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EDITORIAL

Enhancing glycaemic control with impetus on weight management: Observing for early worsening of diabetic retinopathy

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GLP-1 receptor agonists (GLP-1RA) analogues have revolutionised the management of patients with type 2 diabetes mellitus (T2DM) and have proven to reduce mortality, decrease the risk of cardiovascular events, and slow down the progression of diabetic kidney disease. However, the attainable doses and effectiveness of GLP-1RA can be limited by their gastrointestinal side effects [1]. In the pursuit for the next phase beyond GLP-1RA, the search for substitute adjunct therapies to gain greater effectiveness was explored and the other incretin, glucose-dependent insulinotropic polypeptide (GIP) was considered the natural partner to GLP-1 and the more dominant insulinotropic hormone in normal physiology [2]. Tirzepatide; a single molecule dual agonist of GLP-1 and GIP receptors, was established with this label of the twincretin concept. Tirzepatide, the first dual incretin mimetic is similar to GLP-1RA but offers a synergistic enhancement of the incretin effect to optimise blood glucose levels, with the impetus to reduce weight in patients with diabetes and obesity and has been described as a potent new armament in the arsenal against diabetes [2], but patients with diabetic retinopathy (DR) were excluded in the SURPASS-2 trial [3]. Tirzepatide has now been licensed and approved for use in the UK.

Semaglutide is the most recent GLP-1RA which has been effectively used in the management of patients with T2DM and obesity. Of note, recent comparative studies have demonstrated the impact of Tirzepatide and its superiority over Semaglutide both with respect to significant improvements in weight as well as glucose levels over a 40-week period [4]. In this setting with the effect of twincretins and the enhanced impact on intensive treatment and improvement in glucose control as well as weight reduction, all prescribers and allied healthcare professionals treating patients with T2DM, should be mindful of the risk of early worsening of DR [5], with rapid improvements in the glycaemic profile.

This clinical paradox tends to happen with a prolonged duration of diabetes, far from ideal glucose control prior to optimising treatment strategies with a higher HbA1c, pre-existing DR and the extent of HbA1c reduction within a short time. This aspect has now had renewed interest lately, although it is not directly due to an intrinsic consequence of GLP-1RA per se [5].

The same notion has been applicable to surgical treatments offered for patients with T2DM and obesity in the form of bariatric surgery. Several studies have highlighted the need for ensuring a close watch on patients who have achieved remission of T2DM, with the call for continued monitoring for any changes in the eyes in the post-operative period from the perspective of DR screening [6–11]. Nonetheless, systematic reviews and meta-analyses have reassuringly shown that there were fewer patients who developed sight-threatening DR, although bariatric surgery did not prevent the progression of DR and early worsening was more in patients with pre-existing DR [12–14].

Exenatide was the initial GLP-1RA used extensively from a medical viewpoint and a retrospective assessment of patients with T2DM in receipt of this treatment daily for longer than 6 months, confirmed that DR had progressed in 30% of patients accompanied by large reductions in HbA1c; but there was no comparator group [15]. In this cohort of patients, DR had improved and remained stable thereafter during follow-up, signifying that early transient worsening did not progress [16]. This follow-up study applied rigorous methods for evaluating DR prospectively by analysing and reviewing retinal images [15, 16], whereas several of the DR findings described in trials involving GLP-1RA therapy, were based on standard adverse event-related reporting. Likewise with intensification of glycaemic control with Semaglutide, similar and more profound findings were reported, in the SUSTAIN trial [17, 18]. Cardiovascular outcome trials provide the longest available randomised, placebo-controlled follow-up studies for GLP-1RA [19, 20], but none of these trials was designed or powered to obtain robust evaluations of exact GLP-1RA treatment-related impact on DR.

It is pertinent to note that there is a noticeable paucity of GLP-1 receptors (GLP-1R) in the human retina, and GLP-1R expression was not identified by means of immunohistochemistry [21], making a direct consequence of this class of drugs less likely. This is further reinforced by the sparse expression of GLP-1R in the normal human eye and being undetectable in advanced stages of proliferative DR. Therefore, the early worsening of pre-existing DR is not likely to be due to an intrinsic effect of GLP-1RA directly on the retina, but more so because of rapid glucose control [15–18].

The precise mechanism of action is not conclusive, and several feasible descriptions have been proposed in this context:

- The rise of Insulin-like Growth Factor-1, which is correlated with prompt improvement in glucose control appears to portray a pathophysiological role in the initiation and the continuation of this process [22];
- A further suggestion is that changes in blood glucose concentrations could change osmotic pressure, and sequentially influence water retention affecting both the extracellular and intravascular areas in the retina, which could possibly explain the reasons for the conspicuous changes noticed in DR [23];
- The role of the Vascular Endothelial Growth Factor (VEGF) has also been assumed to be a plausible reason where optimisation of glucose control in a hypoxic environment might lead to VEGF upregulation [24], leading to early worsening of DR.

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Despite the explanation that the progression of DR could be due to the rapid lowering of blood glucose, it is important to establish this with longer-term clinical trials. A dedicated ophthalmic trial (FOCUS), is currently ongoing with results expected in 2026, to evaluate the long-term effect of Semaglutide on DR development and progression using validated, standardised ophthalmic assessments [25]. These results will be relevant for newer dual and triple incretin mimetic drugs that will widen the landscape of newer medications for T2DM.

It is prudent to assess and counsel patients to reiterate that the early worsening of pre-existing DR is transient [5, 12], and this should not dissuade clinicians from endeavouring to optimise and tighten glycaemic control given the profound cardiovascular benefits [19, 20]. Nevertheless, it is vital for patients with pre-existing DR who are being commenced on GLP-1RA or planned for bariatric surgery to be evaluated and advised of the possible risk of DR progression and the necessity for closer monitoring during the initial few months and post-operative period [12, 14].

It is therefore crucial to ensure collaborative working between clinicians managing diabetes and the retinal specialists for timely monitoring based on baseline DR status and deciding on appropriate treatment options.

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AUTHOR CONTRIBUTIONS

SJ (Consultant Ophthalmologist) and GIV (Consultant Physician in Diabetes and Endocrinology) contributed equally to this editorial.

COMPETING INTERESTS

The authors declare no competing interests.