

Prevalence of Clinically Significant Macular Edema [CSME] among Glitazone users and Non- users of type-2 DM patients with Diabetic Retinopathy

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Abstract

A comparative, Non - randomized, Prospective, Cohort Study was conducted with the intention to identify the association of existence of Clinically Significant Macular Edema (CSME) with Thiazolidinedione (Glitazone) use among type-2 Diabetes Mellitus patients with Diabetic Retinopathy (DR); which was carried out for a period of 3 years at Retina Vitreous clinic of Aravind Eye Hospital, Madurai. A total of 100 subjects of Diabetic Mellitus with Diabetic Retinopathy are enrolled with Inclusion and exclusion criteria as per protocol. Among two arms; Group 1 (N=50) is Glitazone users & Group 2 (N=50) is Non-Users. Bilateral Retinal evaluation done for Diabetic retinopathy and Macular edema (ME) through slit lamp biomicroscopy for grading Clinically Significant Macular Edema and its prevalence. The overall Prevalence of CSME in the population is 37% in Glitazone users which states that the exposure group is at higher risk rate for getting CSME than did the Glitazone Non- User group Subjects. The Relative Risk Ratio (RR) by Fisher's Exact Test done through 2*2 contingency table for the cohort data is 1.423. Statistically analyzed in Graph pad version 3 for the 2 X 2 contingency table for calculating Relative Risk ratio by Fisher's Exact test in 2 sided method. The Relative Risk ratio is greater than 1 which signifies that the Glitazone exposure group had the higher risk of getting CSME when compared to Glitazone non users. Usage of Thiazolidinediones at the optimal doses will help in preventing hyperglycemia and also dose related adverse effect such as CSME. Therefore rational use of the Glitazones among Diabetic mellitus patients is advisable.

Key words:

Clinically Significant Macular Edema, Diabetic Retinopathy, Thiazolidinedione, Glitazones, PioGlitazone, RosiGlitazone

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INTRODUCTION:

India is being the diabetic capital of the world, 19% of the world's diabetic population is found here. According to International Diabetes Federation (IDF), India currently leads the world with an

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estimated 41 million people with diabetes; this figure is predicted to increase to 66 million by 2025^[1]. Type 2 diabetes has reached epidemic proportions, fueled by an aging population and the rapid increase in obesity ^[10]. DR is a major cause of vision loss in patients with diabetes.

The longer patients have diabetes, the higher the prevalence of DR ^[11]. In developed countries, DR is recognized as the leading cause of blindness in the working-age population (20–74 years old) and is responsible for 12% of new cases of blindness each year ^[12].

Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have a sudden and debilitating impact on visual acuity (VA), eventually leading to blindness. The thiazolidinediones (TZDs) are of insulin sensitizer having PPAR- γ (Peroxisome Proliferator-Activated Receptor- γ) activity found to be associated with edema more frequently^[6]. The incidence of DME was found to be at higher rate among the thiazolidinediones (TZDs) users of type 2 diabetic mellitus subjects. RosiGlitazone and PioGlitazone, belong to the class called Thiazolidinediones (TZDs). Both RosiGlitazone and PioGlitazone are indicated either as monotherapy or in combination with a sulfonylurea, metformin, or Insulin when diet, exercise, and a single agent do not result in adequate glycemic control. ^[3, 4]

If DME is present, it is divided into mild (some retinal thickening or hard exudates in the posterior pole, but distant from the center of the macula), moderate (retinal thickening or hard exudates approaching the center of the macula but not the center), and severe (involving retinal thickening or hard exudates involving the center).

Clinically significant macular edema (CSME) occurs if there is thickening of the retina involving the center of the retina (macula) or the area within 500 μ m of it, if there are hard exudates at or within 500

μ m of the center of the retina with thickening of the adjacent retina, or if there is a zone of retinal thickening one disk area or larger in size, any part of which is within one disk diameter of the center of the retina ^[7]

The International Clinical Diabetic Macular Edema Disease Severity Scale includes two major levels: absent and present. Ophthalmologists generally use the term clinically significant macular edema (CSME) as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS)^[8]. An increased incidence of ME (Macular edema) has been associated with the presence of more severe retinopathy ^[2] making risk factors for retinopathy relevant to ME.

Hence this work was carried out as a cohort design among south Indian population to measure the relative risk of pioGlitazone and rosiGlitazone users for the existence of macular edema.

METHODOLOGY

Study Location:

The study was carried out at Aravind Eye Hospital, Madurai, India. The study received ethical clearance from an Independent Ethical Committee. The patients were explained about the purpose of study and a voluntary Informed Consent Form was obtained and enrolled in to study.

Study Population:

One hundred Diabetic Mellitus patients identified with Diabetic Retinopathy were recruited based on Inclusion and Exclusion criteria.

The selected patients recruited after explaining the study and obtaining a voluntary Informed Consent Form. The subjects were recruited from August 2007 to December 2007. A baseline examination done and the patient were followed annually for 3 years and the changes recorded. Last patient completed follow up on December 2010.

A comprehensive ocular examination was performed on all study subjects and their visual acuity was

recorded for every visit. The pupils were dilated until the best possible mydriasis was obtained and the ophthalmologist performed retinal evaluation for the DR and DME through slit lamp biomicroscopy to identify and classify as per the standard criteria for classification. It is documented by clinical examination of Retina.

The patient's medical history and diabetic medication history were collected from the respective medical record file. Adverse effects were assessed using the macular edema grading. The data from the patient file and other primary source of information were transformed to study specifically designed Case Report Form (CRF).

Study Design:

A comparative, Non - randomized, Prospective, Cohort Study. The subjects were grouped under two groups, Where group 1 subjects were Glitazone users and group 2 subjects were Glitazone Non- Users. Each Group consists 50 patients in number. Both the groups compared for the existence of CSME; here the Glitazone Non- User group will act as a Control group.

Relative Risk Ratio (RR):

The cohort study envisages the observation of groups of persons who differ in exposure and then determines if they differ in the Adverse Drug Reaction investigated. The results of cohort studies provide direct measures of risk of ADR in exposed and Non- exposed groups. [9]

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

a- Exposure group with ADR present, b- Exposure group with ADR absent, c- Non-Exposure group with ADR present, d- Non-Exposure group with ADR absent

RESULTS:

In the 100 subject, early onset of DR cases were found to be lower with the only 3 subjects in age group 35 to 45 years and the rest of them are > 50-65 years, Among the total study population 67 male and 33 female participants. Diabetes mellitus duration from 5 to 15 years contribute major proportion of the study subjects with total of 60 cases having 33 Users and 27 Non users.

Diabetic Retinopathy Evaluation

Diabetic Retinopathy (DR) severity is measured for Non Proliferative Diabetic Retinopathy (NPDR) as Mild, Moderate and severe NPDR and Proliferative Retinopathy (PDR), High Risk PDR, and the later stage of PDR is Vitreous Haemorrhage (VH).

Group I: TZD's users had 25 subjects each of NPDR and PDR. 13 bilateral and 12 unilateral cases in both NPDR and PDR among group 1 subjects.

Group II: Subjects with 28 NPDR and 22 PDR in 20 bilateral & 8 unilateral of NPDR and 18 bilateral & 4 unilateral of PDR is found.

Table 1: Diabetic duration DR severity between the TZD's Users and Non- Users
Severity Scale: NPDR– Mild, Moderate (mod), Severe (sev)
 PDR – High Risk Proliferative Diabetic Retinopathy (HR), Vitreous Hemorrhage (VH)

S No.	DM Duration (yrs)	Group 1				Group 2			
		NPDR (mild, mod, sev)		PDR (PDR, HR VH)		NPDR (mild, mod, sev)		PDR (PDR, HR VH)	
		Bilateral Eye	Unilateral Eye	Bilateral Eye	Unilateral Eye	Bilateral Eye	Unilateral Eye	Bilateral Eye	Unilateral Eye
1	0-5	0	0	0	0	3	1	2	0
2	6-10	5	5	5	5	5	2	4	1
3	11-15	5	4	5	4	4	2	6	3
4	16-20	2	2	2	2	4	2	1	0
5	21-25	1	0	1	0	2	0	2	0
6	26-30	0	1	0	1	1	1	3	0
7	> 30	0	0	0	0	1	0	0	0

Clinically Significant Macular Edema (CSME)

Evaluation:

The subjects were followed for 3 years to study the prevalence and distribution of types of Clinically Significant Macular Edema among Group 1 and Group 2. Clinically Significant Macular Edema (CSME) was graded as Focal CSME & Diffuse CSME

Prevalence and Distribution of CSME:

Group 1:

Focal CSME in unilateral eye is observed in 18 subjects & bilateral eye of 7 subjects. Similarly Diffuse CSME case has seen only unilateral in 7 cases. Both type of CSME seen in unilateral eyes of 2 subjects. Fresh case of CSME noticed in 3 subjects which were also unilateral.

Group 2:

Non users reported with 17 focal CSME cases having 11 unilateral and 7 bilateral occurrences. 4 diffuse CSME observed bilateral and unilateral, 2 each. Both focal & diffuse CSME in 4 unilateral eyes of 4 subjects.

Relative Risk Ratio (RR):

Existence of CSME among the Glitazone users and their relative risk ratio is >1 only in case of on therapy duration 6 months and 5 years which shows the relative risk is greater in Glitazone users. The risk of time of exposure to drug 12 month to 42 month have Relative Risk ratio (RR) < 1 showing lesser chance of getting CSME.

Table 2: Existence of CSME and its Relative risk ratio among group 1 subjects (TZD's users)

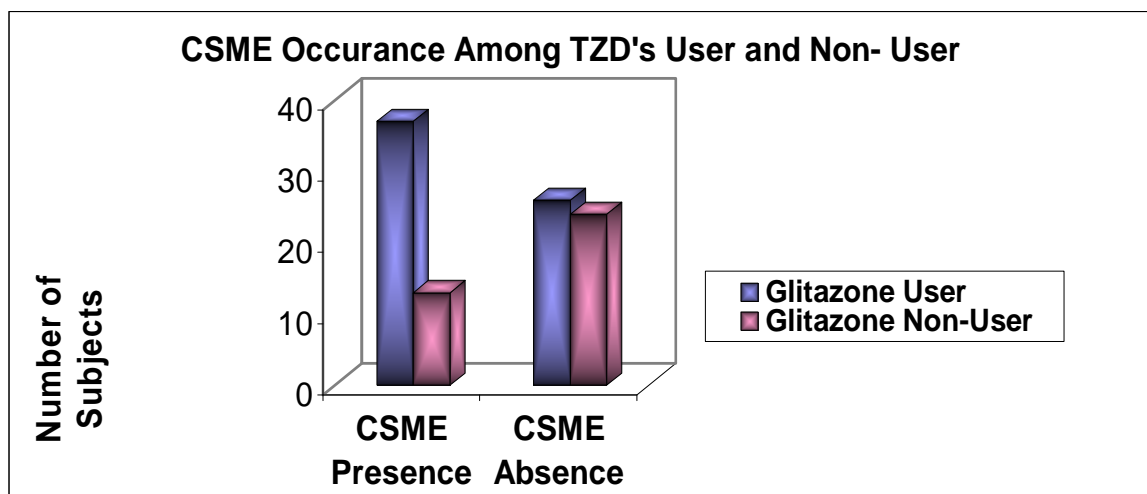
S No	Time of Exposure	Presence of CSME (Patient in number)	Absence of CSME (Patient in number)	Relative Risk (Ratio)
1	Control group	26	24	1.4230
2	6	5	5	1.0400
3	12	13	3	0.6400
4	18	37	0	0.5200
5	24	3	2	0.8667
6	30	4	1	0.6500
7	36	7	1	0.5943
8	42	1	0	0.5200
9	48	0	0	0.0000
10	54	0	0	0.0000
11	60	1	1	1.0400

Group 1 Subjects were on therapy from 6 month to 5 years. CSME presence observed in 15 bilateral & 22 unilateral among 37 subjects and CSME absence in 13 subjects were found out of 50 Glitazone users.

Table 3: Contingency table data from Cohort study

Factor Status	CSME Present	CSME Absent	Total
TZD Exposure Group (N = 50)	37 (a)	13 (b)	50
TZD Non-Exposure Group (N = 50)	26 (c)	24 (d)	50
Total (N = 100)	63	37	100

FIG 1: CSME EXCISTANCE AMONG TZD' USER AND NONUSER



The relative risk value for the whole study population irrespective of the exposure time is done. The overall prevalence of CSME in the population was 37 % in Glitazone users which states that the exposure group is at higher risk rate for getting CSME, showing 95 % confidence interval between the two proportion is 0.5968 to 0.8537 and 0.3743 to 0.6637 for the group 1 and Group 2 respectively.

The difference between the fractions is 0.2200 with 95% CI [0.03070 to 0.4093] and Standard Error of the difference is 0.09656 which is statistically significant.

Relative Risk ratio for the study population is 1.423 having 95 % CI [1.041 to 1.946] using the approximation of Kartzwith p- value as 0.0377. This is statistically significant.

DISCUSSION:

The Relative Risk ratio is a quantitative expression of the likelihood of disease development in people exposed to the risk factor, compared with those not exposed. In the case of pharmacovigilance, the risk factor is the drug suspected of causing a 'disease' or adverse reaction (ADR).

The Glitazone user subjects had a higher frequency of all the grades of CSME than did the Glitazone Non- User group Subjects. The existence of CSME was significantly

higher in TZD's user group 37% (37/50) compares with 26 % (26/50) in TZD's Non-user group on considering for $p < 0.05$.

Diabetes is a risk factor for Macular Edema and Diabetic Retinopathy. Patients already affected with CSME, Early stage DM type- 2 Patients who were found to be under poor Glycemic control, Dyslipidaemic Patients with uncontrolled lipid profile, and later stage of Diabetes (DM Type-2) should be warned that thiazolidinedione medications such as RosiGlitazone and PioGlitazone may lead to the development of macular edema.

Significant number of ME cases among TZD's User is found. This CSME is suspected to be associated with the use of RosiGlitazone and pioGlitazone.

Among the TZD's users pioGlitazone is used by 38 subjects with the report of CSME presence and absence is 29 and 9 respectively. RosiGlitazone is used by 8 patients out of which 6 had CSME and 2 with CSME absent report, whereas 4 patients were using both RosiGlitazone and PioGlitazone at different time reported with CSME presence and absence, each of 2 cases.

LIMITATIONS:

The limitation of this study was that the patients were recruited irrespective of investigation drug exposure time and duration of DM. Other etiology

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like Dyslipidaemia was not considered here. Future study must be performed considering all these limitations.

CONCLUSION:

In this study 100 DM cases identified with Diabetic retinopathy are recruited where Group 1(n=50) were Glitazone users and the Group 2 (n=50) were Glitazone Non-users. The Drug exposure group and Non-exposure group were statistically analyzed for the relative risk ratio for existence of Clinically Significant Macular Edema. The RR ratio is greater than 1 which signifies that the Glitazone exposure group had the higher risk of getting CSME when compared to Glitazone non users.

Therefore Patients already reported with CSME may take caution up on the decision to continue with Glitazone. Usage of Thiazolidinediones at the optimal doses will help in preventing hyperglycemia and also dose related adverse effect such as CSME. Prevention of DR and DME through optimal level of metabolic control and periodical fundus evaluation and early treatment is advisable. The Pharmacological and surgery treatments of the method becomes useless if the optimal metabolic level is not maintained after treatment, which further requires additional treatment for remission. Treatment procedure coupled with metabolic control through diet, exercise etc., and rational use of Glitazones gives desired outcome.

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