Original Article

The role of concomitant immunosuppressants in impeding the progression of diabetic retinopathy: A pilot study

Premnath Raman, Rupal Kathare

Purpose: Hallmark of Diabetic Retinopathy (DR) is blood-retinal barrier alteration. Vascular endothelial growth factor (VEGF) and inflammation are involved in the pathogenesis of DR. Anti-VEGFs and lasers are effective in treating DR but have numerous drawbacks, hence the need to develop alternative therapies that may delay the onset or progression of DR. **Methods**: Fifteen patients were recruited in each group; the study group was on immunosuppressants for some other coexisting disease and the control group was not on them. Each subject underwent detailed history, ophthalmic examination, and glycosylated hemoglobin (HbA1c) and renal function tests at the time of recruitment and the end of one year. Primary outcome measure was to compare the progression of DR in diabetics on immunosuppressant versus those not on it. **Results**: Median age in the study and control group was 57 years and 60 years, respectively (P = 0.6). Median duration of diabetes was 11 and 12 years in the study and control group, respectively (P = 0.7). HbA1c for the 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). Hypertensives in the study and control groups were 9 and 4, respectively (P = 0.065); renal disease in the study and control groups was 4 and 2, respectively (P = 0.361). The control group showed 33.3% progression of DR, and no progression was seen in the study group (P = 0.014). **Conclusion**: Immunosuppressants seemed to delay the onset and progression of DR in the earlier stages.

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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%.[2] 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-α) levels have been detected in vitreous, serum, and ocular fibrovascular membranes in patients with DR.[7-9] TNF-α gene polymorphism is associated with increased susceptibility to the disease.[10] Similarly, interleukin-1 beta (IL-1β) 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-1β, IL-6, soluble interleukin-2 receptor (sIL-2R), and Interleukin-8 (IL-8) were found.[15,16] The mean serum TNF- α, 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

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to develop novel concepts that act on the inflammatory process for delaying the onset and halting the progression of DR.[21]

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 500–2000 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.

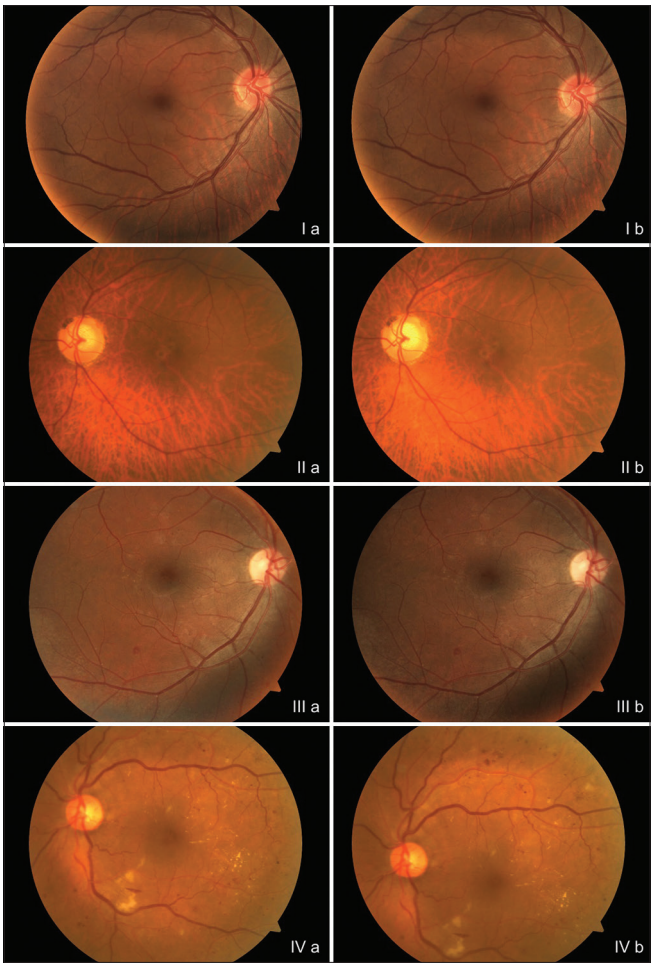

Figure 1: Fundus images of the first and second visit of the study and control groups. "I" and "II" represent study cases; "III" and "IV" represent control; "a" represents 1st visit; "b" represents 2nd visit.

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

group, 53.3% (8) and 46.7% (7) were males and females, respectively (*P* value for gender = 0.06). The values of mean LogMAR best-corrected visual acuity (BCVA) (average of RE and LE) in the study group on the first and second visits were 0.070 ± 0.095 and 0.076 ± 0.097, respectively (*P* = 0.326), and in the control group on the first and second visit were 0.060 ± 0.086 and 0.088 ± 0.098, respectively (*P* = 0.024). The values of mean LogMAR BCVA on first visit for study and control group were 0.070 ± 0.095 and 0.060 ± 0.086, respectively (*P* = 0.673), and on second visit for study and control group were 0.076 ± 0.097 and 0.088 ± 0.098, respectively (*P* = 0.636).

The median duration of diabetes was 11 years in the study group versus 12 years in the control group (*P* = 0.7). The mean duration was 11.87 ± 3.07 and 12.47 ± 3.02 years (*P* = 0.6) in the study and control group, respectively. Hypertension was present in 60% of the study group and 26.7% of the control group (*P* = 0.065). Renal disease was present in 26.7% (4) subjects in the study group and 13.3% (2) subjects in the control group (*P* = 0.361). Cardiac disease was present in 13.3% (2) subjects in the study and control group (*P* = 1).

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 the for 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*	
	Median	Mean±SD	Median	Mean±SD	Median	Mean
Age (years)	57	60.2±8.82	60	60.33±6.45	0.6	0.133
Duration of diabetes (years)	11	11.87±3.07	12	12.47±3.02	0.7	0.6
Gender						
Males^	3 (20%)		8 (53.3%)			
Females^	12 (80%)		7 (46.7%)		0.06	
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	Median	Mean
HbA1c (%)	1st	7.6	7.613±0.589	8.0	7.78±0.487	0.26*	0.406
	2nd	7.5	7.51±0.576	8.1	7.746±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

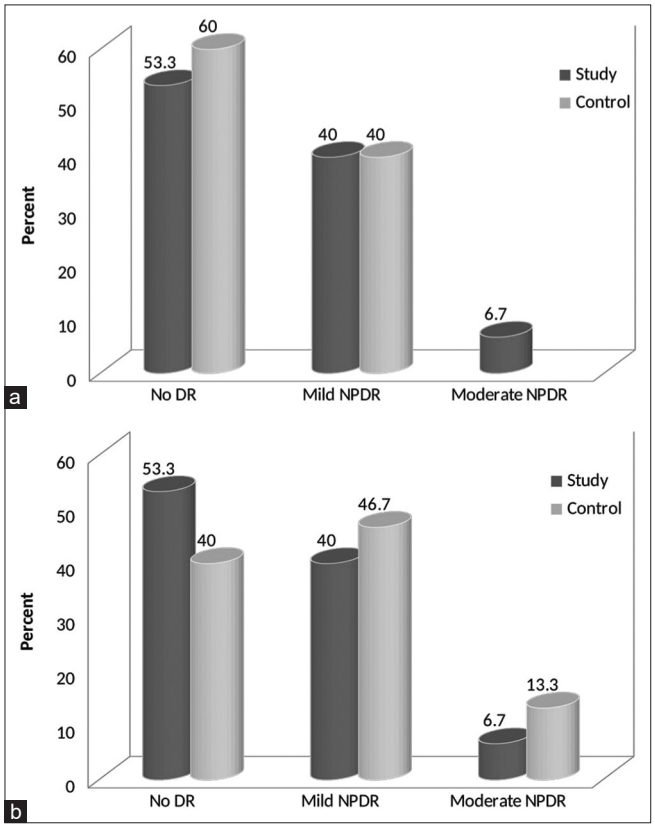

Figure 2: (a) Distribution of DR status between the two groups at 1st visit. (b) Distribution of DR status between the two groups at 2nd visit

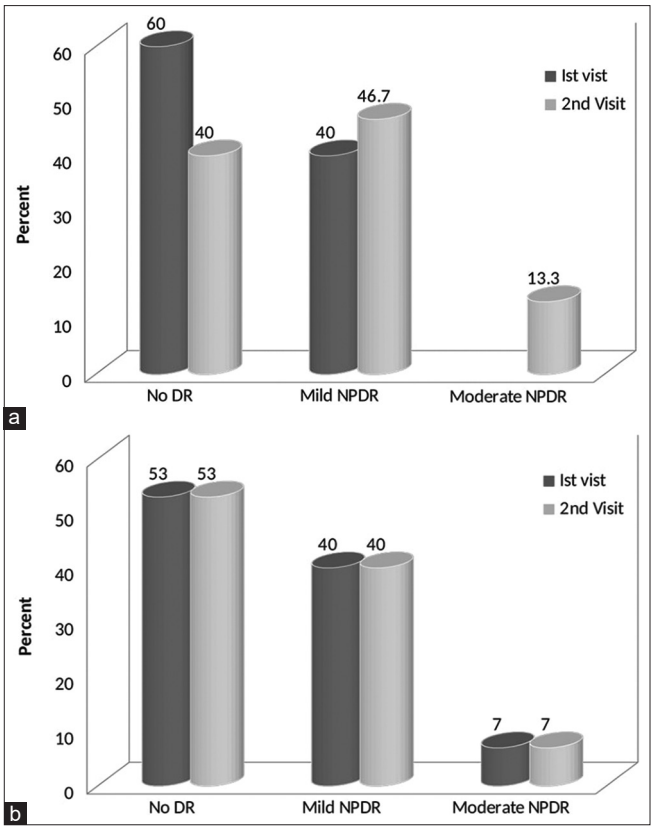

Figure 3: (a) Distribution of DR status at 1st and 2nd visit in the control group. (b) Distribution of DR status at 1st and 2nd visit in the study group

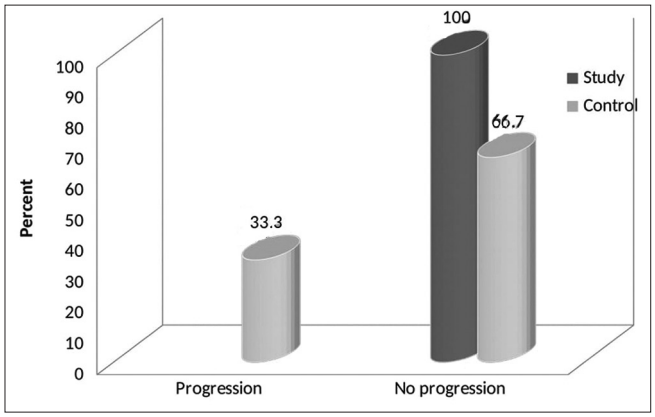

Figure 4: Distribution of DR progression between the two groups at 1 year

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.[22] Approximately one-quarter of eyes do not respond fully to currently used anti-VEGF.[23]

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.[22]

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.[17] 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.[24] 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.[25] Thus, different pathways predominate at different stages of the disease, therefore giving different potential targets at different stages of the disease.[22]

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.[26]

In, a study by Rupak Roy *et al*.[27] 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.[28] 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 alkalization followed by a decrease in free radicals. By contrast, leflunomide is a dihydroorotase inhibitor and mycophenolate acts as an inosine monophosphate dehydrogenase inhibitor.[29]

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.

References

1. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, *et al*. Causes of vision loss worldwide, 1990-2010: A systematic analysis. Lancet Glob Health 2013;1:e339-49.
2. Hussain R, Rajesh B, Giridhar A, Gopalakrishnan M, Sadasivan S, James J, *et al*. Knowledge and awareness about diabetes mellitus and diabetic retinopathy in suburban population of a South Indian state and its practice among the patients with diabetes mellitus: A population-based study. Indian J Ophthalmol 2016;64:272-6.
3. Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. Semin Immunopathol 2008;30:65-84.
4. Zhang W, Liu H, Rojas M, Caldwell RW, Caldwell RB. Anti-inflammatory therapy for diabetic retinopathy. Immunotherapy 2011;3:609-28.
5. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res 2011;30:343-58.
6. Rangasamy S, McGuire PG, Das A. Diabetic retinopathy and inflammation: Novel therapeutic targets. Middle East Afr J Ophthalmol 2012;19:52-9.
7. Joussen AM, Poulaki V, Mitsiades N, Kirchhof B, Koizumi K, Döhmen S, *et al*. Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF-α suppression. FASEB J 2002;16:438-40.
8. Demircan N, Safran BG, Soylu M, Ozcan AA, Sizmaz S. Determination of vitreous interleukin-1 (IL-1) and tumour necrosis factor (TNF) levels in proliferative diabetic retinopathy. Eye 2006;20:1366-9.
9. Limb GA, Chignell AH, Green W, LeRoy F, Dumonde DC. Distribution of TNF alpha and its reactive vascular adhesion molecules in fibrovascular membranes of proliferative diabetic retinopathy. Br J Ophthalmol 1996;80:168-73.
10. Hawrami K, Hitman GA, Rema M, Snehalatha C, Viswanathan M, Ramachandran A, *et al*. An association in non-insulin-dependent diabetes mellitus subjects between susceptibility to retinopathy and tumor necrosis factor polymorphism. Hum Immunol 1996;46:49-54.
11. Vincent JA, Mohr S. Inhibition of caspase-1/interleukin-1β signaling prevents degeneration of retinal capillaries in diabetes and galactosemia. Diabetes 2007;56:224-30.
12. Kowluru RA, Odenbach S. Role of interleukin-1β in the development of retinopathy in rats: Effect of antioxidants. Invest Ophthalmol Vis Sci 2004;45:4161-6.
13. Mocan MC, Kadayifcilar S, Eldem B. Elevated intravitreal interleukin-6 levels in patients with proliferative diabetic retinopathy. Can J Ophthalmol 2006;41:747-52.
14. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology 2003;110:1690-6.
15. Yuuki T, Kanda T, Kimura Y, Kotajima N, Tamura JI, Kobayashi I, *et al*. Inflammatory cytokines in vitreous fluid and serum of patients with diabetic vitreoretinopathy. J Diabetes Complications 2001;15:257-9.
16. Murugeswari P, Shukla D, Rajendran A, Kim R, Namperumalsamy P, Muthukkaruppan V. Proinflammatory cytokines and angiogenic and anti-angiogenic factors in vitreous of patients with proliferative diabetic retinopathy and eales' disease. Retina 2008;28:817-24.
17. Doganay S, Evereklioglu C, Er H, Türköz Y, Sevinc A, Mehmet N, *et al*. Comparison of serum NO, TNF-α, IL-1β, sIL-2R, IL-6 and IL-8 levels with grades of retinopathy in patients with diabetes mellitus. Eye 2002;16:163-70.
18. Limb GA, Hickman–Casey J, Hollifield RD, Chignell AH. Vascular adhesion molecules in vitreous from eyes with proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci 1999;40:2453-7.
19. Hernández C, Burgos R, Cantón A, García-Arumí J, Segura RM, Simó R. Vitreous levels of vascular cell adhesion molecule and vascular endothelial growth factor in patients with proliferative diabetic retinopathy: A case-control study. Diabetes Care 2001;24:516-21.
20. Joussen AM, Poulaki V, Qin W, Kirchhof B, Mitsiades N, Wiegand SJ, *et al*. Retinal vascular endothelial growth factor induces intercellular adhesion molecule-1 and endothelial nitric oxide synthase expression and initiates early diabetic retinal leukocyte adhesion *in vivo*. Am J Pathol 2002;160:501-9.
21. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, *et al*. The role of inflammation in diabetes: Current concepts and future perspectives. Eur Cardiol 2019;14:50-9.
22. Lahoti S, Nashawi M, Sheikh O, Massop D, Mir M, Chilton R. Sodium-glucose co-transporter 2 inhibitors and diabetic retinopathy: Insights into preservation of sight and looking beyond. Cardiovasc Endocrinol Metab 2021;10:3-13.
23. Boyer DS, Rippmann JF, Ehrlich MS, Bakker RA, Chong V, Nguyen QD. Amine oxidase copper-containing 3 (AOC3) inhibition: A potential novel target for the management of diabetic retinopathy. Int J Retina Vitreous 2021;7:1-2.
24. Nebbioso M, Lambiase A, Armentano M, Tucciarone G, Sacchetti M, Greco A, *et al*. Diabetic retinopathy, oxidative stress and sirtuins: An in depth look in enzymatic patterns and new therapeutic horizons. Surv Ophthalmol 2021; S0039-6257 (21) 00101-6. doi: 10.1016/j.survophthal. 2021.04.003.

25. Buyuktepe TC, Demirel S, Batıoğlu F, Özmert E. The correlation of inflammation and microvascular changes with diabetic retinal neurodegeneration. Curr Eye Res 2021;1-8. doi: 10.1080/02713683.2021.1908567.
26. Zhang W, Liu H, Al-Shabrawey M, Caldwell RW, Caldwell RB. Inflammation and diabetic retinal microvascular complications. J Cardiovasc Dis Res 2011;2:96-103.
27. Roy R, Das MK, Pal BP, Ganesan S, Raman R, Sharma T. The effects of renal transplantation on diabetic retinopathy: Clinical course and visual outcomes. Indian J Ophthalmol 2013;61:552-6.
28. Mittal NS, Bajwa GS, Sandhu JS. Diabetic retinopathy before and after renal transplantation: A longitudinal study. Transplant Proc 2005;37:2077-9.
29. Gary S. Firestein, Ralph C. Budd, Sherine E Gabriel, Iain B McInnes, James R O'Dell and Gary Koretzky (Editor). Firestein & Kelley's Textbook of Rheumatology. 11th Edition, Elsevier, 2020. p. 1007-1045.