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Comprehensive review of glucagon-like peptide 1 receptor agonist treatment on the risk of cardiovascular outcomes and retinopathy as diabetic complications

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Abstract. **Cardiovascular and microvascular disorders are serious complications of diabetes. Intensive glucose control is believed to hinder the pathological progression of these complications. In this review, we focus on the risk of diabetic retinopathy (DR) under intensive treatment with recently introduced glucose-lowering drugs, including glucagon-like peptide 1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter-2 (SGLT2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1RAs are more suitable for patients with diabetes at risk for, or established, cardiovascular complications, while SGLT2 inhibitors are more appropriate for complications of heart failure and chronic renal diseases. Accumulating evidence indicates that GLP-1RAs may provide a greater reduction in the risk of DR in patients with diabetes compared to DPP-4 inhibitors, sulfonylureas, or insulin. GLP-1RAs may be ideal antihyperglycemic drugs with direct benefits for the retina, since GLP-1R can be expressed in photoreceptors. Topical administration of GLP-1RAs induces direct retinal neuroprotection against DR by multiple mechanisms, such as preventing both neurodysfunction and retinal neurodegeneration; relieving the disruption of the blood-retinal barrier and associated vascular leakage, and inhibiting oxidative stress, inflammatory action, and neuronal apoptosis. Hence, it seems reasonable to utilize this strategy to treat patients with diabetes and early-stage DR, rather than exclusively using neuroprotective agents.**

Key Words:
Diabetic retinopathy, Glucagon-like peptide 1 receptor agonists, Blood retina barrier, Neuroprotection, Diabetes mellitus.

Abbreviations

DR, Diabetic retinopathy; GLP-1RAs, glucagon-like peptide 1 receptor agonists; SGLT-2, sodium-glucose co-transporter-2; DPP-4, dipeptidyl peptidase-4; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANVAS, CANaglifozin cardioVascular Assessment Study; DECLARE-TIMI, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; TIMI, thrombolysis in myocardial infarction; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; MACE, major adverse cardiovascular events; ERG, electroretinogram; GCL, ganglion cell layer; STZ, streptozotocin; NPDR, non-proliferative diabetic retinopathy; IGC, intensive glucose control; EDIC, Epidemiology of Diabetes Interventions and Complications; CSME, clinically significant macular edema; ADRRT, advanced DR requiring treatment; BRB, blood retina barrier.

Introduction

In the recent decades, numerous glucose-lowering drugs with a low risk of hypoglycemia have been introduced and studied in the literature. These include glucagon-like peptide 1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter-2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Glucose-lowering drugs present numerous advantages and are widely used as add-on therapies after metformin when the latter is not well tolerated or inefficient, with multiple options for their administration being currently available[1,2]. Additionally, their cardiovascular benefits have been reported in accumu-

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lating studies, thus are accordingly recommended for patients with cardio-renal disease[3].

This narrative review comprehensively summarizes the different effects of relatively new glucose-lowering drugs on the risk of cardiovascular and microvascular outcomes as diabetic complications in Western and Asian populations. Many advantages of GLP-1RAs in reducing the concurrent risk of nonfatal stroke and diabetic retinopathy (DR) in patients with diabetes are introduced, along with a detailed explanation of their multiple mechanisms. Subsequently, the clinical outcomes of intensive treatment and GLP-1RAs on the risk of DR in patients with diabetes are also discussed.

Relationship Between Glucose-Lowering Agents and Adverse Cardiovascular Outcomes

A PROSPERO-registered network meta-analysis (No.: CRD42016050146) recruited fourteen trials of glucose-lowering drugs, including five trials of GLP-1RAs (ELIXA[4], LEADER[5], SUSTAIN-6[6], Harmony Outcomes[7], and EXSCEL[8]), five trials of SGLT-2 inhibitors (EMPA-REG OUTCOME[9], CANVAS[10], CANVAS-R[11], DECLARE-TIMI 58[12], and CREDENCE[13]), and four trials of DPP-4 inhibitors (SAVOR-TIMI 53[14], EXAMINE[15], TECOS[16], and CARMELINA[17]).

Of these trials, the main endpoint of major adverse cardiovascular events (MACE) was defined as the manifold of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke[3]. In addition, cardiovascular mortality, all-cause mortality, hospitalization for heart failure, and renal composite outcomes were also analyzed. Using a random-effects model, the network meta-analysis indicated that the risk profile of DPP-4 inhibitors was the same as that of the placebo in all outcomes. Distinctly, both SGLT-2 inhibitors and GLP-1RAs significantly decreased the risk of MACE, hospitalization for heart failure, all-cause mortality, and renal composite outcomes compared to the placebo. The effect of SGLT-2 inhibitors on reducing hospitalization for heart failure and the renal composite outcome was markedly better than that of GLP-1RAs. In addition, only administration of GLP-1RAs resulted in lower nonfatal strokes and nonfatal myocardial infarction than those receiving the placebo. P-rank scores confirmed that GLP-1RAs reduced the risk of nonfatal stroke by 80.6%.

Similar findings were also supported by other critical reviews and clinical trials[18-21]; thus, it was inferred that GLP-1RAs could be considered in patients with diabetes at a high risk of, or with established, cardiovascular diseases, while SGLT2 inhibitors could be recommended for patients with heart failure or chronic kidney diseases.

Another systematic review[22] summarized the hazard ratios of MACE in Asian diabetic populations. In this systematic review and meta-analysis of seven trials[22], those who were administered GLP-1RAs (n=4,298) showed a significant reduction in MACE compared to those receiving the placebo. However, there was no significant reduction in MACE in patients administered SGLT2 inhibitors (n=4,987). Of note, Dr. Bernard Man Yung Cheung declared that the factors that decisively influenced these results needed further evaluation[62].

In patients with diabetes and concurrent obesity[23], a systematic review recruiting 12 trials (n=102728) showed that GLP-1RAs led to a significant reduction in the risk of MACE when compared to the placebo, whereas SGLT2 inhibitors only resulted in a tendency. Thus, it suggested that only GLP-1RAs were more effective at preventing MACE than the placebo in patients with type 2 diabetes mellitus complicated by obesity.

Differential Effects of Glucose-Lowering Drugs on the Risk of DR

Eye disorders, including DR, vitreous hemorrhage, age-related macular degeneration, retinal detachment, cataracts, and glaucoma, are critical complications in patients with diabetes[24]. As microvascular-related DR is the most prevalent eye disease in patients with diabetes, we have discussed this retinal disorder in the following text.

Retinoprotective studies[25] of SGLT2 and DPP-4 inhibitors have mainly focused on rodents. In a systematic review[26] of nine studies (n=39,982) on SGLT2 inhibitor treatment in patients with diabetes, there were 624 DR events in 1,414 total ocular events. SGLT2 inhibition did not change the risk of total ocular events or retinopathy[26]. In addition, the odds ratio of eye amputation (11 trials; n=93,922) when compared with the placebo was increased with SGLT2 inhibitor canagliflozin and reduced with GLP-1RA liraglutide[21].

The related clinical data of DPP-4 inhibitors on DR are also limited. In a meta-analysis study[21], the odds ratio of DR (38 trials; n=25,151) increased with sulfonylureas when compared to the placebo. DPP-4 inhibitors are associated with a remarkable

increase in DR risk in a pairwise meta-analysis [OR, 1.27 (1.05-1.53)][27]. In another study[24], the adjusted hazard ratio of DPP4 inhibitors when compared to sulfonylureas (n=39,292 and 87,073) and thiazolidinediones (n=51,410 and 22,231) for advanced DR requiring treatment (ADRRT) was 0.91 [0.79-1.04] or 0.91 [0.75-1.11]. Contrastingly, the adjusted hazard ratio of GLP-1RAs compared to thiazolidinediones (n=10,355 and 27,345) for ADRRT was 0.75 [0.53-1.06], which was related to the trend of risk reduction. Furthermore, the risk reduction of GLP-1RAs was significant when compared to long-acting insulin (n=9,561 and 82,849).

Overall, the aforementioned studies have inferred that GLP-1RAs result in a greater reduction in the risk of DR in patients with diabetes compared with DPP4 inhibitors, sulfonylureas, or insulin, which presented a higher risk of ADRRT or DR.

Underlying Mechanisms of GLP-1RAs Against DR Based on Experimental Studies

It is well known that DR affects both neural and vascular endothelial cells of the retina, as well as neurovascular communication. Many emerging therapies have been considered to modulate vascular biology against neuroretinal dysfunction, as retinal microvascular lesions are recognized as the hallmarks of DR and as a major standard for assessing disease progression (Table I)[28]. GLP-1RAs are expected to possess direct benefits for the retina, since GLP-1R can be expressed in photoreceptors[29]. GLP-1R is also considered the main therapeutic target for neurovascular disorders and exerts neuroprotective effects in both the central and peripheral nervous systems[30,31]. GLP-1 is expressed in the human retina mainly in the ganglion cell layer (GCL), where it is downregulated in diabetes. In contrast, diabetic disorders did not affect the expression of GLP-1R in either the retinal pigment epithelium or neuroretina[29]. Intravitreal injections of GLP-1RA exendin-4 inhibited electroretinogram (ERG) abnormalities and morphological abnormalities after glial activation and neural apoptosis in streptozotocin (STZ)-induced diabetic rats[32,33] and Goto-Kakizaki rats[34]. In addition to invasive administration, topical administration of GLP-1RAs also prevented both neurodysfunction and retinal neurodegeneration in db/db mice[29]. GLP-1RAs not only inhibited reactive gliosis but also restored neuronal cells in db/db mice to show a neurogenic effect, without influencing blood glucose levels[35].

The main neuroprotective mechanisms of GLP-1RAs are conferred as follows (Figure 1)[36]. (1) Through their anti-inflammatory action, GLP-1RAs can decrease NF-κB, inflammasomes and key proinflammatory factors such as IL-1β and IL-6[29,35]. (2) They also inhibit excitotoxicity by reducing glutamate-mediated neuronal death by preventing GLAST downregulation in diabetic rats[29,32,33]. (3) GLP-1RAs possess anti-apoptotic activity as they prevent the hyperglycemia-induced upregulation of apoptosis-related proteins (FasL, caspase 8, P53/p-P53, Bax) and the downregulation of survival pathways (Bcl-xL and Bcl-2) in the neuroretina[29,34,35]. In addition, the promotion of GLP-1RAs on the p-AKT/AKT ratio and the signaling pathway Akt/GSK3b/β-catenin was proved to contribute to neural survival[29,35]. (4) Furthermore, these agents modulate antioxidant stress by enhancing the expression of glutathione reductase, glutathione peroxidase, CuZnSOD, and MnSOD in diabetic retinas against oxidative stress[37]. In addition, intravitreal injections of exendin-4 could reduce retinal cell death and ROS generation by upregulating Sirt1 and Sirt3 expres-

Table I. Main mechanisms of the most representative topical treatments (eye drops) for DR in diabetic rodents.

Treatment	Main mechanisms			
	Glial-mediated inflammation	Neuronal apoptosis	Oxidative stress	Vascular permeability
Pigment epithelium-derived factor	√	√		√
Somatostatin	√	√		
GLP-1RAs	√	√	√	√
DPP-4 inhibitors	√	√	√	√
Bosentan	√	√		√
Suppressors of cytokine signaling-1	√	√		√

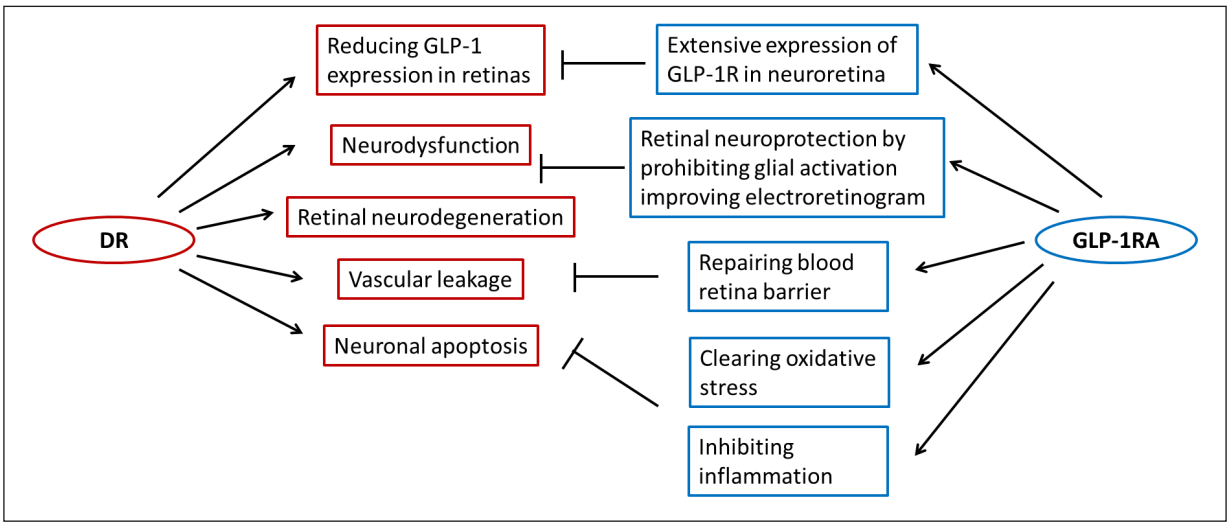

Figure 1. The underlying mechanisms of GLP-1RAs against DR.

sion in the retinas of STZ-induced diabetic rats[38]. (5) Finally, they exhibit neuroprotection by exerting microvascular protection on vascular permeability. This can be done by either preventing the diabetes-induced downregulation of tight junction proteins (i.e., claudin-5 and occludin)[39], or by downregulating essential mediators related to vascular permeability, such as vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) *via* AKT/PKB pathways[29,39]. These agents can also prohibit the overexpression of pro-inflammatory cytokines (i.e., IL-1β, TNF-α), which contribute to endothelial damage[29,35].

Topical administration of GLP-1RAs relieved the disruption of the blood-retinal barrier (BRB) and associated vascular leakage, and all these activities of GLP-1RAs adjusted the vascular impairment-related pathways to stop DR progression (Figure 1)[36]. Further clinical studies are warranted to confirm the directive effectiveness of GLP-1RAs by topical administration in the early stages of DR.

Clinical Paradox of GLP-1RAs on the Risk of DR

Short-Term Effects of GLP-1RAs with High Risk of DR Outcomes

In the SUSTAIN6 and LEADER trials[5,6], both semaglutide and liraglutide showed macrovascular benefits. However, both studies[5,6] observed an obvious increase in DR-associated events in GLP-1RA-treated patients. The Diabetes Control and Complications Trial[40] (DCCT) also reported a similar paradox at the early stages of DR deterioration. In the DCCT trial[41], the majority of patients experiencing this phenomenon did not show sustained effects or loss of vision. Instead, a retrospective study[42] of exenatide (n=165) with a median treatment period of 10 months indicated an association between exenatide treatment and transient worsening of DR; however, DR in 80% of these patients improved with continued treatment.

In an insulin-treated trial[43], worsening retinopathy might be followed by a rapid lowering of HbA1c from an initial level of 11.9% to 7.1%. This was explained by a significant reduction in retinal blood flow when blood glucose was reduced too quickly from 15 to 8 mmol/L, which might induce retinal ischemia and promote retinopathy. In addition, a sudden increase in insulin intake might induce an increase in insulin-like growth factor 1 (IGF-1), which is associated with worsening retinopathy[44]. Hence, further trials are needed to clarify the negative effect of GLP-1RA on retinopathy[45].

Thirty-five of 113 trials were included in a meta-analysis to report the risk of worsening retinopathy[46]. Overall, GLP1-RAs were not associated with a significant increase in the incidence of retinopathy. In subgroup analyses, GLP1-RAs were associated with a lower risk of retinopathy than sulfonylureas. Only nine trials reported the incidence of macular edema with no signs of increased risk. For different GLP-1RAs compared with other comparators, the MH-OR was as follows [albiglutide in eight trials[63-70]: 1.04 (0.77-

1.41), p=0.79; dulaglutide in six trials[71-76]: 0.62 (0.24-1.59), p=0.32; liraglutide in 12 trials[77-88]: 0.70 (0.49-0.99), p=0.043; lixisenatide in seven trials[89-95]: 0.89 (0.33-2.39), p=0.81; semaglutide in one trial[96]: 1.75 (1.10-2.78), p=0.018].

To further confirm the high risk of semaglutide on DR outcomes[47], another meta-analysis recruited two semaglutide trials (SUSTAIN-6 and PIONEER-6[48]) showed different results. These two studies[6,48] (SUSTAIN-6 and PIONEER-6) were quite different from others as their DR findings were based on fundoscopy/fundus photography, followed by the application of robust methods to assess DR, while others were based on standard adverse-events reporting only[49]. The main difference between the studies[6,48] (SUSTAIN-6 and PIONEER-6) was that the latter excluded people at high risk for DR or those with advanced non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), which might partially account for their distinct results. Moreover, the effect of semaglutide on HbA1c reduction was greater than that of other GLP-1RAs. Meta-regression showed a significant negative association between the incidence of retinopathy and average reduction in HbA1c, but no significant relationship was observed for systolic blood pressure or weight[47]. A retrospective analysis[42] of patients treated with exenatide for more than six months also indicated that DR progression was associated with greater reductions in HbA1c when compared to HbA1c levels, and changed little with placebo treatment (-0.23%, 0.10%, and -0.13% for placebo versus GLP-1RAs, DPP-4 inhibitors, and SGLT-2 inhibitors, respectively). Among these new antihyperglycemic agents, GLP-1RAs are the most effective for weight loss and HbA1c reduction[50]. Therefore, excessive glycemic control and HbA1c decline are other important risk factors for DR.

In brief, early worsening of DR was also observed in trials[51] treated with insulin and other agents, including a few GLP-1RAs, demonstrating a glycemia-related mechanism. However, other possible mechanisms should be considered to explain early worsening in patients with diabetes. The potential risk factors for DR outcomes were summarized as pre-existing maculopathy or worse retinopathy, higher baseline HbA1c, and long-standing severe hyperglycemia[52,53]. Our experience suggests that annual retinal screening may be insufficient and that early repeat retinal screening should be considered in all patients with a significant decrease in HbA1c levels.

Long-Term Benefits of Intensive Treatment and GLP-1RA on DR Outcomes

In a meta-analysis of intensive glucose control (IGC) for a median of 5.0 years, 795 primary eye events were recorded during the follow-up period[54]. IGC was associated with a lower risk of primary eye outcome. The effects on the primary eye outcome emerged in the fifth year of follow-up and were primarily driven by a reduced risk of progression of retinopathy (≥3 steps on the Early Treatment of DR Study Severity Scale). IGC also reduces the risk of secondary eye outcomes, such as the need for cataract extraction.

In another IGC trial[55] (DCCT), 726 cases with no DR (primary prevention cohort) and 715 cases with mild DR (secondary intervention cohort) were included and followed for a mean of 6.5 years. IGC resulted in a lower risk of DR by 76% and slowed progression of DR by 54% compared with the placebo. Especially, severe retinal outcomes and the development of neovascularization of the optic disk or elsewhere reduced by 50% and 48% in the IGC treatment, respectively. These beneficial effects were evident and continued to extend throughout the study from the fourth year of follow-up. In addition to the beneficial outcomes of DR progression, IGC has also been reported to benefit from risk reductions in the development of PDR (47%), onset of macular edema (26%), and application of laser therapy (56%)[56]. In the DCCT trial[57,58], it was inferred that the rate of retinopathy progression was highly associated with HbA1c, with each 10% reduction in HbA1c followed by a 44% decreased risk of DR progression. Even in the DCCT trial, the phenomenon "early worsening" occurred within one year, as well in the IGC treatment, compared to placebo, which underlies the crossing of cumulative incidence of DR progression curves for IGC and placebo between two and three years in the secondary intervention cohort[55]. Overall, the limited early worsening and long-term benefits indicated that IGC treatment was strongly supported for most patients with diabetes.

In the EDIC study[59], IGC benefit on secondary eye outcomes at years 8-10 of follow-up led to a significant risk reduction in the development of DR (63%, p=0.0001) and PDR (56%, p=0.001) compared to placebo. For other end-points of eye outcomes, odds reduction at EDIC year 10 included onset of NPDR or worse (58%, p=0.001), onset of PDR or worse (58%, p=0.001), and onset of clinically significant macular edema (CSME) (38%,

p=0.009), among others. Thus, it can be inferred that IGC benefits for the cumulative incidence of major eye disease endpoints (PDR, CSME, or development of blindness) was strong clinical evidence, in relation to increasing IGC duration, to delay the onset and progression of DR.

In addition to total IGC[40,60], GLP-1RAs also showed similar effects. Compared to IGC containing two or more glucose-lowering drugs, GLP-1RAs did not contribute to a higher risk of incident DR [HR, 1.00 (0.85-1.17)][61]. However, compared with insulin, GLP-1RAs were markedly associated with a 33% reduction in the risk of DR [HR, 0.67 (0.51-0.90)] after more than one year of treatment.

Perspectives on DR Prevention in Diabetic Treatments

The following short-term outcomes can be concluded from animal studies: (1) that intensive treatment with anti-hyperglycemic agents might induce the early worsening of DR by several underlying mechanisms. (2) GLP-1RAs might reduce the risk of DR outcomes in patients with diabetes compared with DPP4 inhibitors, sulfonylureas, or insulin, which presented a higher risk of ADRRT or DR. As a long-term outcome, (1) intensive treatment with anti-hyperglycemic agents could effectively delay the onset and progression of DR and other eye disorders. (2) Compared with insulin in long-term duration, GLP-1RAs were markedly associated with a lower risk of DR. 5) The topical administration of GLP-1RAs induced direct retinal neuroprotection against DR by multiple mechanisms, such as preventing both neurodysfunction and retinal neurodegeneration, relieving the disruption of the BRB and associated vascular leakage, and also inhibiting oxidative stress, inflammatory action, and neuronal apoptosis. Hence, it seems reasonable to utilize this holistic strategy to treat the early stages of DR rather than exclusively using neuroprotective agents. GLP-1RAs may be ideal antihyperglycemic drugs, since GLP-1R can be expressed in photoreceptors. Furthermore, topical administration of these agents provided direct retinal neuroprotection in rodent diabetes models.

Conclusions

To the best of our knowledge, the intricate relationship between diabetes-induced retinal neurodegeneration and microvascular diseases remains unclear[36]. GLP-1RAs could be recommended as a targeted and more efficient strategy in the early stages of DR. The possibility of applying topical therapy for the early stages of DR may provide a new and safe scenario; however, multi-center clinical trials are required for further confirmation. In addition, more detailed phenotyping and stratification of patients with diabetes are necessary to analyze their potential DR risk.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

H. Liu: conceptualization, writing-review and editing; J.-T. Zhang: conceptualization, writing-review and editing; S.-H. Xin and W.-N. Ren: writing-review and editing; Q.-K. Lu, conceptualization, supervision.

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