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Ocular Complications Associated with GLP1 Agonist Therapy

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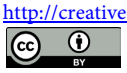

Abstract

Diabetes mellitus (DM) has proven to be an ever growing non communicable disease (NCD) of pandemic proportions, which continues to affect millions of people globally either directly or indirectly. From contributing to increasing morbidity, decreasing quality of life and increasing mortality rates, DM executes its actions via its effects on both microvascular and macrovascular pathways. Diabetic Retinopathy (DR) is an affliction that is seen in the majority of DM affected individuals in varying stages from mild disease to vision loss. In vast majority of people, a routine evaluation for diminished vision is often the first point of diagnosis for DM. Uncontrolled sugars have often been the causative agent for the development of DR. However, in recent times, the incidence of DR and its progression has also been attributed to the rate of decrease of hyperglycemia and the incidence of hypoglycemia in diabetic individuals. Recent advances in medications like the use of GLP1 agonists for the control of hyperglycemia in uncontrolled obese diabetics have significantly shown benefit by offering cardiorenal protection and neuroprotection. This article aims to look at the effects of reduction of hyperglycemia and weight loss caused by GLP1 agonists on the incidence and progression of DR.

Keywords

Diabetes Mellitus, Diabetic Retinopathy, GLP1 Agonists, Hypoglycemia, HbA1c, Vision Loss

1. Introduction

Diabetes mellitus (DM) is an ever-growing global burden that has reached pan-

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demic proportions. Diabetic retinopathy (DR) is one of the major causes of visual disturbances and vision loss among those with DM. The spectrum of DR ranges from variable degrees of the presence retinal microaneurysms, haemorrhages, cotton-wool spots, hard exudates, retinal venous changes, and neovascularization seen in either the macula, with or without the involvement of the peripheral retina [1]. The 2021 report of the International Diabetes Federation (IDF) mentions 10.5% of the adult population, between 20 - 79 years, are affected by diabetes and this is projected to grow to 46% by 2045, *i.e.*, 1 in every 8 adults would be affected by diabetes [2]. The incidence of DR in diabetic individuals is estimated to be at 30% - 40% and with the projected rise in DM, these would also proportionately increase over this period [3]. Hence, along with the urgency shown in addressing the pandemic of DM, there should also be a sense of urgency in preventing this cause of potential vision loss among diabetic individuals. The risk factors that contribute towards DR include the duration of DM, the period of euglycemia (diabetes control), presence or absence of Hypertension, population ethnicity, levels of education and socio-economic standings of the individual. DR tends to evolve from absent or subclinical presentations to mild DR and progressing later to much more sinister presentations of vision threatening DR (VTDR). The latter is seen in 5% - 10% of cases and usually accompanied by macular edema and varying degrees of retinal neovascularization [4]. Majority of the cases of Type 1 DM (T1DM) and about 60% of those with Type 2 DM (T2DM) who have had it for at least 10 years, are affected by DR resulting in an impairment in vision or in blindness. Approximately, 1 out of 5 individuals with diabetes have been shown to have some degree of DR. In addition to the morbidity associated with DR, it also does have a huge economic impact with increases in health care spending per diabetic individual and global annual economic productivity loss. In 2020, the latter stood at approximately US$ 411 billion [5].

2. Pathogenesis of DR

The basis of the changes seen in diabetes can be summarized because of hyperglycemia, oxidative stress and inflammation. The vascular endothelial cells (ECs) have an increased production of mitochondrial superoxides which causes an increased influx through the polyol pathways. The resultant production of advanced glycation end-products (AGEs) and the upregulation of the AGEs receptors including their corresponding activating ligands cause the activation of the protein kinase C pathways and an increased activity of the hexosamine pathways. All these changes in concert lead to the formation and increase in reactive oxygen species which contributes to irreversible cell damage.

Monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and IL-6 are some of the pro-inflammatory cytokines and chemokines that are commonly seen to be elevated in DR eyes. Leucocyte adhesion and infiltration damage the vascular ECs and neuroglial cells via physical capillary occlusion and the release of superoxide and other inflammatory media-

tors. Therapies targeting these inflammatory markers have been considered in the treatment of DR.

Vascular endothelial growth factors such as VEGFA, VEGFB, VEGFC, VEGFD, and Placental growth factor (PlGF) binds to transmembrane tyrosine kinases VEGFR1, VEGFR2, and VEGFR3 and regulate lymphangiogenesis. The retinal pigment epithelium (RPE) cells secrete VEGFA and are helpful in maintaining the choroidal vessels.

Hypoxia transcriptionally upregulates the VEGFA and isoforms such as VEGFA121, VEGFA165, and VEGFA189 binds to extracellular matrices and activates several signal transduction cascades. The phosphatidyl inositol 3-kinase (PI3K)/Akt pathway and the mitogen-activated protein kinase pathway activations cause neovascularization by promoting call proliferation and migration. Vascular hyperpermeability and fluid extravasation occurs due to the activation of VEGFA-VEGFR2 signal which disrupts the EC-EC adherens and tight junctions.

Angiopoietin-1 (Ang1) and Angiopoietin-2 (Ang2) are angiopoietins that have antagonist actions to each other. Ang1 binds to tyrosine kinase with immunoglobulin-like loops and epidermal growth factor homology domains 2 (Tie2) receptor and activates the PI3K/Akt pathway which promotes EC survival, prevents vascular permeability and suppresses inflammatory responses. Whereas Ang2-induced activation of forkhead box O1 (FOXO1) upregulates Ang2 which in turn causes angiogenesis, vascular permeability, and inflammation.

The blood-retina barrier (BRB) is tightly sealed by the retinal vascular ECs and RPE cells and this prevents the leakage of plasma into the neural tissues. Retinal pericytes in the retinal capillary walls help in maintaining the integrity of the EC via both a direct cell to cell contact and via secretory signals. EC-derived platelet-derived growth factor (PDGF) B aids in the recruitment of PDGF receptor (PDGFR) β-expressing pericytes to nascent blood vessels. Hence, any alterations to this would result in the enlargement of retinal vessels, increased permeability, decreased perfusion, retinal edema and even hemorrhage. Pericyte deficiency also induces an inflammation of the EC and results in macrophage infiltration in the perivascular spaces [6].

3. The Incretin Effect

Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP). GLP-1 is released from the intestinal L cells in the distal ileum and colon while GIP is released by the intestinal K cells in the duodenum and jejunum. Both these hormones are inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme. In diabetic individuals, this incretin response is blunted, and this further contributes to the hyperglycemic response in addition to the decreasing beta cell activity/mass. Both GIP and GLP-1 exert their effects by binding to their specific receptors, the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R), belong to the G-protein coupled receptor family, activating adenylate cyclase and increasing

levels of intracellular cyclic Adenosine Monophosphate (cAMP) in pancreatic beta cells, thereby stimulating insulin section glucose dependently. Both GIP and GLP-1 exert their insulinotropic effects by binding to GIP and GLP-1 receptors that are expressed on pancreatic beta cells. Incretin-bound receptors increase intracellular cAMP levels, thereby activating protein kinase A (PKA) and exchange protein activated by cAMP2 (EPAC2)/cAMP-guanine nucleotide exchange factor (GEF) II. PKA and EPAC2 are involved in a wide variety of intracellular events including altered ion channel activity, elevated cytosolic calcium levels and enhanced exocytosis of insulin-containing granules, all of which contribute to stimulation of insulin section in a glucose-dependent manner [7].

4. Effects of GLP-1 in the Retina

In vivo and in vitro studies have demonstrated anti-inflammatory actions of GLP-1Ras acting via the activation of GLP-1R causing a reduction in macrophage infiltration, and in expression and secretion of proinflammatory cytokines. In diabetic individuals, the high availability of glucose in the ocular tissue predisposes the individual to a higher oxidative stress and retinal inflammation. Additionally, there is also a decreased level in antioxidant enzymes which further aids in the onset and perpetuation of DR [8].

In experimental diabetic models, the effect of GLP-1R activation shows retinal thickness preservation, preventing the breakdown of the BRB, preventing pericyte loss and neurodegeneration, inhibition of macrophage infiltration and activation and preventing the loss of the b-wave amplitude. Intracellularly, GLP-1 demonstrates a decreased release of proinflammatory markers, preventing the upregulation of intracellular adhesion molecules (ICAM) and apoptotic factors along with facilitating the maintenance of the antioxidant defence mechanisms [9].

The retinal ganglion cells (RGC) are among the first to be affected and damaged in DR owing to their increased vulnerability and thinning due to increased glucose levels. This neurodegeneration that precedes retinal microvascular injury plays an important role in visual impairment and permanent vision loss. The high concentration of mitochondria in the RGC makes them susceptible to hyperglycaemia induced oxidative stress which in turn activates a vicious cycle wherein more apoptotic pathways are activated due to mitochondria damage [10].

In the retinal pigment epithelium (RPE), increased glucose leads to the increased production of reactive oxygen species (ROS), increased expression of adhesion molecules and monocyte adhesion along with increased release of metalloproteinases. These events are prevented by the activation of GLP-1R in the RPE [11].

Retinal endothelial cells (REC) have decreased amounts of superoxide dismutase (SOD). This, when coupled with hyperglycemia, causes an increased production of ROS, decreased protective antioxidant enzymes and increased cell apoptosis, ultimately leading to the cascade of events in DR. Increased blood glucose decreases the expression of GLP-1R and promotes inflammation by an

increased expression of sphingosine 1-phosphate (S1P) leading to activation of the S1P/sphingosine-1-phosphate receptor 2 (S1P/S1PR2) [12].

5. Exenatide

Retrospective studies in 165 patients who started with Exenatide showed that after starting the drug, there was an initial transient or permanent progression of diabetic retinopathy. In many instances, the transient deterioration is seen to be reversed (80%) with continued treatment with the medication. Permanent deterioration (20% - 30%) is seen in those individuals who have had a higher grade of retinopathy or longer duration of diabetes or have had maculopathy prior to starting the drug [13]. In another case report, it was seen that a poorly controlled 55-year-old diabetic woman with macular edema showed resolution of her macular edema and visual impairment after starting with exenatide 10 μg subcutaneously twice daily [14]. Dramatic deteriorations in DR were seen in those subjects where the HbA1c reduced from 11.9% to 4.8% after 4 months of starting Exenatide therapy. It was seen that the background retinopathy had progressed to proliferative DR and macular edema in those individuals [15].

6. Liraglutide

The 2010, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial evaluated 9340 Type 2 diabetes patients in a multicenter, double-blind, placebo-controlled trial at 410 sites over 32 countries. The primary outcomes measured included in the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Following 3.8 years of median follow up, it was seen that, when compared to placebo, those in the liraglutide group had a significantly lower incidence of primary outcomes (13% vs 14.9%, Liraglutide vs placebo). Similarly, the occurrences of nonfatal stroke, nonfatal myocardial infarction and need for hospitalization for cardiac failure were lower (nonsignificant) in the liraglutide group. However, the rates of retinopathy were higher in the liraglutide group (nonsignificant) when compared to the placebo group (0.6 vs. 0.5 events per 100 patient-years; hazard ratio, 1.15; 95% CI, 0.87 to 1.52; P = 0.33) [16].

Experimental cellular studies have shown that Liraglutide reduces the hyperglycemia induced increased expression of IL-6 and VEGF-A along with levels of p53, p21 and cellular aging and death. Endothelial sirtuin 1 (SIRT1), a type III histone deacetylase (HDAC) of nicotinamide adenine dinucleotide (NAD) and a member of the Sirtuins family, showed protective effects on retinal cells and its activity has been augmented by liraglutide. Hence, administration of Liraglutide has shown to be beneficial in diabetic individuals [17]. Other animal experimental models, on diabetic mice, have shown that liraglutide has a certain protective effect on diabetic retinal injury, possibly due to the up-regulation of p-Erk1/2 and Trx antioxidant protein, long with a down-regulation of apoptosis-related protein ASK1 [18].

A case report showed that liraglutide administration, started for weight loss, in a non-diabetic woman was associated with a progressive unilateral decline of visual acuity following one month of initiation of therapy. Examination findings revealed ONH (optic nerve head) swelling in the right eye and an inferior hemifield scotoma. In the absence of potential risk factors, the visual decline was attributed to non-arteritic ischemic optic neuropathy (NAION) [19].

A study in Type 1 diabetic adults was conducted to check if Liraglutide treatment could induce or promote nerve regeneration in peripapillary retinal nerve fiber layer (RNFL) via its neurotrophic and inti inflammatory properties. In this prospective, double-blinded, randomized (1:1), placebo-controlled trial; Type 1 diabetic adults who had distal symmetric polyneuropathy (DSPN) and confirmed diabetic retinopathy were included and divided into placebo and liraglutide treatment groups over 26 weeks. Of the 37 participants, no significant differences were noticed between the groups in respect to the mean peripapillary RNFL thickness in any of the quadrants (liraglutide −1 (±8) μm (−1%) vs. placebo −1 (±5) μm (−1%), P = 0.78) [20].

A retrospective cohort analysis on 181 adults and adolescents (>14 years) with Type 2 diabetes who were on Liraglutide and insulin between 2015 and 2021 was performed in those who had a documented retinal assessment. 81.6% of the individuals who had no retinopathy at baseline continued to show no retinopathy whereas 18.4% showed to have developed retinopathy. Among those who had documented retinopathy at baseline; 25.5% of the patients showed an improvement in the retinopathy and 44.7% demonstrated no change, while 29.8% showed a worsening of the retinopathy status. The study showed that among the patients that were treated with both Liraglutide and insulin, there existed a higher risk of retinopathy development and worsening. This was more so due to the effects of insulin than Liraglutide [21].

7. Dulaglutide

The Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial in Type 2 diabetic was done to investigate the reduction in major cardiovascular events and other serious outcomes while on Dulaglutide. This multicenter trial was performed in 24 countries at 371 sites and was a randomized, double-blind, placebo-controlled trial involving older adult (>50 years) diabetics. 9901 patients were enrolled and were to receive 1.5 mg of Dulaglutide or placebo, with a mean follow-up period of 5.4 years. Ocular microvascular endpoints were diabetic retinopathy requiring laser therapy, vitrectomy, or anti-vascular endothelial growth factor therapy (VEGF). These were seen in 95 adults in the dulaglutide group (4949 patients) and 76 in the placebo group during 5.4 years of follow-up [22] [23].

A Case report was published which examined the evolution of diabetic retinopathy in an obese type 2 diabetic woman, who was initially given Exenatide and then subsequently changed to Dulaglutide for control of HbA1c and weight loss.

During the initial phase of treatment with Exenatide, there was no evidence of retinopathy reported. However, upon switching to Dulaglutide, and being on it for 1 year, the patient was shown to have developed mild NPDR (non-proliferative diabetic retinopathy), progressing to moderate NPDR after 6 months [24].

8. Semaglutide

The Peptide Innovation for Early Diabetes Treatment (PIONEER)-6 trial was a randomized, double-blind, placebo-controlled trial, involving 3183 type 2 adult (≥50 years) diabetics who had a high cardiovascular risk. Conducted in 214 sites in 21 countries, the participants were to receive either oral Semaglutide or placebo over a trial period of 15.9 months. The primary outcome for the study was the time from randomization to the first occurrence of a major adverse cardiovascular event (MACE), a composite of death from cardiovascular causes (including undetermined causes of death), nonfatal stroke or nonfatal myocardial infarction (MI). 3.8% in the Semaglutide group and 4.8% in the placebo group had primary outcomes, thereby showing a noninferiority for oral Semaglutide when compared to a placebo. Additionally, 7.1% of patients in the Semaglutide arm and 6.3% in the placebo arm developed diabetic retinopathy, mostly NPDR [25].

The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN)-6 trial was a randomized, double-blind, placebo-controlled trial performed to evaluate cardiovascular and other long-term outcomes with semaglutide in 3297 adults (≥50 years) with type 2 diabetes. The primary outcome for the study was the time from randomization to the first occurrence of a major adverse cardiovascular event (MACE), cardiovascular (CV) death, nonfatal stroke or nonfatal myocardial infarction (MI). Conducted in 229 sites in 20 countries, the participants were to receive either subcutaneous Semaglutide or placebo over a trial period of 104 weeks. 6.6% in the Semaglutide group and 8.9% in the placebo group had primary outcomes, thereby showing a noninferiority for subcutaneous Semaglutide when compared to a placebo (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; $P < 0.001$ for noninferiority). The rates of ocular complications like vitreous hemorrhage, blindness, or other presentations that required treatment with an intravitreal agent or photocoagulation were significantly higher in the subcutaneous Semaglutide group when compared to placebo (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; $P = 0.02$) [26].

A retrospective matched cohort study was performed involving 710 type 2 diabetic adults and 979 obese or overweight adults, out of 16,827 adults, who were prescribed Semaglutide to evaluate the potential risk of nonarteritic anterior ischemic optic neuropathy (NAION). Out of those with diabetes, 194 were prescribed Semaglutide and out of those that were either overweight or obese, 361 were prescribed Semaglutide. Within the diabetes cohort of the study, the incidence of NAION was higher in the Semaglutide arm as compared to the non–GLP-1 RA (17 versus 6; 8.9% (95% CI, 4.5% - 13.1%) and 1.8% (95% CI, 0% - 3.5%), respectively. Similarly in the overweight or obese cohort, the incidence of

NAION was higher in the Semaglutide arm as compared to the non-GLP-1 RA (6.7% (95% CI, 3.6% - 9.7%) and 0.8% (95% CI, 0% - 1.8%, respectively). Subjects who had diabetic retinopathy prior to Semaglutide treatment initiation, those with a rapid reduction of HbA1c were at a higher risk of worsening of the retinopathy and progression to proliferative diabetic retinopathy and/or new onset macular edema [27].

A meta-analysis of 20 randomized controlled trials (RCT) which included 24,832 persons with type 2 diabetes who were treated with GLP-1RA versus placebo revealed no significant effect on the development of diabetic retinopathy (Odds Ratio (OR) = 1.17, 95% CI: 0.98 - 1.39, P = 0.25). A subgroup analysis of liraglutide (OR = 0.86, 0.50 - 1.49), subcutaneous semaglutide (OR = 1.12, 0.67 - 1.86), lixisenatide (1.5, 0.06 - 37.08), albiglutide (1.02, 0.77 - 1.35), and efpegenatide (1.69, 0.08 - 35.58), showed similar findings. However, a significant increase in diabetic retinopathy was observed with oral semaglutide usage (OR = 1.43, 1.09 - 1.87) [28].

A retrospective, cohort study involving 810,390 type 2 diabetic adults ($\geq$18 years), who were first time users of Semaglutide, was performed to determine if there was an association between the use of semaglutide and DR. When compared to Dulaglutide, the risk of proliferative DR in the Semaglutide group was similar (HR 0.81, 95% CI 0.42 to 1.54, P = 0.51) [29].

A meta-analysis of 78 trials involving 73,640 adults with type 2 diabetes, who were on Semaglutide, did not reveal any significant increase or decrease in the risk of DR (OR, 1.04; 95% CI, 0.92 - 1.17) or other ophthalmic disorders (OR, 1.01; 95% CI, 0.91 - 1.12). However, there were increased number of NAION cases in the Semaglutide treated individuals (OR, 3.92; 95% CI, 1.02 - 15.02) [30].

Increased transmural capillary pressure, weakening of the capillary walls, increased capillary exudation, venous congestion leading to edema and increase in interstitial pressure which also leads to increased congestion and poor perfusion (compartment syndrome) have been attributed as pathological hallmarks for the development of NAION. Additionally, there is an increased amount of retinal arteriovenous oxygen extraction in diabetic individuals. An increased rate of reduction of hyperglycemia can cause retinal vasodilation which thereby compromises retinal metabolism and promote NAION development [31].

9. Conclusions

The convenience of using once weekly, non-insulin injections like GLP-1 agonists have significantly contributed towards a better control of glycemia in affected diabetic individuals. However, like all modalities of treatment, the benefit to risk ratios of treatment is an ever changing and evolving matter. Retrospective analyses of adult type 2 diabetic subjects who were prescribed GLP-1 agonists, to look for DR development, NAION or DR related complications showed an increased risk of DR but few occurrences of blindness or other sight threatening DR [32].

The U.S. Food and Drug Administration (FDA) Adverse Event Reporting

System (FAERS) database was examined to see the association between GLP-1RA and DR events. Between April 2005 and September 2017, 389 cases of DR were reported which were associated with the use of GLP-1 agonists (exenatide, liraglutide, albiglutide and dulaglutide). There was no conclusive evidence that the use of GLP-1 agonists contributed to an increased risk of DR [33].

For diabetic individuals who are planned to be started on GLP1 agonists, there should be detailed ophthalmic evaluation, and the patients should be detailed about the risks for potential visual deterioration after starting therapy. Regular fundoscopic follow up to look for signs of increased venous congestion or capillary leaks, disk changes, the development of newer hemorrhages will help to attenuate or prevent any retinal damage that might lead to permanent vision loss in the affected eyes. Stricter monitoring, in the first 3 - 6 months of initiating therapy along with a planned gradual slower reduction in HbA1c will also contribute towards reducing the incidence of NAION. In individuals who already have signs of retinal involvement due to DM or hypertension, especially in obese individuals, the risk of further retinal damage exists upon starting GLP-1 agonist therapy. Hence, it is suggested to have earlier and regular follow up at 1 - 3-month intervals in such cases who are on GLP-1 agonist treatment, until a stable HbA1c in achieved and adequate weight loss has been obtained.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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