found that topical administration of GLP-1RAs in *db/db* mice prevents vascular leakage through the downregulation of two of the most important players in the pathogenesis of the breakdown of the BRB: VEGF and IL-1β (22).

Recent studies have revealed that GLP-1 enhances proliferation and differentiation of endothelial progenitor cells through upregulation of VEGF (37). In addition, there is emerging experimental evidence indicating the angiogenic effects of GLP-1RA using human umbilical vein endothelial cells (38,39), or in in vivo models of hind-limb ischemic injury (40,41) and myocardial infarction (42,43). Therefore, it might be hypothesized that the worsening of DR observed in the SUSTAIN study could be partially accounted for by the inclusion of patients with advanced nonproliferative DR or proliferative DR (stages in which hypoxia plays a crucial pathogenic role) in whom semaglutide could have triggered angiogenesis, thus favoring neovascularization. However, to the best of our knowledge, there is no information regarding any potential in vitro or in vivo angiogenic effect of GLP-1RA in the retina. In fact, it has been shown that GLP-1 did not affect the spontaneous release of VEGF from retinal pigment epithelium cells (the primary source of VEGF in the retina) (44). Additionally, as mentioned above, we have found that subcutaneous administration of liraglutide downregulated retinal expression of VEGF in *db/db* mice (22). Nevertheless, specific studies addressed to investigate whether the presence of hypoxia can modulate the effect of GLP-1RAs on retinal VEGF expression seem warranted. In addition, topical or intravitreal administration of GLP-1RAs would be useful in determining whether the potential effect on angiogenesis is directly mediated by GLP-1R rather than by indirect systemic effects related to their rapid reduction of blood glucose levels.

LESSONS FROM THE CLINICAL TRIALS AND GAPS TO BE COVERED

Clinical Trials Primarily Addressed to Examine the Effectiveness and Safety of GLP-1RAs

Prospective clinical trials that mainly aimed at evaluating GLP-1RA effectiveness in lowering HbA_{1c} were too short to permit us to draw valid results in terms of DR outcomes. In addition, in most of these studies, the information regarding the presence and degree of DR is lacking. By contrast, recent clinical trials examining cardiovascular risk have generally included a larger population with a more prolonged follow-up. Therefore, analysis of these studies could be useful for ascertaining the differential effect of GLP-1RAs and new antidiabetes agents on DR.

Clinical Trials Addressed to Evaluate Cardiovascular Outcomes

In recent years, cardiovascular disease has been the focus of the regulatory authorities when establishing the safety of new antidiabetes therapies to treat type 2 diabetes. In this regard, it should be noted that in 2008, following the withdrawal of rosiglitazone from the market due to its apparent association with increased cardiovascular risk, the U.S. Food and Drug Administration (FDA) published a guide for the sponsors regarding how to demonstrate that a new antidiabetes therapy to treat type 2 diabetes was not associated with an unacceptable increase in cardiovascular risk (45). This FDA recommendation led the pharmaceutical companies to design studies that would test the cardiovascular safety of new antidiabetes drugs.

Since then, there have been seven published multicenter prospective randomized controlled trials assessing the cardiovascular safety of drugs used in the treatment of type 2 diabetes, totaling more than 60,000 participants. Three of these trials evaluated the dipeptidyl peptidase 4 (DPP-4) inhibitors saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 [SAVOR-TIMI 53]) (46), alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]) (47), and sitagliptin (Trial Evaluating Cardiovascular Outcomes

With Sitagliptin [TECOS]) (48); three evaluated the GLP-1RAs lixisenatide (Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA]) (49), liraglutide (LEADER) (6), and semaglutide (SUSTAIN-6) (7); and one evaluated the sodium–glucose cotransporter 2 inhibitor empagliflozin [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)] (50). All the DPP-4 inhibitors studied, as well as lixisenatide, demonstrated noninferiority to placebo for cardiovascular morbidity and mortality, which was the primary outcome of these trials. However, both empagliflozin (EMPA-REG OUTCOME) (50) and liraglutide (LEADER) (6) were superior to placebo in reducing cardiovascular morbidity and mortality. In all these studies, the effects of the new drugs on DR were either not reported (7,8,13) or neutral (46,47,51).

More recently, the SUSTAIN-6 trial (7) demonstrated the superiority of semaglutide for the primary composite outcome (the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in comparison with placebo. However, an unexpected higher rate of severe DR complications (i.e., vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) was detected in the semaglutide group. Certainly, this was a surprising finding because, as mentioned above, beneficial rather than deleterious effects on the development of DR were reported in preclinical studies by using GLP-1RAs (22,25–30). The possible reasons for these findings are as follows:

1) A short follow-up period. The length of observation is another challenge, bearing in mind the slow nonlinear progression of DR. Although there is no fixed rule, the duration of the trial must be consistent with the natural history of DR and, in consequence, 5 years seems to be sufficient time for separating the behavior of retinopathy in the intervention and control groups. The duration of follow-up of the LEADER and SUSTAIN-6 trials was 3.8 and 2 years, respectively (6,7), and, therefore, they did not satisfy the minimal period necessary for obtaining a sufficient outcome by using the standard methods for measuring DR progression. This could explain the neutral effects detected in the clinical trials using GLP-1 analogs (ELIXA and LEADER), but the worsening of DR in the short period of SUSTAIN-6 is really surprising.
2) A lack of grading of DR at baseline and during follow-up. The above-mentioned studies were aimed at assessing cardiovascular but not DR outcomes. In fact, retinal photographs were not taken systematically at baseline. Therefore, it is impossible to know whether the two arms (placebo and tested drugs) were matched by their degree of DR. This is a crucial point because the presence and degree of DR at baseline is an important factor in determining both the early and long-term evolution during follow-up. In consequence, a bias toward more advanced cases of DR in the arm of semaglutide at baseline might be one of the reasons accounting for the higher rate of photocoagulation, intravitreal injections of anti-VEGF agents, vitreous hemorrhage, or blindness detected during the follow-up of SUSTAIN-6 (7). It could be argued that the randomization process should minimize any bias related to DR status at baseline, but it should also be noted that the number of events (DR complications) was small (3%, n = 50 in patients receiving semaglutide and 1.8%, n = 29 in the placebo arm) and, therefore, this possibility cannot be ruled out. Although data on the basal status of DR and during follow-up were not displayed either in LEADER or SUSTAIN-6 studies, the information collected from clinical records regarding routine ophthalmological examinations could help to add valuable information on this issue.
3) Another potential factor accounting for the results reported on DR from SUSTAIN-6 is the deleterious effect of a rapid lowering of HbA_{1c}. This was actually the main reason given by the authors. In fact, the divergence of DR events between the two arms occurred relatively early in both the LEADER and the SUSTAIN studies, thus supporting this hypothesis. However, the rapid improvement of blood glucose levels and the magnitude in the reduction of HbA_{1c} was similar to that obtained in other studies in which no effect on worsening DR was reported (6,51,52). Therefore, a subanalysis addressed to ascertain whether those patients who experienced a worsening of DR were also those with poor metabolic control and in whom a greater improvement of HbA_{1c} was achieved could be useful in shedding light on this issue.
4) Finally, as the authors of SUSTAIN-6 stated, a direct deleterious effect of semaglutide on the retina cannot be ruled out. Two situations can be contemplated. The first is a potential angiogenic action of GLP-1RA, in which worsening preproliferative and proliferative DR cannot be ruled out. The second is a direct toxic effect of semaglutide. However, this latter possibility is very unlikely because of the high content in the retina of stearic acid (a main component of semaglutide), the unproven capacity of semaglutide to cross the BRB, and the lack of experimental evidence supporting any retinal toxicity of this compound.

Nevertheless, it should be emphasized that despite the observed negative effect on DR, the beneficial effect on other key outcomes, including cardiovascular risk, makes the overall benefit-risk profile of semaglutide in type 2 diabetes favorable.

Finally, it should be noted that the baseline status of DR and its progression was not reported in the SAVOR-TIMI 53, EXAMINE, and ELIXA studies. However, the TECOS study (48) showed that patients treated with sitagliptin exhibited higher diabetic eye disease in comparison with placebo (3.1% vs. 2.5%). The experimental evidence on the effects of DPP-4 inhibitors in DR is limited and controversial (53–56). Interestingly, Gonçalves et al. (55) demonstrated that sitagliptin alleviates increased BRB permeability in STZ-induced diabetic rats, which could not be attributed to a normalization of glycemia. However, Lee et al. (56)

have recently reported that intraperitoneal administration of sitagliptin induced vascular leakage in the retinas from mice with either retinopathy of prematurity or STZ-induced diabetes. Consequently, further research to clarify whether DPP-4 inhibitors exert beneficial or deleterious effects in the diabetic retina seems warranted.

FUTURE PERSPECTIVES AND CONCLUDING REMARKS

Improvements in diabetes care and management have been crucial in lowering the incidence and severity of DR. Nevertheless, DR remains the most common cause of vision impairment in working-age adults in the U.S. and Europe. The potentially substantial worldwide public health burden of DR highlights the importance of searching for new approaches beyond current standards of diabetes care.

The clear repercussions of cardiovascular disease on the global morbidity and mortality of patients with diabetes have been the main reason for the FDA regulatory requirements for the safety of new antidiabetes medications. However, we might now find on the market a new drug for the treatment of diabetes with a well-proven cardiovascular safety record or even with beneficial effects in cardiovascular outcomes but with a significant sight-threatening risk. In addition, since cardiovascular risk associated with DR is much higher than classic cardiovascular risk factors such as cholesterol or hypertension, it would be a big mistake to dismiss the presence and the degree of DR in the randomization process of the studies aimed at assessing cardiovascular events. Overall, a more holistic and cost-efficient approach to these types of clinical trials would appear to be highly recommendable.

In practical terms, obtaining objective information on the presence and degree of DR from all large clinical trials regardless of their primary end point is strongly recommended. This information will help us to increase our knowledge regarding the potential specific actions of new antidiabetes drugs on the retina. The results of retinal photographs performed at baseline and every 6 months during follow-up could be easily incorporated into the database of a clinical trial. The frequency of DR monitoring could even be increased when a dramatic reduction of blood glucose levels was anticipated. Obviously in the case that DR was included as a primary or secondary end point, seven-field retinography with a central reading should be mandatory.

As greater knowledge of the molecular mechanisms involved in the pathogenesis of DR has been obtained, new therapeutic products have been developed. However, an obvious difference between the clinical trials and the studies in experimental diabetes is that most clinical trials testing new drugs for DR have been performed on patients with advanced retinopathy, whereas the preclinical studies have targeted prevention. In this regard, it should be noted that most of the neuroprotective and antiangiogenic drugs that have been tested on animals have been effective in preventing the development of neurodegeneration and microvascular abnormalities rather than the regression of neurodegeneration or the already established microangiopathy. On this basis, the difference in the success rate for treating DR between experimental and clinical studies is easily understandable. GLP-1RAs are a good example of this issue, and specific clinical trials addressed to determine the effect of these drugs on the development and progression of DR are urgently needed. An issue that remains to be elucidated is whether or not GLP-1RAs have angiogenic properties in the retinal microvessels. This is a crucial point that requires not only experimental research but also an urgent pilot clinical trial.

Although there is robust experimental clinical evidence that GLP-1RAs prevent neurodegeneration, their effect in microcirculation has been studied less often. In addition, the neurodegenerative process is found at very early stages in both experimental and clinical settings, but its relevance for the pathogenesis of retinal microvascular abnormalities remains to be elucidated. In this regard, the identification of patients in whom retinal neurodegeneration plays a key role for the development of microvascular disease is a challenge that needs to be met. In this subset of patients, treatment with neuroprotective agents such as GLP-1RAs could be particularly recommended. In addition, in the event that the ongoing clinical trials aimed at demonstrating the beneficial effects of GLP-1 analogs on the cognitive impairment that occurs in type 2 diabetes lead to positive results, there will be important repercussions regarding the selection of treatment, thus allowing us to implement a more personalized medicine, one not based only on cardiovascular safety.

In summary, the results obtained in the LEADER and SUSTAIN-6 studies are an important landmark and could change the clinical management of patients with diabetes who have already presented with a cardiovascular event. However, clinical trials specifically designed to assess the effects of not only GLP-1 analogs but also DPP-4 inhibitors on the appearance and progression of DR are required. The development of new technologies in both retinal imaging and functional assessment will permit us to detect early changes and to further clarify whether therapies based on GLP-1R activation are friend or foe for the human diabetic retina. For this purpose, coordinated activity among diabetologists, ophthalmologists, basic researchers, pharmaceutical companies, and health care providers is needed.

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References

1. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012; 366:1227–1239

2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–136

3. Yau JW, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556–564

4. Heintz E, Wiréhn AB, Peebo BB, Rosenqvist U, Levin LA. Prevalence and healthcare costs of diabetic retinopathy: a population-based register study in Sweden. Diabetologia 2010;53:2147–2154
5. International Diabetes Federation. *IDF Diabetes Atlas, 7th edition* [Internet], 2015. Available from http://diabetesatlas.org. Accessed 15 January 2017
6. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
7. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
8. Simó R, Hernández C. Novel approaches for treating diabetic retinopathy based on recent pathogenic evidence. Prog Retin Eye Res 2015;48:160–180
9. Stitt AW, Curtis TM, Chen M, et al. The progress in understanding and treatment of diabetic retinopathy. Prog Retin Eye Res 2016;51:156–186
10. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874–886
11. Funatsu H, Yamashita H, Ohashi Y, Ishigaki T. Effect of rapid glycemic control on progression of diabetic retinopathy. Jpn J Ophthalmol 1992;36:356–367
12. Shurter A, Genter P, Ouyang D, Ipp E. Euglycemic progression: worsening of diabetic retinopathy in poorly controlled type 2 diabetes in minorities. Diabetes Res Clin Pract 2013;100:362–367
13. Henricsson M, Nilsson A, Janzon L, Groop L. The effect of glycaemic control and the introduction of insulin therapy on retinopathy in non-insulin-dependent diabetes mellitus. Diabet Med 1997;14:123–131
14. Roysarkar TK, Gupta A, Dash RJ, Dogra MR. Effect of insulin therapy on progression of retinopathy in noninsulin-dependent diabetes mellitus. Am J Ophthalmol 1993;115:569–574
15. Gorman DM, le Roux CW, Docherty NG. The effect of bariatric surgery on diabetic retinopathy: good, bad, or both? Diabetes Metab J 2016;40:354–364
16. Casson RJ, Wood JPM, Osborne NN. Hypoglycaemia exacerbates ischaemic retinal injury in rats. Br J Ophthalmol 2004;88:816–820
17. Simó R, Hernández C; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration is an early event in diabetic retinopathy: therapeutic implications. Br J Ophthalmol 2012;96:1285–1290
18. Abcouwer SF, Gardner TW. Diabetic retinopathy: loss of neuroretinal adaptation to the diabetic metabolic environment. Ann N Y Acad Sci 2014;1311:174–190
19. Simó R, Hernández C; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration in the diabetic eye: new insights and therapeutic perspectives. Trends Endocrinol Metab 2014;25:23–33
20. Hölscher C. Potential role of glucagon-like peptide-1 (GLP-1) in neuroprotection. CNS Drugs 2012;26:871–882
21. Yarchoan M, Arnold SE. Repurposing diabetes drugs for brain insulin resistance in Alzheimer disease. Diabetes 2014;63:2253–2261
22. Hernández C, Bogdanov P, Corraliza L, et al. Topical administration of GLP-1 receptor agonists prevents retinal neurodegeneration in experimental diabetes. Diabetes 2016;65:172–187
23. Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. J Pharmacol Exp Ther 2002;302:881–888
24. Pulido JE, Pulido JS, Erie JC, et al. A role for excitatory amino acids in diabetic eye disease. Exp Diabetes Res 2007;2007:36150
25. Zhang Y, Wang Q, Zhang J, Lei X, Xu G-T, Ye W. Protection of exendin-4 analogue in early experimental diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 2009;247:699–706
26. Zhang Y, Zhang J, Wang Q, et al. Intravitreal injection of exendin-4 analogue protects retinal cells in early diabetic rats. Invest Ophthalmol Vis Sci 2011;52:278–285
27. Fan Y, Liu K, Wang Q, Ruan Y, Ye W, Zhang Y. Exendin-4 alleviates retinal vascular leakage by protecting the blood-retinal barrier and reducing retinal vascular permeability in diabetic Goto-Kakizaki rats. Exp Eye Res 2014;127:104–116
28. Fan Y, Liu K, Wang Q, Ruan Y, Zhang Y, Ye W. Exendin-4 protects retinal cells from early diabetes in Goto-Kakizaki rats by increasing the Bcl-2/Bax and Bcl-xL/Bax ratios and reducing reactive gliosis. Mol Vis 2014;20:1557–1568
29. Fu Z, Kuang HY, Hao M, Gao XY, Liu Y, Shao N. Protection of exenatide for retinal ganglion cells with different glucose concentrations. Peptides 2012;37:25–31
30. Zeng Y, Yang K, Wang F, et al. The glucagon like peptide 1 analogue, exendin-4, attenuates oxidative stress-induced retinal cell death in early diabetic rats through promoting Sirt1 and Sirt3 expression. Exp Eye Res 2016;151:203–211
31. Tomas E, Stanojevic V, Habener JF. GLP-1-derived nonapeptide GLP-1(28-36)amide targets to mitochondria and suppresses glucose production and oxidative stress in isolated mouse hepatocytes. Regul Pept 2011;167:177–184
32. Sharma R, McDonald TS, Eng H, et al. In vitro metabolism of the glucagon-like peptide-1 (GLP-1)-derived metabolites GLP-1(9-36)amide and GLP-1(28-36)amide in mouse and human hepatocytes. Drug Metab Dispos 2013;41:2148–2157
33. Giacco F, Du X, Carratú A, et al. GLP-1 cleavage product reverses persistent ROS generation after transient hyperglycemia by disrupting an ROS-generating feedback loop. Diabetes 2015;64:3273–3284
34. Wang D, Luo P, Wang Y, et al. Glucagon-like peptide-1 protects against cardiac microvascular injury in diabetes via a cAMP/PKA/Rho-dependent mechanism. Diabetes 2013;62:1697–1708
35. Simó R, Guerci B, Schernthaner G, et al. Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study. Cardiovasc Diabetol 2015;14:116
36. Kang YM, Jung CH. Cardiovascular effects of glucagon-like peptide-1 receptor agonists. Endocrinol Metab (Seoul) 2016;31:258–274
37. Xiao-Yun X, Zhao-Hui M, Ke C, Hong-Hui H, Yan-Hong X. Glucagon-like peptide-1 improves proliferation and differentiation of endothelial progenitor cells via upregulating VEGF generation. Med Sci Monit 2011;17:BR35–BR41
38. Kang HM, Kang Y, Chun HJ, Jeong JW, Park C. Evaluation of the in vitro and in vivo angiogenic effects of exendin-4. Biochem Biophys Res Commun 2013;434:150–154
39. Aronis KN, Chamberland JP, Mantzoros CS. GLP-1 promotes angiogenesis in human endothelial cells in a dose-dependent manner, through the Akt, Src and PKC pathways. Metabolism 2013;62:1279–1286
40. Kang HM, Sohn I, Jung J, Jeong JW, Park C. Exendin-4 protects hindlimb ischemic injury by inducing angiogenesis. Biochem Biophys Res Commun 2015;465:758–763
41. Sheu JJ, Chang MW, Wallace CG, et al. Exendin-4 protected against critical limb ischemia in obese mice. Am J Transl Res 2015;7:445–459
42. Sun Z, Tong G, Kim TH, et al. PEGylated exendin-4, a modified GLP-1 analog exhibits more potent cardioprotection than its unmodified parent molecule on a dose to dose basis in a murine model of myocardial infarction. Theranostics 2015;5:240–250
43. Du J, Zhang L, Wang Z, et al. Exendin-4 induces myocardial protection through MKK3 and Akt-1 in infarcted hearts. Am J Physiol Cell Physiol 2016;310:C270–C283
44. Puddu A, Sanguineti R, Montecucco F, Viviani GL. Retinal pigment epithelial cells express a functional receptor for glucagon-like peptide-1 (GLP-1). Mediators Inflamm 2013;2013:975032
45. U.S. Food and Drug Administration. Guidance for Industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes [Internet], 2008. Available from www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm071627.pdf. Accessed 2 July 2016
46. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
47. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335
48. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242

49. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
50. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
51. Garber A, Henry R, Ratner R, et al.; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473–481
52. Pettitt DJ, Okada Wollitzer A, Jovanovic L, He G, Ipp E. Decreasing the risk of diabetic retinopathy in a study of case management: the California Medi-Cal Type 2 Diabetes Study. Diabetes Care 2005;28:2819–2822
53. Gonçalves A, Leal E, Paiva A, et al. Protective effects of the dipeptidyl peptidase IV inhibitor sitagliptin in the blood-retinal barrier in a type 2 diabetes animal model. Diabetes Obes Metab 2012;14:454–463
54. Maeda S, Yamagishi S, Matsui T, et al. Beneficial effects of vildagliptin on retinal injury in obese type 2 diabetic rats. Ophthalmic Res 2013;50:221–226
55. Gonçalves A, Marques C, Leal E, et al. Dipeptidyl peptidase-IV inhibition prevents blood–retinal barrier breakdown, inflammation and neuronal cell death in the retina of type 1 diabetic rats. Biochim Biophys Acta 2014;1842:1454–1463
56. Lee CS, Kim YG, Cho HJ, et al. Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. Sci Rep 2016;6:29393