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COMPARATIVE STUDY OF DIABETIC RETINOPATHY IN ALTERED LIPID PROFILE VERSUS NORMAL LIPID PROFILE AND VISUAL OUTCOME AFTER THE TREATMENT OF DIABETIC RETINOPATHY WITH LIPID LOWERING AGENTS (STATINS) AND ANTI-VEGF BEVACIZUMAB

Ophthalomology

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ABSTRACT

Diabetic retinopathy (DR) remains a significant cause of visual impairment among individuals with diabetes, with dyslipidemia playing a potential role in disease progression. This prospective cross-sectional study evaluated the correlation between serum lipid levels and DR severity, and assessed the efficacy of intravitreal anti-VEGF (bevacizumab) therapy with or without concurrent statin use. A total of 150 patients with non-proliferative DR (NPDR) and clinically significant macular edema (CSME) were enrolled and divided into three equal groups: Group A (normal lipid profile), Group B (altered lipid profile), and Group C (altered lipid profile with oral atorvastatin for at least 3 months). All patients received intravitreal bevacizumab (1.25 mg). Clinical parameters including best corrected visual acuity (BCVA), central macular thickness (CMT), and fundus characteristics were recorded and analyzed over a 3-month follow-up. At baseline, Group C demonstrated higher CMT and lipid parameters. Post-treatment, Group C showed the most significant reduction in CMT (mean change: 258.52 ± 77.64 µm) and greatest improvement in BCVA (-0.35 ± 0.17 logMAR), suggesting enhanced therapeutic efficacy of combined statin and anti-VEGF therapy. Group A also showed significant improvement, while Group B demonstrated the least recovery. These findings suggest that dyslipidemia exacerbates DR severity and that lipid-lowering agents may potentiate the benefits of anti-VEGF therapy. In conclusion, lipid regulation significantly influences treatment outcomes in diabetic macular edema. Combining statins with anti-VEGF therapy may offer superior results in patients with dyslipidemia. The study emphasizes a multidisciplinary approach and highlights the need for larger, long-term studies to further substantiate these findings.

KEYWORDS

Diabetic Retinopathy, Anti-VEGF, Statins, Lipid Profile

INTRODUCTION

Plasma lipids and lipoproteins have been suggested as potential risk factors for DR, particularly for hard exudates formation, for several decades.[1] Numerous clinical trials and epidemiological investigations have established positive associations between plasma Low-Density Lipoprotein (LDL) and DR.[2] A common characteristic of DR is lipid exudation. Research has established that patients with elevated serum lipid levels face an increased risk of retinal hard exudate formation when DR is present.[3] Research from the ACCORD study indicated that simvastatin monotherapy failed to yield additional protective effects, and a separate small-scale trial found statins ineffective in preventing diabetic retinopathy[4]. Despite these findings, comprehensive database analyses from multiple countries have indicated possible advantages of statin therapy[5]. The early breakdown of the blood-retinal barrier in DR pathogenesis allows increased non-specific LDL levels and elevated retinal concentrations, further exacerbated by decreased retinal cholesterol efflux in diabetes. In the diabetic environment, this can lead to increased glycation and oxidation of LDL. Oxidized glycated LDL demonstrates significant pro-inflammatory and pro-atherogenic effects: retinal cell studies show it induces Müller cell activation and exhibits cytotoxicity toward retinal capillary pericytes and retinal pigment epithelial (RPE) cells . Anti-VEGF therapy may be useful for stopping the progression of proliferative DR, as demonstrated in the RECOVERY trial.[6,9] Anti-VEGF causes reduced peripheral vision loss, reduced rates of vitrectomy and reduced number of cases with onset of DME compared to laser photocoagulation.

AIM & OBJECTIVES

To study the relationship between DR and serum lipid levels, the prevalence of DR in diabetic patients and to correlate the best corrected visual acuity after treatment with lipid lowering agents (statins) and Anti-VEGF Bevacizumab.

MATERIAL & METHODS

Prospective Cross-sectional study was conducted for a period of 1 year. 700 patients of type 2 diabetes mellitus presenting to out-patient department complex of Regional Institute of Ophthalmology, Government Medical College, Amritsar were screened over a period of 1 year. 468 (66.85%) patients were found have some form of DR upon fundus examination out of which 354 had non proliferative DR and 114 had proliferative DR. 168 (47.45%) out of 354 patients with non proliferative retinopathy were found to have CSME. The patients with proliferative DR and without CSME were excluded from the study. The remaining 168 patients of NPDR with CSME were enrolled. The patients were divided in following three groups : Patients with DR and normal lipid profile requiring injection bevacizumab, Patients with DR and altered lipid profile requiring injection bevacizumab and Patients with DR and altered lipid profile with oral intake of statins for a minimum period of three months requiring injection bevacizumab. Patients not willing to participate, or with ocular diseases like glaucoma, uveitis, retinal detachment, acute infectious/autoimmune diseases, patients having cognitive impairment were excluded from study. 56 patients out of 168 had normal lipid profile and 112 had altered lipid profile. After exclusion criteria 150 patients were included in the study and were divided into 3 groups of 50 each. A thorough clinical examination of each case was done including- Blood Pressure, Random Blood Sugar (RBS), HbA1c, Blood Urea, Serum Creatinine and Lipid Profile. A detailed clinical examination of both the eyes was done, it included visual acuity, refraction, slit lamp biomicroscopy, intraocular pressure, fundus examination, optical coherence tomography(OCT) and Fundus fluorescein angiography(FFA). Prior to procedure initiation, we obtained informed patient consent after thoroughly explaining the associated benefits and risks. Patients satisfying the inclusion criteria were then selected for the interventional study and dyslipidemia was defined using NCEP AT III guidelines as: Total cholesterol ≥ 200 mg/dl, HDL cholesterol < 40 mg/dl, LDL cholesterol ≥100mg/dl and Triglycerides ≥ 150 mg/dl. Patients were divided into three groups (Group A, Group B and Group C) and the relationship between the serum lipid levels and the severity of DR was evaluated. Injection bevacizumab (1.25mg) was administered intravitreally to all the three groups (Group A, Group B and Group C). Regular follow up at 1-month interval was done for a period of 3 months. The data was collected, analysed and comparison was done between the three groups. All variables were analysed using One Way ANOVA (Analysis of variance) test.

RESULTS

Prospective Cross-sectional study was conducted for a period of 1 year. The study participants were divided into three groups: Patients with DR and normal lipid profile requiring injection bevacizumab,

Patients with DR and altered lipid profile requiring injection bevacizumab and Patients with DR and altered lipid profile with oral intake of statins for a minimum period of three months requiring injection bevacizumab. The mean ages were similar across groups, with Group A at 63.90±6.59 years, Group B at 62.78±7.02 years, and Group C at 61.12±4.01 years. The p-value in age, gender, hypertension, duration of diabetes and laterality of eyes was > 0.05% indicating that there was no statistical difference between three groups. HbA1c levels were significantly lower in Group A compared to Groups B and C, indicating better blood sugar control (p=0.000). Similarly, total cholesterol, triglyceride levels and LDL were significantly higher in Groups B and C than in Group A (p=0.000). Renal function parameters, including serum creatinine and blood urea, were comparable among all groups, with no statistically significant differences (p>0.05). Focal leakage was observed in the majority of cases in all groups—82% in Groups A and B, and 84% in Group C. Diffuse leakage was present in all participants (100%) across all groups. CNP areas were least frequent in Group A (8%), but more common in Groups B (46%) and C (48%), indicating greater retinal ischemia in the latter groups. The mean CMT at baseline was significantly higher in Group B (516.90 ± 118.47) and Group C (517.14 ± 102.92) compared to Group A (453.64 ± 104.77), with a p-value of 0.004. At 3 months, Group C showed the greatest reduction in mean CMT (257.42 ± 67.67), followed by Group A (395.84 ± 75.02) and Group B (437.04 ± 121.08), with a p-value of 0.001 indicating a significant difference. The mean change in CMT was significantly higher in Group C (258.52 ± 77.64) compared to Group A (153.84 ± 108.04) and Group B (80.10 ± 82.02), with p-values less than 0.001 for both comparisons. At baseline, Group A had 46 participants (30.7%) with moderate non-proliferative DR (NPDR) with CSME and 4 (2.7%) with severe NPDR with CSME. By 3 months, the number of moderate NPDR with CSME cases in Group A reduced to 23 (15.3%), while 3 cases (2.0%) of severe NPDR with CSME and 3 cases (2.0%) of mild NPDR were noted. Additionally, 21 participants (14.0%) showed moderate NPDR without CSME. In Group B, there was no change over the 3 months: 27 (18.0%) had moderate NPDR with CSME and 23 (15.3%) had severe NPDR with CSME, with no shift to other grades. In Group C, a noticeable improvement was seen, with moderate NPDR with CSME dropping from 26 (17.3%) to 6 (4.0%) and severe NPDR with CSME decreasing from 24 (16.0%) to 11 (7.3%). Additionally, 26 participants (17.3%) showed moderate NPDR and 7 (4.7%) progressed to severe NPDR without CSME by the end of 3 months. The BCVA at baseline was 0.83 ± 0.12 in Group A compared to Groups B (0.83 ± 0.15) and C (0.84 ± 0.15), with a p-value of 0.9. After 3 months, the BCVA showed significant improvement in all groups, with Group A having a BCVA of 0.51 ± 0.13, Group B 0.66 ± 0.13, and Group C 0.50 ± 0.21. The improvement in BCVA was statistically significant across all groups. Group C demonstrated the greatest improvement with a mean change of -0.35±0.17, followed by Group A (-0.33±0.18), while Group B showed the least improvement (-0.18±0.09).

Table 1: HbA1c, Lipid Profile and Renal Profile

	Group A (Mean±S.D.)	Group B (Mean±S.D.)	Group C (Mean±S.D.)	'p' value
HbA1c-glycosylated haemoglobin (Normal Range <5.7%)	7.30±1.11	8.79±1.91	8.26±1.45	0.000 HS
Lipid Profile				
• Serum Total Cholesterol (Normal Range <200mg/dl)	177.28 ± 14.15	240.76 ± 23.54	240.2 ± 32.51	0.000 HS
• Serum Triglycerides (Normal Range <150mg/dl)	152.92 ± 22.61	326.98 ± 132.87	293.24 ± 155.64	0.000 HS
• Serum LDL (mg/dL) (Normal Range <100mg/dl)	102.96 ± 14.28	122.16 ± 22.05	123.86 ± 26.25	0.003 S
Renal Profile				
• Serum Creatinine (mg/dl) (Normal Range 0.7-1.3mg/dl)	1.14 ± 0.33	1.17 ± 0.40	1.16 ± 0.51	0.928 NS
• Blood Urea (Normal Range 7-20 mg/dl)	47.66 ± 15.15	47.98 ± 13.28	49.04 ± 20.22	0.908 NS

NS=Not Significant (p>0.05); HS=Highly Significant (p<0.001)

Table 2: Fundus Fluorescein Angiography Findings at Baseline

	Group A				Group B				Group C			
	Yes		No		Yes		No		Yes		No	
	No. of cases	% age	No. of cases	% age	No. of cases	% age	No. of cases	% age	No. of cases	% age	No. of cases	% age
Focal Leakage	41	82	9	18	41	82	9	18	42	84	8	16
Diffuse Leakage	50	100	0	0	50	100	0	0	50	100	0	0
CNP Areas	4	8	46	92	23	46	27	54	24	48	26	52

CNP=Capillary non-perfusion

Table 3: Oct Parameters

OCT Parameters	Group A (Mean±S.D.)	Group B (Mean±S.D.)	Group C (Mean±S.D.)	'p' value
Mean CMT (m) at Baseline	453.64±104.77	516.90±118.47	517.14±102.92	0.004
Mean CMT (m) at 3 Months	395.84±75.02	437.04±121.08	257.42±67.67	0.001
Mean MV (mm3) at Baseline	12.57±1.45	12.77±1.95	12.76±1.47	0.791
Mean MV (mm3) at 3 months	9.82±0.76	11.76±1.79	9.63±0.72	0.001

CMT- Central Macular Thickness; MV-Macular Volume

Table 4: Visual Acuity

Visual Acuity	Group A (Mean±S.D.)	Group B (Mean±S.D.)	Group C (Mean±S.D.)	'p' value
BCVA (LogMAR) at baseline	0.83±0.12	0.83±0.15	0.84±0.15	0.9
BCVA (LogMAR) at 3 months	0.51±0.13	0.66±0.13	0.50±0.21	'p'<0.001

BCVA= Best Corrected Visual Acuity

DISCUSSION

Diabetic macular edema is the leading cause of blindness amongst patients with DR. With the rise of incidence of DR, this progressive complication has become a major sight threatening problem which affects the quality of life of the patients. This calls for the early diagnosis and follow up of the patients to prevent or start early treatments. Intravitreal anti-VEGF therapy has become one of the mainstays in treatment of DME. Intravitreal anti-VEGF therapy requires multiple 4 to 6 weekly injections. 4-week injections provided better VA gains as reported in the RISE and RIDE ranibizumab studies.[10] In our study, group A (n=50) & Group B (n=50) who had normal lipid profile and altered lipid profile respectively were treated with intravitreal anti-VEGF injections bevacizumab 1.25mg/0.05ml and group C (n=50) who had altered lipid profile and were on oral intake of Tab. Atorvastatin 20mg HS for a minimum period of 3 months were treated with intravitreal anti-VEGF injections bevacizumab 1.25mg/0.05ml. Comparative analysis of the treatment result in the three groups was done at 3 months from baseline and results are discussed a head. Our results regarding glycemic control, lipid parameters, and kidney function across the three study groups correspond with findings from multiple previous investigations examining these variables in diabetes care. In our research, Group A exhibited superior glycemic management with notably reduced HbA1c values relative to Groups B and C. This observation parallels findings by Salaria NS and Vyas M (2019)[11], who identified a meaningful correlation between elevated cholesterol and clinically significant macular edema ($p < 0.05$). The Wisconsin Epidemiologic Study of DR (WESDR) likewise noted a significant pattern of

worsening DR severity with rising cholesterol levels, as reported by Larsson LI et al (1999)[12]. The baseline findings from FFA in our study, which reveal significant focal and diffuse leakage in all three groups, are in line with previous studies that highlight the high prevalence of retinal leakage and ischemia in DR. The significant prevalence of CNP in Groups B and C indicating that increased CNP is strongly associated with more advanced stages of DR, indicating greater retinal ischemia. The findings from our study on OCT parameters show significant differences in CMT across the three groups, both at baseline and after three months. These results are comparable to several other studies as done by Ihsan G et al (2024)[13], where patients underwent evaluations at baseline, one week, and one month following the injection. In our study, we observed that Group B and Group C had higher baseline CMT compared to Group A, who reported that DME is typically associated with increased CMT and that higher CMT values correlate with more advanced stages of DR. Our results also show a significant reduction in CMT after 3 months, particularly in Group C. which suggests that treatment with statins along with anti-VEGF injection gives better results compare to when anti-VEGF given alone especially in patients with altered lipid profile as in group B and Group C. Group C had the lowest mean CMT after 3 months, which suggests a significant improvement which is likely due to the presence of effective treatment regimens which are intravitreal antiVEGF injections combined with statins. Similarly the study by Kang EY et al (2019)[14], also supported our findings study where patients who received statin therapy experienced a noticeably lower incidence of DR compared to those who did not receive statins. The statin group also showed reduced risks of vision-threatening complications such as vitreous hemorrhage, tractional retinal detachment, and macular edema. Additionally, these patients required fewer ocular treatments, including laser therapy, intravitreal injections, and vitrectomy procedures. Our study found a complete resolution of both moderate and severe Non-Proliferative DR (NPDR) with CSME across all groups within three months. At baseline, Group A had a mix of moderate and severe NPDR with CSME, but by three months, there was a notable reduction in moderate cases and a slight change in severity distribution, with some participants shifting to milder forms or presenting without CSME. Group B showed no changes over the same period, maintaining the same distribution of moderate and severe NPDR with CSME. In contrast, Group C demonstrated marked improvement, with significant reductions in both moderate and severe NPDR with CSME. By the end of three months, several participants in Group C had transitioned to moderate NPDR without CSME, though a few progressed to severe NPDR without CSME. Our study found that Group C demonstrated the greatest improvement in BCVA, followed by Group A, while Group B showed the least improvement. This outcome aligns with the study by Massengill MT et al (2024).[15]

CONCLUSION

The findings of this study strongly suggest that all treatment groups experienced meaningful improvements in both visual acuity and anatomical outcomes over a 3-month period, highlighting the effectiveness of the interventions employed. Notably, Group C demonstrated the most significant gains in visual acuity and reduction in central retinal thickness, suggesting a superior therapeutic benefit of intravitreal Anti-VEGF Bevacizumab combined with tablet Atorvastatin. Additionally, there was a marked regression in DR severity across all groups, reinforcing the overall positive impact of the interventions. The study also revealed a significant correlation between systemic metabolic control—particularly glycemic and lipid management—and improved ocular outcomes. Early intervention and continuous monitoring emerged as critical components in preventing irreversible vision loss. In conclusion, the study strongly advocates for intensive, multidisciplinary management strategies tailored to individual patient profiles as a key to preserving vision and improving quality of life in patients with diabetic eye disease.

Limitations

There were some inherent limitations in our study. The most significant of them all would be the small sample size and short follow up period of 3 months as compared to the chronic disease process under study.

Conflict of Interest

The authors declare no conflict of interest.

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