Diabetic retinopathy (DR) is one of the leading causes of visual loss in adults aged 20–74 years. DR is ranked among the top five causes of preventable blindness and moderate to severe visual impairment.\(^1\) It constitutes 4.8% of the global causes of blindness, with prevalence in India ranging from 7.3% to 25%.\(^1\) There is increasing evidence suggesting the role of immunological mechanisms in the pathogenesis of DR. The upregulation of cytokines and other inflammatory mediators leads to persistent low-grade inflammation, which contributes actively to DR-associated damage to the retinal vasculature. Various studies have shown increased levels of the immune mediators in the vitreous humor of patients with DR, thus implicating their role in the pathogenesis.\(^3\)

Multiple studies suggest that inflammation is associated with both the major causes of impairment of vision in DR, namely increased retinal vascular permeability manifesting as diabetic macular edema (DME) and neovascularization, resulting in proliferative diabetic retinopathy (PDR).\(^4\)\(^6\) High tumor necrosis factor (TNF-\(\alpha\)) levels have been detected in vitreous, serum, and ocular fibrovascular membranes in patients with DR.\(^7\)\(^8\) TNF-\(\alpha\) gene polymorphism is associated with increased susceptibility to the disease.\(^10\) Similarly, interleukin-1 beta (IL-1\(\beta\)) is found in high concentrations in the vitreous and retina of diabetic patients.\(^11\)\(^13\) Interleukin6 (IL-6) levels in the vitreous are significantly correlated with the severity and progression of DR.\(^12\)\(^14\) In patients with PDR, increased vitreous concentrations of the IL-1\(\beta\), IL-6, soluble interleukin-2 receptor (sIL-2R), and Interleukin-8 (IL-8) were found.\(^15\)\(^16\) The mean serum TNF-\(\alpha\), IL-8, and sIL-2R levels increased with the stage of DR, with the highest levels being detected in patients with the proliferative form.\(^17\)

Also, an increase in adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) promote chemo-attraction of leukocytes into the vascular walls and their migration into retinal tissues.\(^18\)\(^19\) Besides disrupting the inner blood-retinal barrier, leukocytes produce VEGF that increases vascular permeability and promotes angiogenesis.\(^20\)

Treatment options available include laser photocoagulation, intravitreal triamcinolone (IVTA), and anti-VEGF, which are applicable only for PDR and DME. Other than controlling the risk factors, there is no option available currently for preventing the onset and progression of DR. The Purpose of the study was:
to develop novel concepts that act on the inflammatory process for delaying the onset and halting the progression of DR.[301]

**Methods**

A prospective observational case-control study was carried out in the Department of Ophthalmology at a tertiary care center in South India for 18 months. The study was carried out as per the guidelines of the Declaration of Helsinki. Ethical committee approval number JSS/MC/PG/4623/2018-19.

**Inclusion criteria:** Study group: Patients with type 2 Diabetes mellitus (DM) of 10 years or more duration without DR and on immunosuppressants and patients with type 2 DM with DR and on immunosuppressants. Control group: Patients with type 2 DM of 10 years or more duration without DR and patients with type 2 DM with DR.

**Exclusion criteria:** Diabetics with media opacities hindering fundus examination and optical coherence tomography (OCT), those who have undergone pan-retinal photocoagulation or intravitreal anti-VEGF or steroid injection, pregnancy, proliferative DR, and hypertensive retinopathy.

Fifteen patients recruited in the study group were on immunosuppressants for some other coexisting disease such as rheumatoid arthritis (RA) and post-renal transplantation. Consecutive patients with DM on immunosuppressants attending rheumatology and renal clinics for regular follow-up were actively sought and invited for screening. Consecutive patients of DM from medicine clinics too were sought for the study as controls.

In the study group, 11 were RA patients and 4 were post-renal transplant patients.

The RA patients were on disease-modifying anti-rheumatic drugs (DMARD) such as Hydroxychloroquine 200–400 mg/day, methotrexate 7.5–25 mg/week, and leflunomide 10–20 mg/day; some were also on a low dose of steroids such as prednisolone 0.1 mg/kg/day. The post-renal transplant patients were on immunosuppressants such as prednisolone 20 mg, mycophenolate mofetil 300–2000 mg/day, and tacrolimus 1–4 mg/day. None of the patients had post-transplant DM (PTDM). The minimum duration of use of immunosuppressants was 1 year, the mean duration was 2.5 ± 1.6 years, and the median duration was 2 years.

Fifteen patients in the control group were not on immunosuppressants. Patients were matched for age, duration, control of diabetes, and other co-morbidities such as hypertension, renal disease, and cardiac disease. Each subject underwent detailed history, slit lamp evaluation, and dilated fundus examination with +90D for DR and staged according to Early Treatment of DR Study (ETDRS) classification. Fundus photos were taken using Zeiss Visucam NM/FA in central 45 degrees. [Fig. 1] Cirrus HD-OCT Model 500 was used to take OCT macular cube 512 × 128 scans whenever macula was involved. Subjects also underwent blood investigations such as HbA1c, blood urea, and serum creatinine. All the above mentioned procedures were repeated at the second visit after 1 year. A complete examination was carried out by the same observer at each visit. As there was no center involving DME, no additional treatment was given.

**Statistical analysis**

Data were entered into a Microsoft Excel datasheet and were analyzed using SPSS 21 version software. Categorical data were represented in the form of frequencies and proportions. The Chi-square test was used as a test of significance for qualitative data. An unpaired t-test was used to obtain the P value from quantitative data. Continuous data were represented as the median. Graphical representation of data: Microsoft word was used to obtain bar diagrams and graphs. P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

**Results**

A total of 30 patients aged between 47 and 83 years were included in the study, out of which 15 patients were with type 2 diabetics and on immunosuppressants (study group) and 15 patients were with type 2 diabetics but not on immunosuppressants (control group). The median age of the study group and the control group [Table 1a] was 57 years and 60 years, respectively (P = 0.6). The mean age for the study and control group was 60.2 ± 8.82 and 60.33 ± 6.45, respectively. In the study group, 20% (3) and 80% (12) were males and females, respectively; in the control
The renal status between the two groups [Table 1b] was comparable as the median blood urea levels between the study and control group at 1st visit were 25 mg/dl in both groups ($P = 0.93$) and at 2nd visit were 25 mg/dl and 26 mg/dl ($P = 0.61$). The median serum creatinine levels between the study and control group at 1st visit were 0.9 mg/dl in both groups ($P = 0.68$) and at 2nd visit were 1 mg/dl in both groups ($P = 0.81$). The $P$ value for blood urea between 1st and 2nd visit for the study group was 0.75 and for the control group was 0.23. The $P$ value for serum creatinine between 1st and 2nd visit for the study group was 0.1 and for the control group was 1. The median HbA1c at 1st and 2nd visit for study group was 7.6% and 7.5%, respectively ($P = 0.11$), and at 1st and 2nd visit for control group was 8.0 and 8.1, respectively ($P = 0.78$). The median HbA1c for study and control group for first visit was 7.6% and 8.0%, respectively ($P = 0.26$), and for second visit was 7.5% and 8.1%, respectively ($P = 0.11$).

None of the patients in either group were smokers or on Fenofibrate. None of the female patients in either group were pregnant.

### Table 1a: Baseline characteristics of subjects among the two groups

| Variables                   | Study group (n=15) | Control group (n=15) | $P$ |
|-----------------------------|-------------------|----------------------|-----|
| Age (years)                 | Median 57         | 60±8.82             | 0.6 | 0.133 |
| Duration of diabetes (years)| 11                | 11.87±3.07          |     |       |
| Gender                      |                    |                      |     |       |
| Males$^*$                   | 3 (20%)           | 8 (53.3%)           |     | 0.06  |
| Females$^*$                 | 12 (80%)          | 7 (46.7%)           |     |       |
| Hypertension$^*$            | 9 (60%)           | 4 (26.7%)           |     | 0.065 |
| Renal disease$^*$           | 4 (26.7%)         | 2 (13.3%)           |     | 0.361 |
| Cardiac disease$^*$         | 2 (13.3%)         | 2 (13.3%)           |     | 1     |

$^*$Frequency (percentage)

### Table 1b: Median/Mean HbA1C, blood urea, and serum creatinine and DR status at 1st and 2nd visit

| Visit | Study group (n=15) | Control group (n=15) | $P$ |
|-------|-------------------|----------------------|-----|
|       | Median Mean±SD    | Median Mean±SD       |     |
| HbA1c (%) | 1st | 7.6 7.61±0.589 | 8.0 7.78±0.487 | 0.26$^*$ 0.406 |
|       | 2nd | 7.5 7.51±0.576 | 8.1 7.74±0.728 | 0.11$^*$ 0.326 |
| $P$   |      | 0.11$^*$         | 0.78$^*$           |     |
| Urea (mg/dl) | 1st | 25 25.73±4.11 | 25 25.8±3.67 | 0.93$^*$ 0.96 |
|       | 2nd | 25 25.67±4.29 | 26 26.27±3.86 | 0.61$^*$ 0.69 |
| $P$   |      | 0.75$^*$         | 0.23$^*$           |     |
| Creatinine (mg/dl) | 1st | 0.9 0.91±0.15 | 0.9 0.94±0.19 | 0.68$^*$ 0.67 |
|       | 2nd | 1 0.97±0.2 | 1 0.95±0.18 | 0.81$^*$ 0.85 |
| $P$   |      | 0.1$^*$          | 1$^*$              |     |
| No DR$^*$ | 1st | 8 | 9 | 0.57$^*$ |
|         | 2nd | 8 | 6 | |
| Mild NPDR$^*$ | 1st | 6 | 6 | 0.84$^*$ |
|         | 2nd | 6 | 7 | |
| Moderate NPDR$^*$ | 1st | 1 | 0 | 0.24$^*$ |
|         | 2nd | 1 | 2 | |

$^*$Frequency, $^*$test used is Mann Whitney U test, $^*$test used is Wilcoxon test, $^*$test used is Chi-square test. DR: Diabetic Retinopathy, NPDR: Non-Proliferative Diabetic Retinopathy. HbA1c: Glycosylated hemoglobin
At the 1st visit, in the study group, 53.3%, 40%, and 6.7% had No DR, mild non-proliferative DR (NPDR), and moderate NPDR, respectively. In the control group, 60% and 40% of participants had no DR and mild NPDR, respectively. This distribution was not statistically significant between both the groups (\(P = 0.589\)) [Fig. 2a].

On the 2nd visit, in the study group, 53.3%, 40%, and 6.7% had no DR, mild NPDR, and moderate NPDR, respectively, whereas in the control group, 40%, 46.7%, and 13.3% of participants had no DR, mild NPDR, and moderate NPDR, respectively. This distribution was not statistically significant (\(P = 0.706\)) [Fig. 2b]. All cases of DR were bilateral and symmetrical.

Among the control group, in the 1st and 2nd visit, no DR was seen in 60% and 40%, respectively. Mild NPDR was seen at 40% and 46.6%, respectively, and moderate NPDR was seen at 0% and 13.3%, respectively (\(P = 0.262\)) [Fig. 3a].

In the study group, 53.3% of patients had no DR, 40% patients had mild NPDR, and 6.7% patients had moderate NPDR at both the 1st and 2nd visit (\(P = 1\)) [Fig. 3b].

At the end of one year, the control group showed 33.3% progression in DR between the 1st and 2nd visit, whereas the study group did not show any progression between the two visits (\(P = 0.014\) according to Chi-square test, \(P = 0.0422\) according to Fisher exact test) [Fig. 4]. Among the control group, three progressed from no DR to mild NPDR and two progressed from mild NPDR to moderate NPDR.

**Discussion**

The initial step in the management of DR is to reduce the risk of its occurrence and progression by the control of the risk factors such as hyperglycemia, hyperlipidemia, and hypertension. In addition to controlling these modifiable risk factors, regular dilated eye examinations have been shown to reduce the incidence of blindness due to DR through early detection and timely treatment. Despite the standard intervention, loss of vision due to DR still occurs at an alarming rate. Currently, there is no intervention to prevent the development of DR other than tight glycemic control. Treatment options available are only for PDR.
and centers involving DME which carry various adverse effects. Anti-VEGF’s are one of the treatment options; however, they do not act on the cause, and instead, they act on the consequence of the disease, which is elevated secretion of VEGF. Consequently, such a treatment is unlikely to result in sustained improvement.

In addition, anti-VEGF therapy does not always provide resolution of DME, most likely due to causal mechanisms being via pathways other than VEGF leading to DR. Approximately one-quarter of eyes do not respond fully to currently used anti-VEGF.

Therefore, it is of interest to come up with strategies for preventing DR. Understanding the molecular mechanisms behind the occurrence of DR may lead to many effective treatment options.

Advanced glycation end-products bind to proteins and lipids in the basement membrane of retinal cells, leading to its thickening and hyalinization, especially of the endoneural microvessels, thus decreasing the transport of oxygen to and other metabolic products from the tissue. Also, the glycated hemoglobin as a result of hyperglycemia results in impaired oxygen transfer to tissue. The uncontrolled DM patients also show a loss of autoregulation of the retinal blood flow consequent to the loss of neurovascular function, leading to increased retinal blood flow with a resultant rise in the shear stress on retinal microvasculature. This leads to increased reactive oxygen species (ROS) synthesis from the endothelial cells due to its damage from mass effect. This triggers the inflammatory pathway, causing the release of cytokines, which lead to vascular pliability and consequent extravasation of lymphocytes and edema of retinal tissue leading to vision loss. Thus, hyperglycemia leads to inflammation of hypoxic origin. The ROS affect the mitochondrial protein expression and cause pathological changes in the mitochondria, leading to hypoxia and adenosine triphosphate (ATP) depletion. This hypoxia consequently stimulates the production of growth factors. As a result of the hyperglycemia, the increased glucose intracellularly is converted to sorbitol in an excessive amount leading to osmotic effect and cell death.

Inflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-1β were found to be significantly upregulated in diabetic patients, and their expression level was correlated with the severity of DR. Thus, acting on this pathway may suggest the possibility of promising results in patients with PDR as well. Sirtuins, a class of 7 histone deacetylases, play an important role in DR as they regulate the activation of the inflammatory responses. A correlation of DR with the aqueous flare levels in the early stages supports the role of inflammation in the pathogenesis of diabetic retinal neuropathy. Thus, different pathways predominate at different stages of the disease, therefore giving different potential targets at different stages of the disease.

As there is an involvement of inflammatory processes in the form of low-grade chronic inflammation in the pathogenesis of DR, inhibiting the inflammatory pathway could be a novel treatment option.

In a study by Rupak Roy et al. on post-renal transplant patients, the status of DR pre- and post-renal transplant was followed for nearly 4 years. Around 60% of the patients had stable retinopathy; 32% showed worsening and 8% of patients showed improvement in the DR status. This was thought to be due to good glycemic control and other co-morbid factors. Another study by N.S. Mittal also showed stable DR post-renal transplant in type 2 diabetic patients. This study included 19 men and 1 woman with a mean age of 52 years, and the patients were followed up for 12 months. Before the renal transplant, 95% of the patients showed DR (50% NPDR, 45% PDR). There was no change in retinopathy at 3 months after renal transplant. At 1 year, 2 patients (10%) showed deterioration in their DR status, while 90% did not show any change. All patients post-renal transplant were invariably on lifelong immunosuppressants. This could also be thought of as a possible explanation for the non-progression of DR in such patients. However, the authors have not factored in this possibility in their discussion. Also, in the above two studies, it is not mentioned what immunosuppressant’s the post-renal transplant patients were on.

In our study, the glycemic control in both groups was fairly good, as reflected by comparable HbA1c levels in both groups. Patients in both the groups were also matched for age, duration of diabetes, and other co-morbidities. Female preponderance in the study group could be due to the inclusion of patients with RA. It was found that the progression of DR was 33.3% in patients not on immunosuppressants (control group), whereas in the patients on immunosuppressants (study group), the progression was found to be 0% (P = 0.014 – Chi-square test, P = 0.0422 – Fisher exact test).

This pilot study suggests the possibility that long-term immunosuppressants may be of benefit in delaying the onset and progression of DR. Studies with a larger sample size and longer follow-up are needed to confirm these observations.

Immunosuppressants and DMARDs can have varied effects on blood sugar levels, such as steroids and tacrolimus causing hyperglycemia, whereas hydroxychloroquine has a hypoglycemic effect; methotrexate, leflunomide, and mycophenolate mofetil have no bearing on blood sugar levels.

Mechanism of action of steroids is multiple, predominantly being IL1 and IL6 cytokine inhibition; tacrolimus is a calcineurin inhibitor, and methotrexate acts as an adenosine and dihydrofolate reductase inhibitor. Hydroxychloroquine has a multimodal effect, such as antithrombotic, anti-dyslipidemia, and hypoglycemic properties, and increases cell pH, causing alkalinization followed by a decrease in free radicals. By contrast, leflunomide is a dihydroorotate inhibitor and mycophenolate acts as an inosine monophosphate dehydrogenase inhibitor.

The choice between a DMARD and an immunosuppressant purely depends on disease phenotype and disease activity. However, there are certain side effects of systemic immunosuppressants, such as increased susceptibility to infection, nephrotoxicity, bone marrow toxicity, gastrointestinal side effects, and malignancy. The adverse effects of prolonged DMARDs and immunosuppressants need monitoring; thus, monitored use of either will mitigate anticipated adverse effects. It is to be seen if only DMARDs are equally effective in preventing the onset and progression of DR. The DMARDs that can be studied in greater detail include hydroxychloroquine, methotrexate, and leflunomide. Also, the other modes of delivering safer DMARDs can be studied. To the best of our knowledge, this is the first study to evaluate the effect of immunosuppressants on the progression of DR. It
demonstrated that immunosuppressants are useful in earlier stages of DR where the standard of care is not applicable. Also, it is a prospective study, with the two groups being well matched for age, duration, control of diabetes, and hypertension.

Limitations of this study include small sample size; short duration of follow-up; non-inclusion of confounding factors such as lipid profile, anemia, and BMI; and inability to completely match certain confounding factors such as nephropathy due to smaller sample size. Further studies can be done to cover for these shortcomings and a randomized control study with DMARDs alone with a larger sample size and longer follow-up need to be done.

**Conclusion**

There is a substantial unmet need for convenient, non-invasive treatments targeting NPDR before sight is compromised, thus reducing the treatment burden. Hence, an orally administered additional drug with a different mode of action, such as immunosuppressants, can be a potential therapeutic approach for delaying onset and progression of DR in cases of no DR and in mild to moderate NPDR without clinically significant macular edema.

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**Conflicts of interest**

There are no conflicts of interest.

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