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Diabetic Macular Edema

Correlations with Available Diabetes Therapies – Evidence Across a Qualitative Review of Published Literature from MEDLINE and EMBASE

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Abstract

Diabetic macular edema (DME) is the leading cause of visual loss and legal blindness in people with diabetes mellitus. The pathogenesis of DME is complex and multifactorial, and involves both local and systemic risk factors that may alter the blood-retina barrier and allow leakage of protein and fluid into the macula. Recently, in addition to well known risk factors, the use of thiazolidinediones (glitazones) has been related to the development and worsening of DME. This review is based on available literature derived from EMBASE and MEDLINE, from 1950 to May 2010, and focuses on the potential correlations between DME and current available therapies for type 1 and 2 diabetes.

This review reveals that the current literature, with the potential exception of glitazones, is not sufficient for a definite statement on the association between DME and currently available diabetic therapies. In fact, among antidiabetic agents, the class of glitazones appears the only one to be potentially associated with DME. Furthermore, adequately powered, prospective studies are warranted to evaluate the exact causal association between glitazones and DME and to exclude the role of other confounding factors potentially able to induce or exacerbate macular edema. Improvement of the quality and reporting in postmarketing surveillance and the use of the 'dechallenge and rechallenge' approach in case of suspicious cause/effect drug relationship of DME are highly encouraged.

Despite progressive improvement in diagnostic and screening techniques and the proven efficacy of laser treatment in preventing visual loss, diabetic retinopathy and its complications remains the leading cause of legal blindness in the working-age population in industrialized countries. Future perspectives are not encouraging: the WHO estimates that more than 180 million people worldwide have diabetes mellitus and this number is expected to rise to epidemic proportions within the next 20 years, fuelled by increased life expectancy, sedentary lifestyle and obesity.[1,2] Diabetic retinopathy remains today the most common microvascular complication of diabetes, affecting approximately 50% of patients. Loss of vision from diabetic retinopathy results from two primary causes: proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME), which can occur at any stage of diabetic retinopathy. Currently DME is the most common cause of visual impairment in diabetic patients, accounting for about three-quarters of cases of visual loss.

The Early Treatment Diabetic Retinopathy Study (ETDRS) defined DME as retinal thickening or presence of hard exudates within one disc diameter of the centre of the macula. Considering that the vast majority of visual loss occurs when DME involves the centre of the macula, and that the progression of the disease is often asymptomatic, the term 'clinically significant macular edema' (CSME) was coined to characterize the severity of the disease and to provide a threshold level to apply laser photocoagulation.[3,4] According to the ETDRS, CSME is defined to include any retinal thickening involving or approaching the macular centre. If untreated, 25–30% of patients with CSME exhibit a doubling of the visual angle within 3 years. When treated with laser photocoagulation, the risk of doubling of the visual angle within 3 years drops by 50%. Natural history of DME is characterized by a slow progression until the centre of the macula is involved, causing visual acuity deterioration. Spontaneous resolution of DME is rare, and usually secondary to improvement in systemic risk factors, such as glycaemic control, hypertension or hypercholesterolaemia.

Pathogenesis of DME is complex and not fully understood. Chronic hyperglycaemia triggers a series of metabolic events, such as protein kinase C activation, generation of advanced glycation end-products, reactive oxygen species, and inappropriate cytokine production, ultimately leading to thickening of the basement membrane, pericyte loss, and vascular endothelial compromise, with progressive disruption of the blood-retinal barrier (BRB).[5-10] Breakdown of the BRB secondary to endothelial cell dysfunction and consequent increased permeability and incompetence of retinal vasculature, lead to accumulation of plasma protein in the extracellular space, and oncotically obligate fluid within the intraretinal layers, causing retinal swelling and neuronal disorganization.

Although altered BRB plays a pivotal role in the genesis of DME, abnormal vitreomacular interface may contribute significantly to the development and progression of DME; an attached posterior hyaloid may exert tangential macular traction, facilitating edema.[11] The emergence of optical coherence tomography (OCT), a non-invasive, non-contact, diagnostic method that provides cross-sectional images of the retina, has greatly improved the visualization of vitreomacular traction in the course of DME. Furthermore, OCT provides objective and quantitative measurements of retinal thickness and is increasingly used in the diagnosis and follow-up of DME (figure 1).

Significant variations in the incidence and prevalence of DME have been reported in various epidemiological studies, depending on the type of diabetes (type 1 or 2), the treatment modality (insulin, oral hypoglycaemic agents or diet only) and the mean duration of diabetes. DME can develop at any stage of diabetic retinopathy, but it occurs more frequently as the duration of diabetes and severity of diabetic retinopathy increases. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the 10-year rate of developing DME was 20.1% in patients with type 1 diabetes, and 13.9% and 25.4% for type 2 diabetes patients not using and using insulin, respectively. DME prevalence increases with the severity of diabetic retinopathy:

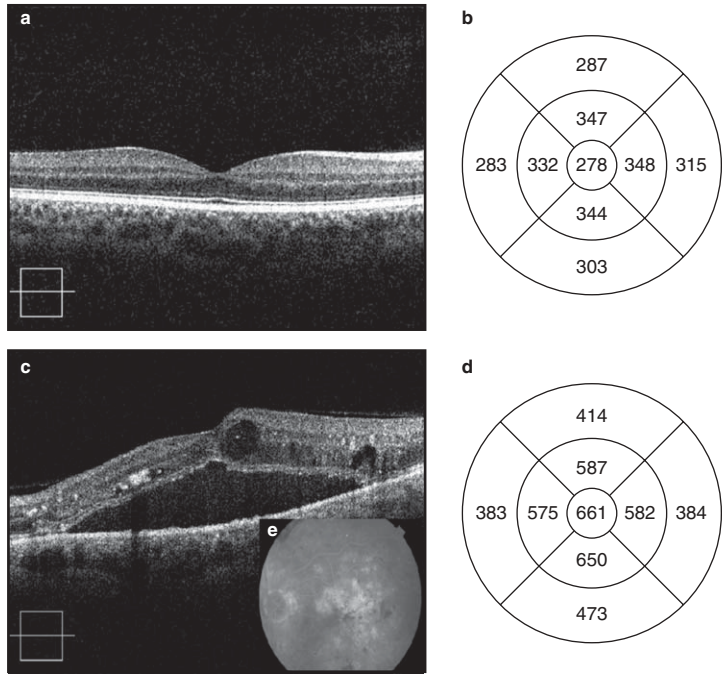

Fig. 1. Optical coherence tomography (OCT) scan of a normal macula (**a**) and of an eye with diabetic macular edema (**c**) with corresponding numerical display of retinal thickness map (**b**, **d**). The physiological foveal depression is clearly visible in normal eyes. In diabetic macular edema OCT shows macular thickening with abnormal foveal contour, and presence of intra- and subretinal hyporeflective areas due to accumulation of fluid. The corresponding late-stage fluorescein angiography reveals petaloid cystoid pooling and leakage (**e**).

it is about 3% in eyes with mild non-proliferative diabetic retinopathy (NPDR), rises to 38% in eyes with moderate to severe NPDR, and reaches 71% in eyes with PDR.[12,13]

Risk factors associated with DME include age, systolic blood pressure, proteinuria, longer duration of diabetes, elevated glycosylated haemoglobin (HbA_{1c}) and panretinal photocoagulation. Recently, some studies have suggested an association between the thiazolidinedione (glitazone) class of drugs and DME. These drugs were modestly associated with an increased 1-year incidence of DME, even after adjusting for confounding factors of age, glycaemic control and insulin use.[14]

1. Thiazolidinediones and Macular Edema: Evidence from the Literature

The authors of this review searched all available literature derived from the MEDLINE and EMBASE databases, from 1950 to May 2010. The following keywords were searched: 'macular edema', 'diabetic retinopathy', 'oral diabetes agents', 'insulins', 'insulin analogues', 'glycemic control', 'hypertension', 'blood pressure control', 'dyslipidemia', 'lipid control' and 'treatments'.

The potential association of glitazones with macular edema initially arose after presentation of DME cases from a retrospective chart review of patients who received rosiglitazone at the American Academy of Ophthalmology Annual Meeting in Anaheim, CA, USA (November 2003). The published report suggested a possible causal association between glitazones use and the exacerbation of DME.[15]

A subsequent study identified cases associated with the use of the glitazones, pioglitazone and rosiglitazone.[16] To be included, patients had to have CSME in at least one eye and lower extremity edema associated with glitazone use. The study cohort involved 19 men and 11 women with

an average age of 61 years. Seventeen patients were taking pioglitazone; 11 were taking rosiglitazone and 2 took both medications sequentially. Two patients received a glitazone as monotherapy; 12 received other oral agents in addition to a glitazone; 7 received insulin alone with a glitazone; 7 received insulin plus oral agents and a glitazone; and for 2 patients, these data were unavailable. All had pitting lower-extremity edema, and the average weight gain after initiation of glitazone therapy was 14.96 kg. Of the 30 patients, 23 had bilateral DME. The average visual acuity at an initial visit was 20/50. Ten patients were followed for more than 3 months after glitazones were discontinued, with an average follow-up of 10 months.

After stopping their glitazone, patients experienced rapid reduction in lower extremity edema, usually returning to baseline in about 2–3 months. The weight loss after stopping glitazone therapy averaged 8.62 kg. A reduction in macular edema in less than 3 months was observed in only three of ten patients, but eventually occurred in seven of ten patients, followed over a 1- to 2-year period. The three patients who showed no decrease in macular edema had discontinued glitazone treatment after less than 3 months. Three eyes experienced a reduction in macular edema with no laser treatment. The average visual acuity at an initial visit among the ten patients was 20/70 and, at the last visit, the average was 20/90. While most patients had a decrease in macular edema, visual improvement was not necessarily seen.

Laser photocoagulation was carried out on 50 of 60 eyes (30 patients) and 24 patients underwent multiple sessions. The DME was unusually resistant to treatment, and visual outcomes were poor despite control of fluid retention. Of note, only one patient experienced spontaneous resolution of macular edema with cessation of the drug and resolution of fluid retention. Because the study was retrospective, it was not possible to identify cause from effect. Despite the weaknesses, the association between fluid retention and macular edema is a logical one. We are aware of other causes of fluid retention that worsen macular edema. Treatment requires control of the systemic disease as well as local laser intervention.

In 2005, an isolated published single-case report had already suggested an association between development of bilateral macular edema and the up-titration of rosiglitazone from 2 to 8 mg/day.[17] Subsequent resolution of DME occurred after rosiglitazone dosing was reduced back to 2 mg. Afterwards in 2008, a case of bilateral severe macular edema induced by pioglitazone (15 mg/day) in a patient with diabetic retinopathy was also described in a Japanese patient with moderate pre-proliferative diabetic retinopathy. Two weeks after stopping pioglitazone, visual acuity improved to 0.8 in the right eye and 0.5 in the left eye but the DME was still severe in the OCT images. Low-dose (25 mg) spironolactone was then given and macular edema resolved. Final visual acuity improved to 0.9 in the right eye and 0.7 in the left eye.[18]

In addition, a case of spontaneous resolution of diabetic maculopathy with cystoid macular edema was reported in 2008 in a diabetic patient after discontinuation of rosiglitazone, documented with serial OCT images.[19] The patient had been started on rosiglitazone 8 months previously. Glitazone treatment was stopped and, following prospective follow up, the patient demonstrated clinically significant macular edema on OCT at presentation. Three months after cessation of rosiglitazone the condition had completely resolved and visual acuity had improved. Resolution of macular edema was confirmed on OCT examination. The patient required no interventional treatment, i.e. no laser or intravitreal therapy. This was the first case where spontaneous resolution of clinically significant macular edema and improvement in visual acuity following discontinuation of a glitazone had been documented.

A further case report was published in 2009 and this reported the experience of a 61-year-old woman referred for bilateral DME.[20] Her visual acuity was 20/70 in the right eye and 20/50 in the left eye. She presented a macular edema on both eyes. Her diabetes and her blood pressure were well controlled. The authors noted that the decrease in visual acuity occurred when the patient began taking rosiglitazone 4 mg/day. Three months after replacing rosiglitazone by gliclazide,

the visual acuity of the patient improved to 20/40 in the right eye and 20/30 in the left eye.

In December 2005, the European Medicines Agency issued a press release stating that 'rare' cases of macular edema (swelling of the back of the eye) were reported with rosiglitazone and pioglitazone containing medicinal products. Following discussions of these postmarketing findings, the Committee for Medicinal Products for Human Use concluded that "a further review should be performed to establish whether there is a possible association between macular edema and the use of rosiglitazone and pioglitazone."[21]

The Summary of Product Characteristics (SPC) for rosiglitazone and for pioglitazone have, in section 4.4, 'Special Warnings and Precautions for use – Eye disorders', a paragraph stating "post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone/rosiglitazone. Many of these patients reported concurrent peripheral edema. It is unclear whether or not there is a direct association between rosiglitazone/pioglitazone and macular edema but prescribers should be alert to the possibility of macular edema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered."[22,23]

In addition, results from an observational study (conducted at Kaiser Permanente, Southern California, CA, USA) on 170 000 persons with diabetes) appear to confirm that glitazones were associated with an increased 1-year incidence of DME (odds ratio [OR] 1.6; 95% CI 1.4, 1.8). After adjusting for confounding factors of age, glycaemic control and insulin use, glitazones remained still modestly associated with DME.[14]

The above evidence becomes controversial with the very recent results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) eye substudy.[24] This study had, as specific objective, 'to assess the cross-sectional association of thiazolidinediones with DME'. The cross-sectional association of DME and visual acuity with glitazones was examined by means of baseline fundus photographs and visual acuity measurements from the ACCORD trial.[24] Visual acuity was assessed in 9690 participants in the ACCORD trial, and 3473 of these participants had fundus photographs that were centrally read in a standardized fashion by masked graders to assess DME and retinopathy from 23 October 2003 to 10 March 2006.

Among the subsample, 695 (20.0%) people had used glitazones, whereas 217 (6.2%) people had DME. Glitazone use was not associated with DME in unadjusted (OR 1.01; 95% CI 0.71, 1.44; $p = 0.95$) and adjusted (OR 0.97; 95% CI 0.67, 1.40; $p = 0.86$) analyses. Significant associations with DME were found for retinopathy severity ($p < 0.001$) and age (OR 0.97; 95% CI 0.952, 0.997; $p = 0.03$) but not for HbA_{1c} ($p = 0.06$), duration of diabetes ($p = 0.65$), sex ($p = 0.72$) and ethnicity ($p = 0.20$). Glitazone use was associated with slightly greater visual acuity (0.79 letter; 95% CI 0.20, 1.38; $p = 0.009$) of uncertain clinical significance. The conclusions of the authors were that in this cross-sectional analysis of data from the largest study to date, no association was observed between glitazone exposure and DME in patients with type 2 diabetes; however, the authors could not exclude a modest protective or harmful association.

To date, the pathogenesis of DME with glitazones is not fully understood. Some authors have hypothesized that the mechanism of induction may be attributable to an upregulation of vascular endothelial growth factor, which has been shown to play a major role in the pathogenesis of DME, inducing increased vascular permeability.[25]

Increases in plasma volume (i.e. edema) may also be relevant. Fluid retention may result from a decrease in renal excretion of sodium and an increase in sodium and free-water retention. The increase in plasma volume can also cause dose-related dilutional anaemia (decreased haemoglobin of about 1 g/dL [0.62 mmol/L], haematocrit approximately 3.3%).[26,27]

2. Other Antidiabetic Treatments: Evidence from the Literature

We found no clinical data in the literature showing any direct cause-and-effect relationship

for currently available oral antidiabetic agents, the appearance of macular edema in direct connection with insulin therapy.[12,13]

Among short-acting insulin analogues, there is one report where acceleration of proliferative retinopathy was seen in three of ten pregnant women with diabetes, treated with insulin lispro.[28] Nevertheless, as far as DME is concerned, there are no consistent reports from studies in pregnant women[29] or including a 6-month postpartum evaluation of lispro versus regular insulin in women with type 1 diabetes.[30]

Potential concerns were based on *in vitro* data, showing the mitogenic effects of novel insulin analogues.[31] In one report, insulin glargine, a long-acting insulin analogue, caused greater insulin-like growth factor-1 (IGF-1) receptor-mediated proliferation than native insulin.[32] Other studies, however, failed to confirm activity greater than that of human insulin.

In 2007, Davis et al.[33] published data from four randomized 28- to 52-week clinical trials comparing insulin glargine and neutral protamine Hagedorn (NPH) insulin based on glycaemic control and frequency of hypoglycaemia, as well as changes on ophthalmological examinations and fundus photographs.

In terms of final results, small and inconsistent differences across these trials and assessment methods were found. Because overall rates were consistent with the natural course of diabetic retinopathy, the conclusion was that it is unlikely that insulin glargine carries a higher risk of early worsening of diabetic retinopathy of DME or other early adverse effects than NPH insulin. These results are also consistent with those published in 2009 from a 5-year randomized trial of insulin glargine versus NPH insulin.[34] In addition, there is no evidence to date of any other available antidiabetic therapy being linked with DME formation or with its worsening.

3. Summary of Findings

This review indicates that findings from the current literature, with the potential exception of those on glitazones (table I), are not sufficient for a definitive statement on the association between DME and currently available diabetic medical therapies.

With the exception of a possible association of DME with glitazones, we did not find any other correlation between macular edema, progression of diabetic retinopathy and the use of currently available antidiabetic agents. Furthermore, we found no evidence that either conventional insulins or insulin analogues can have an impact on formation or worsening of macular edema both in the short term and/or long term.

Considering oral antidiabetic agents, glitazones, which increase insulin sensitivity, have been associated with 'rare' postmarketing episodes of macula edema. Whether the class causes or aggravates macular edema remains difficult to establish from available data and in particular from those from retrospective[35] and/or observational studies.[14] After the latest results from the ACCORD eye substudy, the debate on the potential association of glitazones with DME still remains open.[24] Fluid retention is a well recognized adverse effect of glitazones and a known problem for the management of macular edema. Clinical practitioners should be aware of a possible association between macular edema and glitazone use. Glitazones are associated with edema and weight gain, which may involve a change in fat distribution with an increase in subcutaneous adipose fat and a decrease in visceral fat. Pedal edema occurs in 3–5% of people taking glitazones, and the incidence is greater when use is in combination with other glucose-lowering agents (particularly sulfonylureas). Glitazones are contraindicated in the US in New York Heart Association (NYHA) class 3 or 4 heart failure and lately, after market introduction, they had a related 'black-box warning' added to product labelling.[36] In Europe, a more conservative approach by the regulatory authorities was established, and glitazones were and remain contraindicated in any NYHA class of heart failure. In the rare postmarketing reports of new or worsening macular edema in association with glitazones, most affected individuals had concurrent peripheral edema.

Therapeutic appropriateness should be carefully considered in prescribing glitazones. Based

Table I. Results of the studies published to date showing a potential association of thiazolidinediones (glitazones) with diabetic macular edema

Study	Study details	Glitazone	Outcome
Ryan et al.[16]	Retrospective: 30 pts with clinically significant DME seen over the past 4 years in specialty referral practice in Du Bois, PA, USA	Rosiglitazone and pioglitazone (n = 17 pts on pioglitazone; n = 11 on rosiglitazone, and 2 took both medications sequentially)	Reduction of macular edema in <3 months in only 3 of 10 pts, but eventually observed a reduced degree of macular edema in 7 of 10 pts over a 1- to 2-year period. The report suggests possible causal association between glitazone use and the exacerbation of DME
Colucciello[17]	Case report of bilateral macular edema	Rosiglitazone from 2 mg up-titrated to 8 mg/day	Resolution of DME decreasing the dose down to 2 mg/day of rosiglitazone
Oshitari et al.[18]	Japanese case report of severe bilateral DME in a 30-year-old poorly controlled type 2 diabetic woman with moderate pre-proliferative diabetic retinopathy	Pioglitazone 15 mg/day	2 weeks after stopping pioglitazone, visual acuity improved. DME resolved with low dose of spironolactone (25 mg)
Liazos et al.[19]	A case report of a clinically significant DME on OCT presentation	Rosiglitazone 4 mg/day (2 mg bid) started 8 months previously to this case report	First case to document spontaneous resolution of clinically significant macular edema and improvement in visual acuity 3 months after cessation of rosiglitazone
Tatti et al.[35]	Retrospective: 76 eligible type 2 diabetic subjects who provided their written informed consents amongst all subjects treated with rosiglitaozone referring to that diabetes centre	Rosiglitazone (different daily doses: 4 and 8 mg)	Amongst study subjects, there was one case only of bilateral reversible paramacular edema on rosiglitazone 8 mg/day. Rosiglitazone was given in co-administration with a long-term insulin treatment regimen in a subject with pre-existing diabetic retinopathy
Nyssen et al.[20]	Case report of bilateral DME. Diabetes and blood pressure well controlled	Rosiglitazone 4 mg/day. Decrease in visual acuity occurred when the patient began taking rosiglitazone	3 months after replacing rosiglitazone with gliclazide, the visual acuity of the patient improved to 20/40 in the right eye and 20/30 in the left eye
Fong and Contreras[14]	Observational prospective cohort study (Kaiser Permanente, Southern California, CA, USA) on 170 000 subjects with diabetes. In 2006, detected 996 new cases of DME	Rosiglitazone and pioglitazone	Glitazones were associated with an increased 1-year incidence of DME (OR 1.6; 95% CI 1.4, 1.8). After adjusting for confounding factors of age, glycaemic control and insulin use, glitazones remained still modestly associated with DME

bid = twice daily; **DME** = diabetic macular edema; **OCT** = optical coherence tomography; **OR** = odds ratio; **pts** = patients.

on the available data in favour of a potential association of glitazones with DME, a conservative approach should be to exclude use in patients with diabetic proliferative retinopathy with previous reduction of visual acuity. Particular attention should be given to those patients where a glitazone is used in combination with insulin, where the incidence rate of edema becomes 2–3 times higher than in monotherapy.

It is always difficult to establish a direct drug-related cause/effect relationship between an anti-diabetic agent and macular edema. DME can develop at any stage and at any time during progression of diabetic retinopathy.[37,38] Progression of retinopathy and formation of macular edema correlate with deterioration of glucose, lipid and blood pressure control. A long-term, prospective landmark clinical trial in type 2 diabetes[39] showed that intensive control of blood glucose and hypertension reduced development of CSME. Elevated HbA_{1c} is a known risk factor for persistent CSME.[40] Gross proteinuria is also associated with a 95% increase in the incidence of macular edema[41] and the relevance of serum lipids in exudative DME in type 2 diabetic patients has also been demonstrated.[42] The use

of atorvastatin 6 weeks before focal laser photocoagulation reduced subfoveal migration of lipids in patients with macular edema and dyslipidaemia.[43] Furthermore, in an intention-to-treat analysis from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) randomized study, fenofibrate at the dosage of 200 mg/day reduced (5-year follow-up) the frequency of first laser treatment for macular edema by 31% and for proliferative retinopathy by 30%. The reason for these results is today still unclear; however, they did not appear to be related to plasma lipid concentrations.[44] The mechanism of action of fenofibrate might be related to the ability of peroxisome proliferator-activated receptor-α agonists to inhibit the vascular endothelial growth factor pathway.

In general, the number of cases occurring under treatment with any single agent is at the present time defined as 'rare': for both available glitazones the identified frequency of DME from postmarketing data is ≥1 case/10 000 and <1 case/1000. Clinically, the emphasis today in management of diabetes, should be to optimize glucose, lipid and blood pressure control, and to continue improving screening of diabetic retinopathy. DME currently represents the primary cause of visual loss in diabetic patients and should provide an incentive to improve screening and vigilance for diabetic retinopathy in patients with both type 1 and type 2 diabetes. Early detection and correct diagnosis of macular edema, should be strongly encouraged among clinical practitioners.

The application of most appropriate therapies would ideally benefit from recognizing those patients genetically predisposed to develop macular edema or to its progression, as has been demonstrated in small studies of homogenous patient populations especially with type 2 diabetes.[45,46] Unfortunately, predictive genomics are difficult to apply in large, uncontrolled, postmarketing settings and, in practical terms, any change of therapy should be according to current clinical evidence.

As seen with other chronic diseases such as hypertension, whenever macular edema is detected, 'dechallenge and rechallenge' methodology can be utilized. If the outcome event disappears (or decreases in intensity) when the putative precipitating agent is withdrawn and reappears when it is re-instituted, a strong case can be made for potential drug-relatedness. This approach might help clarify differences, if any, in the incidence of possibly associated adverse effects, even between agents within the same therapeutic class.[47]

We would like to re-emphasize the necessity for clinical practitioners to increase reporting of serious adverse events to all competent authorities. Through such practice, the quality of postmarketing surveillance data can be improved.[48] In the specific case of macular edema, spontaneous reporting systems such as the US FDA's MEDWATCH can be effective in revealing unusual or rare adverse events that occur with the use of medications. In some cases, such reports may contain sufficient information to assign causality.[49]

4. Conclusion

Adequately powered, prospective studies are needed to evaluate the causal association between glitazones and DME and to exclude the role of other confounding factors that may potentially be able to induce or exacerbate macular edema.

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