# EVALUATION OF ROLE OF LONG-TERM TREATMENT WITH METFORMIN IN AFFECTING THE SEVERITY OF DIABETIC RETINOPATHY IN HIGH RISK INDIVIDUALS SUFFERING FROM TYPE 2 DIABETES MELLITUS

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**ABSTRACT:**

**Aim:** To investigate the impact ofmetformin for a prolonged period of time on the severity of diabetic retinopathy (DR) in individuals with type 2 diabetes who are at high risk of developing diabetic retinopathy.

**Methods:** This is a recent retrospective review research comprising 338 DR patients with T2D of less than 16 years and it was carried outduring the period of May 2019 to April 2021. The intensity of DR was evaluated using the scale that was developed for the Early Treatment of Diabetic Retinopathy Research. We looked at the connections between metformin use and the frequency of DR symptoms. When compared with the stratum for usage of sulfonylurea and insulin, the results were determinedto estimate the presence of potentially confusing effects.

**Results:**Retinopathy had been foundmore frequently among individuals who did not take metformin (69/145, 48%) as compared to metformin consumers (51/198, 26%) (p 0. 002). This was the case independent of the patients' gender or race. The statistical method for metformin being linked increasing SNPDR/PDR has been 0.39 in altogether instances (p 0 002), 0.36 in the sulfonylurea use cohorts (p 0 06), 0.46 in the non-sulfonylurea usage cohorts (p 0 02), also 0.43 in the insulin use cohort (p 0 02). Consumers of insulin hadsignificantly greater incidence of SNPDR and PDR. Metformin did not have any effect on expansion of clinically substantial diabetic macular edema in patients taking the medication.

**Conclusions:** In individuals younger than 16 years' old thatare suffering from type 2 diabetes withthe history of long term intake of metformin, there isstatically meaningful decreased risk of developing SNPDR and PDR.

**Keywords:** Severity of Diabetic Retinopathy, Type 2 Diabetes.
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**INTRODUCTION:**

There are 28.4 million persons in Pakistan who are living with diabetes, and diabetic retinopathy is affecting 28.5% of those suffering from diabetes [1]. Roughly one quarter of those diagnosed with DR will eventually develop seriousdiabetic retinopathy or proliferative diabetic retinopathy and retinal damage caused by diabetes. The appearance of macular edema, retinal angiogenesis, vitreous hemorrhage, and retinal detachment are often present in patients diagnosed have SNPDR/PDR, which is typically linked with substantial visual impairment [2]. In Spite of the advances in systemic metabolic management and the widespread use of laser photocoagulation, diabetic retinopathy remains the major cause of legal blindness among people of working age in Pakistan [3].Metformin has been used as a treatment for hyperglycemia since 1960s [4-7]. Currently, it has emerged as the primary treatment for type 2 diabetes and the most extensively used oral medicine for the condition. The recently discovered preventive impact of metformin against micro vascular and macro vascular problems in diabetes mellitus that goes outside glucose control has led to a rise in the use of metformin as the favored therapy for type 2 diabetes (T2D) [9-11].

The Pakistan Prospective Diabetes Investigation, which is considered to be a landmark experiment, indicated that metformin had a significantly favorable influence on the outcomes of cardiovascular disease[12]. This outcome was backed by a variety ofunique research trials as well as meta-analysis, which discovered that metformin, despite possessing no anti-diabetic activity, hassignificantly decreased the risk of vascular diseases in diabetes individuals as compared to any other oral hypo-glycemics or placebo [13]. In addition, it has been shown that metformin may substantially enhance endothelium-dependent vasodilatation and reduce blood indicators of endothelial activation in people with type 2 diabetes[14-18]. These markers include soluble vascular adhesion molecule-1 and also soluble intercellular adhesion molecule-1. However, there is a lack of first-hand medical studies addressing the impact of metformin in DR. This evidence suggests that there is a possible influence of metformin on improving micro vascular diabetes-related complications such as DR [19].

Researchers has analyzed the data from this historical cross-sectional research to determine theconnection between oral intake of metformin for a very long time andseverity of diabetic complications in people who have had type 2 diabetes for 17 years or more. Individuals using metformin were shown to have a lower risk of havingSNPDR/PDR participants compared to those who were not medicated with metformin,regardless of factors such as gender or color, as well as glycated hemoglobin levels. There was no confusion caused by the usage of insulin or sulfonylurea in the findings regarding the connection among metformin and a significantly decreased risk of SNPDR/PDR [20].

**METHODOLOGY:**

This research was retrospectively cross-sectional research that took place at Henry Ford Health System between May 2019 and April 2021. It covered all individuals with the diagnosis of DR who also had the diagnosis of T2D for less than 17 years. The index date for each case was the period of the patient's most recent visit, which was used to identify patients as having the diagnosis of DR according to the International Classification of Diseases, version 9. The participants in this research were split into two separate groups. One of the groups was the one that was managed with metformin, and this category included everyone who had

taken oral metformin for a period of six or more years in a row. Another group was the one thatincludepatients that were not documented as having treatment with metformin for type 2 diabetes and labeled as control group. The administration of insulin or any other hypoglycemic medications simultaneously was not ruled out in any of the categories. Cases that had a history of retinal detachment, intermittent use of metformin, Wet-type age-related macular degeneration or the presence of all other retinal vascular illnesses, including retinal vein obstruction, have been discounted from the research. Researchers decided to restrict our analysis to people who had history of suffering from type 2 diabetes for less than 17 years and had been taking metformin for less than six years because the incidence of visual complications were found to be significantly higher in people whose diabetes had been present for more than 16 years, and it takes time for the effects of medication to become obvious. The RecognizedAppraisalPanel of the Henry Ford Health System gave its blessing to the research project after ensuring that it complied with the precepts of the Declaration of Helsinki.

Thismentioned data was gathered from every case: (1) demographic functionalities including age, sex, also race; (2) basic knowledge of T2D evolution and also strategic planning, just like the date of T2D judgment, 2-year HbA1c levels (such as last, median, also highest levels), also date of T2D treatment(3)medicines for type 2 diabetes (which include metformin, insulin) (4) the scoring of DR also any previous therapies for DR, including infrared photocoagulation and intra-vitreal inter-vascular endothelial neurotrophic agents(5) ophthalmic history, which include retinal vein occlusion and age-related vision problems. A retinal expertwas the one who made the diagnosis of DR. In accordance with these criteria, the intensity of diabetic retinopathy (DR) was graded. In addition existence of medicallyapplicable macular edema was evaluatedconferring to scoring requirements of the Early Treatment Diabetic Retinopathy Homework. In accordance with severity of the symptoms, each patient was classified as having either a mild or severe NPDR or an SNPDR/PDR. In the event where both eyes were affected by DR, seriousness of the condition might be based on the grade in the eye which was more severe.

In all of the instances, and also in the subgroups that were classified as per sex and race, a comparison was made seen between rate of SNPDR/PDR in patient taking metformin and in the control set that did not take metformin. Researchers assessed the connection among hypoglycemic therapy and the intensity of DR in all instances, as well as in procedure cohorts, by calculating the incidence (OR) of SNPDR/PDR.

The software program SAS, version 9.3, was used to carry out the statistical study. In the case of no sparse data, we used the usual chi-square test to evaluate whether or not there was a distinction among categories of descriptive analysis. In availability of sparse data, we used the Fisher exact test. The occurrence of predicted cell countslower than five was the definition of sparsity. In the condition of distributional regularity, a two-sample t-test was used to obtain information. In case of distributional non-normality, a Wilcoxon rank sum test was utilized. The odds ratios and confidence intervals for 96% were derived by an examination of logistic regression, with the statistical significance of OR being evaluated using either chi-square test or Fisher's exact test. When p was less than 0.05, we regarded the hypothesis to be significant.

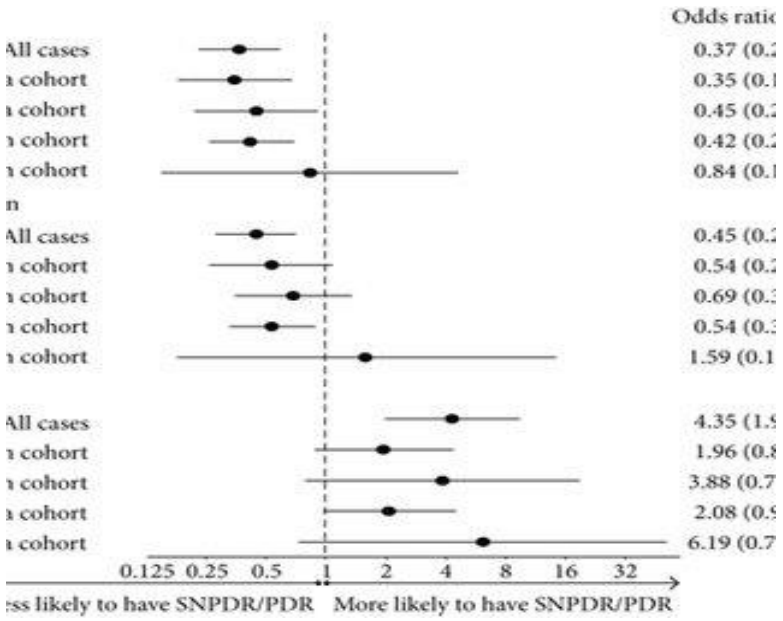
338 DR patients who had type 2 diabetes for 16 years or more participated in this retrospectively cross-sectional research. Metformin usage was present in 195 instances, which accounts for 59% of the totalfor at least six years in a row, and 144 (43%) of them had no record of ever having used metformin. Both groups had similar ages, gender distributions, and racial compositions, among other demographic characteristics (Table 1). In the sample that used metformin, the duration of T2D was 16.2 7.8, but in the person that did not take metformin, it was 16.8 9 (p = 0.38; Table 1). Both the metformin subgroup and the

comparison group that did not take metformin had HbA1c levels that were quite similar to one another in terms of their greatest, lowest, and median values during the last five years (p = 0.411,0.82 and 0.59 correspondingly; Table 1). In the non-metformin group, a higher proportion of patients utilized insulin, whereas in the metformin group, a lower number of patients did so (144 of194 out of 144, or 76%, compared to 133 out of 144, or 95% (p .002; Table 1). On the other hand, 143 out of 194 metformin patients, or 75%, also used sulfonylurea, but only 56 out of 145 non-metformin participants, or 39%, had sulfonylurea therapy (p 0.002; Table 1). This indicates that sulfonylurea treatment is much more effective in glycemic control. Only ten patients made use of any additional oral hypoglycemic medications, just like as thiazolidinedione, glucagon-like peptide-1 receptor agonists, or DPP-4 inhibitors. Intravitreal and focal/grid laser photocoagulation, pan-retinal photocoagulation, and other forms of local treatment for DR are all examples of local therapyinjections of anti-VEGF were given to patients in both groups. When compared with the non-metformin cohort, the number of individuals in the metformin group who were given PRP was considerably lower (49 of 194 or 26% vs. 62 of 145 or 44%; p =.002; Table 1). There wasn't substantial distinction between the two teams in terms of the use of anti-VEGF medicines or focal/grid laser photocoagulation (Table 1).

SNPDR/PDR has been found in 49 (26%) of the participants who had taken metformin for 6 years or more, while it was detected in 68 (48%) of the individuals who had been taking metformin for less than 6 years. At time of our investigation, remainder of the participants in both subgroups had been classified having moderate to moderate NPDR. This was the case for 54 percent of individuals in non-metformin group and 76 percent of patients in followed order. The odds ratio for SNPDR/PDR in metformin users remained 0.38 (96% CI, 0.24–0.57) (p 0.0002; Table 2) once all cases were included, results indicated that therapy using metformin results in a decrease in SNPDR/PDR of 64 percent. Control of gender and ethnic subgroups indicated additionally that longer-term metformin use remainedrelated to the considerably condensed risk of SNPDR/PDR in subgroups of both female and male patients, also black and white patients (Figure 1).



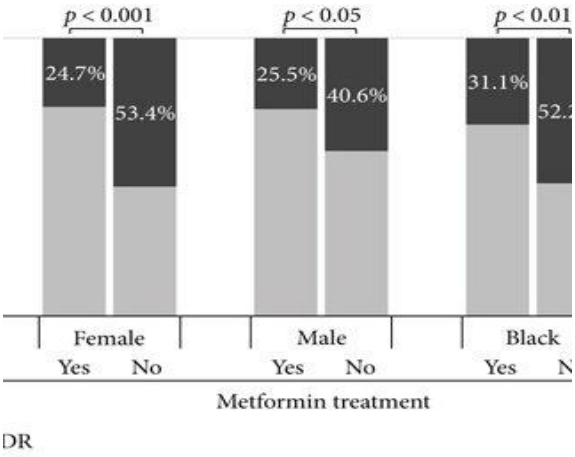
**Figure 1:**




Because hereremained discernible contrast between utilization of insulin and sulfonylureas,connection among these hypoglycemic medications with the incidence of SNPDR/PDR has been assessed here between 2 groups (both of which had p values that were more than 0.0002; Table 1). According to the findings shown in Table 2, a total of 55 out of 197 (or 26%) people on sulfonylurea had SNPDR/PDR, while 64 out of 139 (or 47%) these were not taking sulfonylurea. The odds ratio was 0.47 (96% CI, 0.28–0.71; p 0.0002; Table 2); this indicatesthat people who are treated with sulfonylurea have a reduced risk of developing SNPDR or PDR. a total of 109 out of 275 (38%) insulin-treated individuals were found to have SNPDR/PDR, while just 9 out of 65 non-insulin users (14%) were found to have SNPDR/PDR. The odds ratio for SNPDR/PDR caused by insulin was 5.36 (96% CI, 1.98–8.51) (p 0.0002; Table 2). Because of it, insulin has shown to a correlation with a greater risk of SNPDR/PDR, which was the reverse of what metformin was found to have. In addition, a comparison was carried out using stratification for hypoglycemic therapies in order to establish any potential confusion. The link between metformin with a decreased prevalence of SNPDR/PDR remained stable in both the sulfonylurea cohort and the non-sulfonylurea cohort [OR 0.36 (96% CI, 0.19–0.69), p = 0 04] and the non-sulfonylurea cohort [OR 0.46 (96% CI, 0.23–0.92), p = 0 002], respectively as compared to the insulin cohort [OR 0.43 (96% CI, 0.27–0.8), p = 0.0002]. (Figure 2).



**Figure 2:**




Metformin usage was linked with a corresponding tendency of decreased SNPDR/PDR in the noninsulin group, although this trend had not been significant statistically [OR 0.85 (96% CI, 0.16–6.66), p = 0 839]. (Figure 2). These findings pointed to a connection between the two.

It was shown that connotation among metformin and the decreased risk of SNPDR/PDR was independentof sulfonylurea;in addition it was also expected to be independentof insulin. The consequence of sulfonylurea remained divergent because once categorized for usage of insulin, with just thelesser rate of SNPDR/PDR in insulin cohort [OR 0.56 (96% CI, 0.34–0.89), p = 0 013], sincethe higher rate in non-insulin cohort. Sulfonylurea diagnosis lost its stronger correlation to discounted price of SNPDR/PDR because once categorized for the use of metformin [OR 0.56 (96% (Figure 2). Hence, the impact of the sulfonylurea on the duration of the DR was actually changed when metformin or insulin was being used.That was fascinating to see that customers who were taking insulin had the higher probability of having SNPDR/PDR in cohort studies that had been compartmentalized either by the metformin or mesylate [OR 1.97 (96% CI, 0.87-5.37), p = 0 097 for metformin users; OR 4.87 (96% CI, 0.79-18.98), p = 0 075 for non-metformin subscribers; OR 2.09 (96% (Figure 2).

Before anti-VEGF treatment became developed, the most common type of treatment for CSME was a sort of laser photocoagulation called focal/grid laser photocoagulation. CSME that required focal/grid laser was discovered in 84 of 195 (44%) instances amongst metformin users, while it was recognized in 68 of 143 (48%) cases among non-metformin users. There was found to be no statistically substantialvariance between two assemblages (p = 0.34).



**Table 1:**

| **Character** | **Metformin treated (*n* = 198)** | **Non-metformin treated (*n* = 148)** | **p-value** |
|---|---|---|---|
| Age (years) | 73.8 ± 10.6 | 74.2 ± 9.7 | 0.74 |
| Gender | | | |
| Female | 94 (48) | 74 (52) | 0.68 |
| Male | 99 (51) | 69 (49) | |
| Duration of diabetes | 15.1 ± 6.7 | 15.7 ± 7 | 0.38 |
| HbA1c (%) | | | |
| 5-year median | 8.2 ± 1.4 | 8.2 ± 1.3 | 0.57 |

| | | | |
|---|---|---|---|
| 5-year low | 7 ± 1.3 | 6.9 ± 1.1 | 0.41 |
| 5-year high | 9.5 ± 1.8 | 9.4 ± 2 | 0.82 |

**Table 2:**

| **Diabetes treatment** | **Severity of DR** | **Mil/Mod NPDR number (%)** | **OR (96% CI)** | ***p* value** |
|---|---|---|---|---|
| Outcome of metformin | | | | |
| Metformin users (*n* = 193) | 146 (78) | 49 (26) | | |
| Non-metformin users (*n* = 147) | 67 (47) | 75 (53) | **0.37 (0.23–0.59)** | **<0.002**∗ |
| Effect of insulin | | | | |
| Insulin users (*n* = 275) | 108 (39) | 167 (61) | | |
| Noninsulin users (*n* = 67) | 8 (13) | 54 (87) | **5.36 (1.98–8.51)** | **<0.002**∗ |
| Effect of sulfonylurea | | | | |
| Sulfonylurea users (*n* = 199) | 55 (27) | 144 (73) | | |
| Non-sulfonylurea users (*n* = 138) | 63 (46) | 75 (54) | **0.46 (0.29–0.72)** | **<0.002**∗ |



**DISCUSSION:**

Rendering to the findings of the Pakistan Prospective Diabetes Study, individuals who had diabetes and used metformin had a considerably lower risk of a variety of diabetes-related macro-vascular and micro-vascular complications as contrasted to those who took alternative hypoglycemic medications [21]. As one of several possibleconclusionsof, according to the UKPDS, metformin therapy was linked to a lower risk of DR advancement in individuals who were overweight and diabetic when compared to a diabetes diet treatment [22]. This study examined if metformin affects the prevalence of diabetic retinopathy in elevated diabetics, albeit it differed from UKPDS in certain ways.Rising diabetic patients were defined as those who had a history of T2D for 17 years or more. We discovered an important connection among oral metformin use for more than six years and reduced severity of DR in these individuals. This link was not accompanied by a change in HbA1c level [23]. In addition, this link held true regardless of the gender or race of the participants, and it did not rely on whether or not the participants were taking insulin or sulfonylurea at the same time. According to the findings of our research, insulin usage was linked to more severe DR [24].Because this was retrospective research, we weren't really able to exercise any kind of control over how the patient's used insulin and sulfonylurea. Insulin therapy was administered to 94% of patients who did not use metformin, compared to 74% of metformin patients. On the other hand, there were a greater number of customers in the metformin group [25].

75% of individuals in the non-metformin group got sulfonylurea, opposed to just 39% of those in the metformin group. In cases when oral drugs are unable to adequately manage blood glucose levels, insulin treatment is often recommended as an alternative. Insulin was probably prescribed to non-metformin patients at some time in their lives because their blood sugar levels were difficult to manage [26]. This

may be one factor that contributed to a greater danger of DR in non-metformin patients. Since those multiple clinical specifications are thought to remain the most significantissues that affect the development of DR, having the two groups be identical with regard to their history of diabetes and their 5-year HbA1c levels managed to help provide one comparatively equivalent contrast concerning dangerous aspects of DR in our research[27-31]. Having said that, it is essential to emphasize the fact that tightglycemic control and thelower HbA1c has a small impact on DR in T2D afterprotracted follow-up, as made evident through large-scale and long-term clinical trainingswiththe 5.2-year ADVANCE education, the 6.7-year VADT trial, and a 10-year follow-up of UKPDS. These experiments were conducted over a period of time ranging from 5 to 7 years [32]. We hypothesize that the differences in the taxes of SNPDR and PDR here among two different setsremained not merely a reflection of blood glucose levels that was managed individually, but rather represented metformin's ability to directly regulate the pathogenic susceptibility factors that are connected with DR [33].

Our discovery that therapy using metformin for an extended period of time was related with past clinical and fundamental research findings on preventive benefits of metformin against with the micro-vascular consequences of diabetes provided evidence for dramatically decreased risk of SNPDR and PDR [34-37]. In particularly, this research contributes fresh clinical evidence on the influence of metformin on intensity of DR in individuals who already have type 2 diabetes [38]. Glycemic control was not a factor in this investigation. We employed stratification comparability to account for the potentially confounding impact of both insulin and sulfonylurea, despite the fact, here remained an imbalance in usage of insulin and sulfonylureaamong two sets [39-41]. The raw and adjusted odds ratios for the metformin therapy assist to eliminate the confounding factors. The fact that the crude OR for sulfonylurea was significantly different from its adjusted OR showed that their impact remained influenced by metformin and insulin. Insulin had the opposite impact on the intensity of DR symptoms produced by metformin and sulfonylurea, respectively [42]. In the form of a mono-centric and retrospectivecross-sectional investigation, researchersremainedable to control some of the most significant risk variables of DR. It is possible that unmeasured confounding factors will persist, such as BP, blood lipid, and the degree of micro-proteinuria. In order to have a clearer picture of how metformin affects the development of DR in people with type 2 diabetes, it will be necessary to conduct prospective studies in the near future on a larger scale [43].

**CONCLUSION:**

The significance oflong-term metformin therapy is that it lower incidence of DR in individuals with type 2 diabetes who already have the disease must be evaluated from our findings. This link remains despite the absence of a distinct HbA1c level; it is consistent across gender and racial cohorts; and it is not complicated through the therapy with sulfonylurea or insulin. Insulin patients had thesuggestively increased danger of having serious DR compared to non-insulin patients. Individuals who have had type 2 diabetes for a very long time could benefit from taking metformin in order to slow the growth of diabetic retinopathy. Our analysis is theoretical research, and for a comprehensive assessment of the precise function that metformin plays in the development of DR, more research on a larger scale is required in the prospective methods.



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