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REVIEW ARTICLE

New anti-hyperglycaemic agents for type 2 diabetes and their effects on diabetic retinopathy

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Abstract

There has been an increase in the range of non-insulin anti-hyperglycaemic agents used to treat type 2 diabetes. With the globally rising rates of type 2 diabetes and complications such as diabetic retinopathy, it is important for ophthalmologists to be aware of these new agents and their impacts on diabetic retinopathy and diabetic macular oedema. We conducted a review of the literature to determine if there were any beneficial or harmful effects of the currently used anti-hyperglycaemic agents on diabetic retinopathy or diabetic macular oedema. Our review of the current literature found that apart from thiazolidinediones, anti-hyperglycaemic agents have been reported to have beneficial or neutral effects on diabetic eye complications. Thiazolidinediones (pioglitazone is the only one currently available) have been linked to incident or worsening diabetic macular oedema, although the rate is believed to be low. Glucagon-like peptide 1 (GLP1) agonists (incretins) in general are beneficial except semaglutide which is associated with increased rates of diabetic retinopathy complications. These results have implications for selection of anti-hyperglycaemic agents for patients with diabetic retinopathy or macular oedema. Further studies need to be conducted to identify if reported beneficial effects are independent of the impact of glycaemic control. Early worsening of retinopathy with tight glycaemic control should also be noted in interpretation of future studies.

Introduction

Pharmacotherapy for the management of diabetes mellitus has had enormous impact on glycaemic control and prevention of progression to complications of diabetes. Insulin was the first anti-diabetic pharmacotherapy developed from bovine extracts by Banting and Best in 1922 [1]. Since then, oral anti-hyperglycaemic agents have been developed for the management of type 2 diabetes (T2D), the first of which were the sulfonylureas discovered in the 1940s including tolbutamide, chlorpropamide and acetohexamide [2]. Though the effects of biguanides such as metformin were discovered in the 1920s, they were only available for use in 1959, and were not approved by the US Food and Drug Administration until 1994 due to increased incidence of lactic acidosis.

Over the last two decades, several new classes of anti-hyperglycaemic agents have become available. These include incretins (glucagon-like peptide-1 receptor agonists), dipeptidyl peptidase 4 (DPP4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, thiazolidinediones and alpha-glucosidase inhibitors. These agents may be used as monotherapy or in combination with more established agents and insulin. Diabetic retinopathy (DR) remains a major cause of blindness and visual morbidity and unlike most other causes, is a systemic condition requiring multidisciplinary approach in its management. This review will summarise the new anti-hyperglycaemic agents, their mechanisms of action, indications and contraindications, and any direct effects on DR independent of glycaemic control.

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Methods

We conducted a Medline and PubMed search of published studies involving anti-hyperglycaemic agents and diabetic retinopathy from 1980 to Dec 2018. The search strategy terms were "diabetic retinopathy", "macular oedema", "glucagon-like peptide 1", "dipeptidyl-peptidase IV inhibitors", "sodium-glucose transporter 2", "glucoside hydrolase inhibitors OR acarbose", "thiazolidinediones", "sulfonylurea compounds", "metformin OR biguanides". We identified 173 abstracts for review and retrieved 58 articles (Table 1). Full articles were retrieved if the abstract provided either clinical or laboratory data on the effects of anti-hyperglycaemic agents on retinopathy. We grouped articles by type, i.e., experimental research, population-based studies, review articles and case reports. Information about the mechanism of action, indications and contraindications of the oral hyperglycaemic agents was obtained from the MIMS medical database. The FDA database was cross-referenced to provide additional information.

Results

Relationship with retinopathy

Glucagon-like peptide 1 (GLP-1) agonists

GLP-1 agonists belong to a class of medications called incretins. Incretins are metabolic hormones secreted by intestinal cells in response to nutrient intake that stimulates pancreatic β-cell insulin production and impairs glucagon secretion, slows gastric emptying to reduce glucose absorption, and reduces appetite [3]. Their advantages over older oral anti-hyperglycaemic agents include lower risk of hypoglycaemia, moderate weight loss and the optional convenience of once-weekly dosing [4].

These agents have had mixed associations with DR (Table 2). An interventional case study reported complete regression of DME and improved visual acuity from 20/80 to 20/63 after 1 month of exenatide use [5]. However, another report noted dramatic deterioration in DR from background retinopathy to bilateral PDR and DME with reductions in glycated haemoglobin (HbA1c) from 11.9 to 4.8% after 4 months of exenatide treatment [6]. A retrospective analysis of 165 patients treated with exenatide for 10 months found it was associated with transient worsening of DR (with 30% of patients developing or worsening retinopathy with significant improvements in glycaemic control), but in 80% of these DR improved with continued treatment [7, 8]. Adverse findings on retinopathy were seen in a randomised control trial of 3297 patients looking at the effects of the GLP-1 agonist semaglutide on cardiovascular outcomes (SUSTAIN 6) [9]. This trial found DR complications occurred in 50 patients (3.0%) taking semaglutide compared with 29 (1.8%) in the placebo group (HR 1.76; 95% CI 1.11–2.78; $p = 0.02$). These reported deteriorations may, however, be related to early worsening of DR with rapid improvement of HbA1c [10], imbalance in baseline DR or short follow-up [11]. Hence further studies are needed to confirm the effects of GLP-1 agonists on retinopathy [12], in particular, if this is a group effect or related to semaglutide alone. A recent network meta-analysis found GLP-1 agonists appear to reduce the incidence and progression of nephropathy and to have no specific effect on retinopathy—with the notable exception of semaglutide, which may negatively impact the retina [13].

Experimental research has suggested potential protective effects of GLP-1 agonists on the diabetic retina through improved blood retina barrier (BRB) function and reduced neuronal apoptosis [14]. Intravitreal administration of an Exendin-4-analogue in rats is suggested to protect the retina by reducing glutamate levels through upregulating GLP-1 receptors and glutamate-aspartate transporter (GLAST) [15]. Furthermore, Exendin-4, a long-acting GLP-1 agonist, showed neuroprotective effects in early experimental DR by decreasing placental growth factor and intercellular adhesion molecule-1 expression and maintaining integrity of the BRB [16]. Systemic administration of liraglutide prevented retinal neurodegeneration via reduction of extracellular glutamate and increased pro-survival signalling pathways. Similar neuroprotective effects were seen using lixisenatide and exenatide independent of glucose reduction, thus suggesting GLP-1 receptor activation itself had retinal neuroprotective effects [17]. In summary, there is clinical and experimental evidence that GLP-1 agonists, with the exception of semaglutide, is likely beneficial for DR. It remains unclear if the adverse DR effects of semaglutide are related to early worsening or other factors, or represents a possible toxic effect on the retina.

Table 1 Abstracts identified and articles reviewed

Class of anti-hyperglycaemic agents	Number of search results	Articles reviewed
GLP-1 agonists	15	8
DPP4-inhibitors	6	3
SGLT-2 inhibitors	2	2
Alpha-glucosidase inhibitors	3	3
Thiazolidinediones	64	28
Sulfonylureas	51	7
Biguanides	24	4
Combinations	8	3

Table 2 List of oral hypoglycaemic agents, indications, mechanisms or action and relationship with diabetic retinopathy

Generic name	Administration and dosage	Mechanism of action	Indications, common adverse effects and contraindications	Relationship with diabetic retinopathy
Glucagon-like peptide 1 agonists (incretins) Exenatide (long and short acting) Lixisenatide Dulaglutide Liraglutide Semaglutide	Injection with or just before meals 5–10 mcg BD Once weekly or BD 10–20 mcg daily 0.75–1.5 mg once weekly 0.6–1.8 mg daily 0.5–1.0 mg weekly	- Stimulate pancreatic islet β-cell insulin production - Impair glucagon secretion - Slow gastric emptying and hence reduce glucose absorption, appetite and food intake	*Indications*: Adjunct to sulfonylurea or metformin (+/− sulfonylurea or basal insulin) in T2D *Common adverse effects*: GI side effects (nausea, vomiting, diarrhoea) *CI*: end stage renal disease or severe renal impairment; severe GI disease	Screening study • GLP-1 receptor agonist therapy associated with transient worsening of DR which improved with continued treatment [7, 8] Case reports • Complete regression of DME after injection with exenatide [5] • Dramatic deterioration in DR from background retinopathy to bilateral PDR and DME with reductions in HbA1c after exenatide treatment [6] Clinical trial • Rates of retinopathy complications (vitreous haemorrhage, blindness, or conditions requiring intravitreal treatment or photocoagulation) significantly higher in patients taking semaglutide (SUSTAIN 6) [9] Experimental research • Systemic administration of liraglutide prevents retinal neurodegeneration [17] • Exendin-4 (E4) shows neuroprotective effects in early experimental DR by maintaining BRB integrity [16] • Intravitreal administration of E4 analogue can protect the retina functionally and morphologically from diabetes [15]
DPP4 inhibitors (gliptins) Sitagliptin Vildagliptin Linagliptin Saxagliptin Alogliptin	Oral tablet with or without food 50 mg BD 50 mg BD 5 mg daily 5 mg daily 25 mg daily	Inhibition of DPP4 which is responsible for the breakdown of incretins (GLP-1 and GIP), thus enhancing their actions (see above)	*Indications*: For T2D monotherapy when metformin unsuitable; dual combination with metformin, sulfonylurea or thiazolidinedione; triple combination with metformin and sulfonylurea; add-on combination therapy with insulin (+/− metformin) *Common*: Hypoglycaemia if in combination therapy Reported URTI, GI upset, headache, skin irritation	Case reports • Retrospective chart review showed DPP4 inhibitors may reduce rates of DR progression [21] • However, use of gliptins <12 months may be associated with early worsening of DR [22] Experimental research • Sitagliptin may delay or prevent DR by preventing nitrosative (reactive nitrogen and oxygen species) stress, inflammation and apoptosis in retinal cells, and preventing increase in BRB permeability [18, 19] • Vildagliptin significantly inhibited increase in body weight and decreased average fasting glucose in rats, and inhibited inflammatory and thrombogenic reactions in the retinas of

Table 2 (continued)

Generic name	Administration and dosage	Mechanism of action	Indications, common adverse effects and contraindications	Relationship with diabetic retinopathy
				obese T2D rats [20] • Linagliptin has a neuroprotective effect on the microvasculature of the diabetic retina [67]
SGLT2 Inhibitors Dapagliflozin Empagliflozin Canagliflozin Ipragliflozin	Oral tablet with/without food 10mg daily 10–25 mg daily 100–300 mg daily 50 mg daily	Reversible, competitive inhibitor of sodium-glucose cotransporter-2 (SGLT2) that reduces renal glucose reabsorption, leading to urinary glucose excretion.	*Indications*: For T2D as monotherapy when metformin not tolerated; initial combination with metformin when diet, exercise and poor response to metformin expected; add-on combination with other AHG when diet/exercise/meds inadequate *Common*: UTI, genital infection, hypoglycaemia *CI*: Renal function eGFR <60 mL/min/1.73 m^2	Case reports • Marked regression of DME after 16 weeks of ipragliflozin [26] Experimental research • Control of hyperglycaemia with ipragliflozin slows the progression of retinopathy in spontaneously diabetic Torii fatty rats [25]
Oral tablet immediately before meals or chew with food 50 mg OD–200 mg TDS Average dose 100 mg TDS	Interferes with digestion of complex carbohydrates by alpha-glucosidase (intestinal enzyme) and slows rate of absorption of polysaccharides in proximal small intestine	*Indication*: adjunct to diet/exercise for T2D with inadequate control by diet/AHG agents *Common adverse effects*: Unsociable gastric side effects (flatulence, diarrhoea, abdominal discomfort and bloating) *CI*: severe renal impairment; malabsorption GI conditions; partial intestinal obstruction	Experimental research Acarbose Prevented basement membrane thickening in retinal capillaries [29] [68] • Prevented decrease in retinal blood flow rates after diabetes induction in rats and reduced increase in blood glucose levels [69] • Related to decreased diabetic cataract development through reduced aldose reductase activity and increased lenticular protein and glutathione levels [70]	
Thiazolidinediones Pioglitazone	Once daily with/without food 15–45 mg daily	Peroxisome Proliferator Activator Receptor (PPAR-gamma) agonist: activate genes that regulate lipid and glucose metabolism, improves sensitivity to insulin in muscle and adipose, inhibits hepatic gluconeogenesis	*Indication*: T2D inadequately controlled by diet and exercise (+/− insulin or metformin and/or sulfonylurea) *Common adverse effects*: weight gain, fluid retention (ankle oedema), cardiac failure, bone fractures *CI*: cardiac failure; may be associated with adverse cardiovascular effects	Population-based studies and database reviews *Positive effects* Rosiglitazone use associated with a 59% relative risk reduction in progression to PDR over 3 years and lower rates of visual acuity loss [45] • TZD use associated with decreased mediators of endothelial dysfunction, reduced markers of inflammation and increased markers of angiogenic activity [47] • Inconclusive or no association with DME [48–51] *Negative effects* • TZD repeatedly associated with increased risk of DME [31, 40, 41, 43, 44] Case studies [39, 71–73]

Table 2 (continued)

Generic name	Administration and dosage	Mechanism of action	Indications, common adverse effects and contraindications	Relationship with diabetic retinopathy
				• TZD associated with increased frequency of reporting of MI and fractures [44] • Rosiglitazone use associated with increased rates of laser treatment and vitrectomy [46] Experimental research • Pioglitazone normalised insulin signalling, restored IGFBP-3 levels independent of TNF-alpha and elicited dilatation of retinal arterioles [32–34] • Rosiglitazone attenuated diabetes-induced apoptosis in retinal neurons [35]. • TZDs attenuated pathological microvessel formation and inhibited retinal leukostasis and retinal leakage [37, 38]
Sulfonylureas Gliclazide Glimepiride Glibenclamide Glipizide Tolbutamide	Oral tablet with meals 30–120 mg daily 1–4 mg daily 5–15 mg daily 5–15 mg daily 0.5–1.5 g daily	Insulin secretagogue: binds to sulfonylurea receptors in beta cells, leading to closing of K_{ATP} channels and insulin release	*Indications*: T2D not controlled by diet alone *Common adverse effects*: hypoglycaemia (caution with elderly patients); weight gain common *CI*: severe renal/hepatic insufficiency, treatment with miconazole	Population-based studies • Gliclazide seems to have additional properties compared with other sulfonylurea drugs in preventing deterioration of DR, and particularly in preventing progression to PDR [55] • No action of gliclazide on diabetic microangiopathy, independent of its hypoglycaemic action [56] • Gliclazide might be more effective than glibenclamide with respect to either improving diabetic retinopathy or preventing its progression [54]
Biguanides Metformin (immediate release or prolonged release)	Oral tablet with meals 500 mg–3 g daily	- Lowers fasting plasma insulin concentrations - Enhances insulin sensitivity - Inhibit hepatic glucose output - Action on AMP-kinase - Increased glucose uptake in peripheral tissues [74]	*Indication*: first line therapy for T2D especially for obese patients *Common adverse effects*: GI disturbances when starting therapy (diarrhoea, nausea, vomiting, abdominal pain, loss of appetite); taste disturbance *Serious adverse effect*: lactic acidosis *CI*: renal failure or conditions causing tissue hypoxia and increased lactate production, e.g., cardiac/hepatic failure, recent MI, PE, shock, pancreatitis, sepsis, alcoholism)	Case reports • Retrospective chart reviews suggest metformin may have protective effects on DR [58, 59]

AHG anti-hyperglycaemic, *AHG* anti-hyperglycaemic, *BD* twice daily, *BRB* blood retinal barrier, *CI* contraindications, *DME* diabetic macular oedema, *DPP4* dipeptidyl peptidase 4, *DR* diabetic retinopathy, *GI* gastrointestinal, *MI* myocardial infarction, *PDR* proliferative diabetic retinopathy, *PE* pulmonary embolism, *T2D* type 2 diabetes, *TDS* three times daily, *TNF-α* tumour necrosis factor alpha, *TZD* thiazolidinediones, *URTI* upper respiratory tract infection, *UTI* urinary tract infection

DPP4 inhibitors

DPP4 is an enzyme responsible for the rapid degradation of GLP-1. Consequently, DPP4-inhibitors have been developed to delay the breakdown of incretins, thus prolonging their action. Advantages of DPP4-inhibitors over GLP-1 agonists include oral administration rather than injection, as well as avoiding the side effects of nausea associated with GLP-1 agonist use [3].

Experimental research on DPP4-inhibitors has indicated protective effects on DR (Table 2). This is suggested to occur in sitagliptin use by preventing nitrosative stress, inflammation and apoptosis in retinal cells, and preventing increase in BRB permeability [18, 19]. Vildagliptin has demonstrated beneficial metabolic effects by inhibiting body weight increase in addition to its anti-hyperglycaemic, anti-inflammatory and anti-thrombogenic effects in the retinas of obese T2D rats [20]. A retrospective chart review showed DPP4 inhibitors may reduce rates of DR progression [21] However, use of DPP4 inhibitors <12 months may be associated with early worsening of DR [22].

SGLT-2 inhibitors

SGLT-2 inhibitors are a new class of anti-hyperglycaemic medication that cause reversible, competitive inhibition of the SGLT-2 in the renal proximal tubule, resulting in urinary glucose excretion. Its advantages include acting independently of insulin, weight-lowering and non-association with risk of hypoglycaemia, while offering similar HbA1c control as DPP4-inhibitors, thiazolidinediones and sulfonylureas when added to metformin [23, 24].

Experimental research in spontaneously diabetic Torii fatty rats demonstrated that control of hyperglycaemia by a SGLT-2 inhibitor ipragliflozin slowed progression of diabetic microvascular complications of nephropathy, neuropathy and retinopathy (Table 2). This was demonstrated for retinopathy, slower progression of cataract formation and reduced changes on electroretinography [25]. The effects of SGLT-2 inhibitors on DR in humans have not been well studied. A case report found marked regression of DME after 16 weeks of ipragliflozin [26]. Unfortunately, none of the recent large clinical trials looking at the cardiovascular safety of SGLT-2 inhibitors included development or progression of DR as an outcome. Further studies in this area are warranted.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose inhibit alpha-glucosidase enzymes in the proximal small intestine to prolong carbohydrate digestion time and thus reduce glucose absorption. They are, however, associated with unsociable gastrointestinal side effects in 20% of patients, which may limit their usage [27].

Creutzfeldt reviewed 18 animal studies examining effects of acarbose on long-term diabetic complications [28]. With regards to retinopathy, acarbose treatment was successful in reducing or preventing diabetic changes in the retina and lens, due to improvements in glycaemic control. This occurred through prevention of basement membrane thickening in retinal capillaries, decreased retinal blood flow rates, reduced aldose reductase activity by over 50% and increasing lenticular protein and glutathione levels (helping to prevent cataract formation). Yang et al. affirmed the reduction in basement membrane thickening and reduced retinopathy development in Zucker Diabetic Fatty rats, but attributed the effect to reduction of hyperglycaemia [29].

Thiazolidinediones

Thiazolidinediones (TZD) are peroxisome proliferator-activated receptor agonists that alter transcription of genes regulating glucose and lipid metabolism and reduce insulin resistance in adipose tissue, muscle and liver [30]. They have been equivocally linked with increased risk of developing or worsening DME, potentially by increasing endothelial cell permeability and increasing systemic VEGF levels [31] (Table 2). Experimental research has noted mechanisms by which TZDs may protect retinal vasculature. Pioglitazone normalised insulin signalling by reducing TNF-alpha and suppressor-of-cytokine-signalling-3 (SOCS3) levels, restored insulin-growth-factor-binding-protein-3 (IGFBP-3) levels and elicited dilatation of retinal arterioles [32–34]. Rosiglitazone attenuated diabetes-induced apoptosis in retinal neurons [35], but did not inhibit basement membrane thickening or block increases in VEGF in ocular fluid [36]. TZDs may also attenuate pathological retinal microvessel formation by modulating TNF-alpha production [37] and inhibit retinal leukostasis and leakage in rats [38].

A 2005 case study first reported development of reversible DME with vision loss in a patient taking rosiglitazone [39]. This was followed by Ryan et al. who carried out a non-controlled, non-randomised, retrospective chart review of 30 T2D patients using a TZD and with CSME and lower limb peripheral oedema that had increased since starting TZDs [31]. DME slowly resolved following cessation of TZD and many required laser therapy, hence the study concluded with the impression that fluid retention associated with TZD use could aggravate DME in susceptible patients.

Since then, similar findings have been observed in a cohort study of 996 new cases of DME from the Diabetes Case Identification Database in which TZD users were more likely to develop DME, even after adjusting for age, glycaemic control and insulin use [40]. The largest and most

recent study was a retrospective cohort study of 103,368 patients using The Health Improvement Network database which found an increased risk of DME in TZD users at 1 year (OR 2.3) that persisted at 10-year follow-up [41]. However, limitations of the study including under-ascertainment of early-onset DME and not controlling for confounding factors mean clear conclusions from these findings are somewhat indeterminate [42]. Concerns have also been raised from drug safety reviews, as a 2008 review of TZD safety profiles found DME was a common side effect [43]. A 2012 review of adverse drug reactions in the US FDA Adverse Event Reporting system found significantly more frequent reports of MI, fractures and DME associated with TZD compared with other anti-hyperglycaemic agents, and rosiglitazone use was associated with DME (ROR 3.88) [44].

Other studies have examined the effects of TZDs on retinopathy, with possible adverse results. A longitudinal medical record review found 59% relative risk reduction in progression to PDR over 3 years and lower rates of visual acuity loss with rosiglitazone [45]. A community-based study of 1304 patients on rosiglitazone vs 5385 control patients found rosiglitazone use was associated with increased rates of laser treatment and vitrectomy after a median 3.6 years follow-up [46]. Finally, a 16-week prospective randomised control study of 50 patients assigned to rosiglitazone, pioglitazone or control found TZD use was associated with decreased mediators of endothelial dysfunction, reduced markers of inflammation but increased markers of angiogenic activity, which could be of concern in PDR [47].

In contrast, smaller population-based studies have demonstrated no association between TZD and DME. Studies using OCT measurement have revealed no evidence of fluid retention in the macula and no difference in central retinal thickness [48–50]. Moreover, the ACCORD Eye study observed no association between TZD exposure and DME but could not exclude modest protective or harmful associations [51]. A 2013 literature review of drugs associated with DME concluded no definite association could be drawn between its incidence and TZD use [52], and that at-risk individuals, such as those with a history of DME and subgroup of nephropathy and/or congestive heart failure needed further study.

Thus, while TZD has not been proven to have a causal relationship with DME, evidence suggests there is likely an association and caution is advised in prescribing its use in those with greater risk of developing DME.

Sulfonylureas

Sulfonylureas are insulin secretagogues that bind to sulfonylurea receptors in pancreatic β-cells, leading to closing of K_{ATP} channels and subsequent insulin release [53].

There was a paucity of recent articles on the effects of sulfonylureas on retinopathy. A comparative study of gliclazide vs. glibenclamide in 25 non-insulin-dependent diabetic patients found that gliclazide might be more effective in improving DR or preventing its progression [54] (Table 2). A long-term comparative clinical trial of gliclazide with 159 patients with early or no retinopathy supported the finding that gliclazide appeared to have additional protective properties compared with other sulfonylurea drugs [55]. However, a prospective double-blinded controlled 2-year study comparing gliclazide versus placebo in insulin-treated and gliclazide versus glibenclamide in non-insulin-treated diabetic subjects did not support any action of gliclazide on diabetic microangiopathy independent of its hypoglycaemic actions [56].

Biguanides

Metformin has demonstrated cardioprotective effects independent of glycaemic control [57]. It produces anti-inflammatory and anti-angiogenic effects by increasing levels of thrombospondin-1 which decreases concentrations and activity of plasminogen activator inhibitor-1 and subsequently increases fibrinolytic activity. As inflammation and angiogenesis are implicated in the progression of retinopathy, metformin may have protective effects against retinopathy, though its effects separate to glycaemic control has yet to be investigated [57]. Retrospective chart reviews suggest metformin may have protective effects on DR [58, 59].

Discussion

This review of anti-hyperglycaemic medications used in T2D focuses on newer agents and specifically examines their relationship with diabetic eye complications. There were few well-conducted prospective studies looking at the relationship between anti-hyperglycaemic agents and the progression or regression of DR. It is difficult to determine whether the effect on DR or DME is mediated through improvement in glycaemic control or by direct impact of these anti-hyperglycaemic agents on retinal vasculature. This is also confounded by the possibility of early worsening of DR with rapid lowering of glucose levels on introduction of these medications, before the beneficial effects of improved glycaemic control on microvascular complications become manifested [9, 10, 60]. Most of the evidence consisted of small case studies or experimental studies commenting on benefit or harm associated with medication use. Furthermore, there was a significant paucity of information on the relationship between the older agents (biguanides and sulfonylureas) and retinopathy, with most research from the 1980s. There were also few population-

based studies carried out on alpha-glucosidase inhibitors, DPP4-inhibitors and SGLT-2 inhibitors, likely due to DPP4-inhibitors and SGLT-2 inhibitors being recently introduced medications, and the decline in use of alpha-glucosidase inhibitors.

Newer agents such as DPP4-inhibitors, GLP-1 agonists and SGLT-2 inhibitors have been increasingly utilised in combination with established treatment such as metformin due to their relative safety and separate mechanism of actions. The GLP-1 agonists are also notable as the only non-oral anti-hyperglycaemic agents for T2D and have the option of once-weekly dosage via subcutaneous injections.

The undesirable side effects of alpha-glucosidase inhibitors have contributed to their unpopularity, with 25–45% discontinuing use due to side effects [61]. However, a multinational observational study of 15,661 patients of which 92.6% were of Asian background (predominantly from China, South Korea, and India) found that acarbose was effective regardless of presence of cardiovascular comorbidities or diabetic complications, had 84.9% of patients who reported 'good' or 'very good' tolerability of the drug, and only 3.13% of patients reported adverse events, mainly gastrointestinal [62]. A meta-analysis of 46 studies has also suggested that acarbose may be more efficacious with an Eastern diet compared with a Western diet, raising the possibility for its greater use amongst Asian populations [63]. This may be relevant given the increasing prevalence of DR and DME in Asian populations.

The beneficial effect of tight glycaemic control in reducing risk of microvascular diabetic complications has been established since the UKPDS, particularly with retinopathy, and has since been affirmed by other studies [64]. In addition, the Steno-2 study showed intensive therapy significantly reduced risk of retinopathy by about 60% in T2D patients with microalbuminuria, supporting an aim of tight glucose control [65]. It should be highlighted that evidence of benefit is stronger in younger patients at early stages of disease, whereas effects of tight blood sugar control are weaker once complications have manifested, and hence this should be initiated as early as possible [66].

TZD have repeatedly been associated with increased risk of DME, but further studies must be conducted to determine the nature of the relationship. The reported incidence is rare, at around 1.5–2.6% of patients on TZD [31]. In most cases, cessation of TZD was followed by improvement of the DME although most patients required laser therapy as well. The cardiovascular safety concerns raised regarding TZDs have also led to the decline in their use, in addition to other concerns of increased fracture risk and lower limb oedema.

Other reviews have looked at the relationship between anti-hyperglycaemic medications and nephropathy as another diabetic microvascular complication. In contrast to retinopathy, there are greater restrictions on selection of anti-hyperglycaemic agents in diabetic nephropathy dependent on severity of impaired renal function. Albuminuria alone does not contraindicate use of anti-hyperglycaemic agents, but guidelines suggest contraindication of metformin at GFR <30 ml/min, acarbose <25 ml/min, DPP4 inhibitors <50 ml/min (except for Linagliptin which is safe even for dialysis patients), exenatide <30 ml/min, liraglutide <60 ml/min and sulfonylureas <30 ml/min [65]. This, however, is more likely due to the risk of lactic acidosis in the case of metformin and mechanisms of drug clearance leading to unpredictable pharmacodynamics, rather than specific effects of the agents on renal function itself. Nonetheless, there is still little data on reduction in microalbuminuria with specific anti-hyperglycaemic drugs.

In summary, we reviewed the literature on anti-hyperglycaemic agents and found that apart from thiazolidinediones and one of the GLP-1 agonists, semaglutine, anti-hyperglycaemics have been reported to have beneficial or neutral effects on diabetic eye complications. Thiazolidinediones, of which the only one used in the United Kingdom is pioglitazone, have been linked to incident or worsening DME, although the rate is believed to be low. A detailed medication history may uncover use of this potentially reversible cause of DME. In addition, in the future with large cardiovascular studies mandated for all new anti-hyperglycaemic agents, it may be worthwhile to include the effects on progression of retinopathy as another endpoint to provide further information about the relationship between these agents and development or progression of retinopathy. The phenomenon of early worsening of retinopathy with tight glycaemic control should also be noted in further studies on the effects of anti-hyperglycaemic agents on retinopathy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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