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ORIGINAL RESEARCH

A comparative study on diabetic retinopathy severity, treatment requirement and progression amongst type2 diabetic patients on insulin and those not on insulin

[1]Dr. Chander Mohan Kohli, [2]Dr. Parul Singh, [3]Dr. Preeti Gupta, [4]Dr. Nishant Kanodia

[1-4]Department of Ophthalmology, HIMS, Sitapur, Uttar Pradesh, India

Corresponding Author
Dr. Parul Singh
Department of Ophthalmology, HIMS, Sitapur, Uttar Pradesh, India
Email: parulsinghb2812@gmail.com

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ABSTRACT

Introduction: Diabetic Retinopathy (DR) is an important cause of visual impairment among persons with diabetes mellitus (DM). Therefore, it is important for nonophthalmologists to recognize the importance of eye disease in patients with DM. There are no recent studies on the prevalence of DR across all the geographical divisions of India. This makes it difficult to identify where DR screening and treatment programs are most needed. Aim & Objectives: Comparative study on DR severity, treatment requirement and progression amongst type 2 diabetic patients on insulin and those not on insulin. **Methods**: A prospective comparative study was carried out in Department of Ophthalmology at Hind Institute of Medical Sciences, Mau, Ataria, Sitapur, Uttar Pradesh among 150 patients visiting OPD with clinically diagnosed Type 2 DM, on insulin therapy or on other treatment, after considering the inclusion and exclusion criteria. The subjects were equally distributed into two groups i.e. insulin and noninsulin group. **Results**: In present study frequency of DR was 37.33% in non-insulin group and 57.33% in insulin group at baseline, it increased to 44% and 68% after 9 months respectively. Which shows DR is more common in subjects on insulin therapy when compared to other study group, and rate of progression of disease is more in subjects on insulin therapy. The frequency of subjects with Diabetic Macular Edema (DME) was 29.33% in insulin group and 10.67% in non-insulin group, at baseline, and it increased to 38.67% in insulin group and 17.33% in non-insulin group, showing a statistically significant difference at 9 months interval. **Conclusion:** This study suggest that insulin treatment may be associated with DR, DR severity and DME in T2DM patients belonging to a developing country like India.

Key words:Diabetic Retinopathy, diabetes mellitus, Diabetic Macular Edema, insulin

INTRODUCTION

Diabetes mellitus (DM) is a global epidemic. The World Health Organization (WHO) estimates revealed that the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.[1] The ninth edition of Diabetes Atlas by International Diabetes Federation released in 2019 estimates that there are 463 million persons with diabetes in the world and this figure will go up to 700 million by the year 2045;[2] the increase being disproportionately more in developing countries. This will result in a heavy burden on the health care system because of several DM-related complications. According to WHO, there were nearly 102.26 million cases of diabetes in India in 2016 with a prevalence of 7.8% (7.9% in males and 7.5% in females).[3]Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease leading to multi-systemic complications if left untreated. As its global prevalence increases year by year, it is a significant source of morbidity and mortality worldwide.[4]

Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy, neuropathy (microvascular), ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage.[5]

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Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and a leading cause of blindness worldwide and in the US. [6-8] The individual lifetime risk of DR is estimated to be over 90% in patients with type 1 diabetes and 50–60% in patients with type 2 diabetes. [9] It is the most frequent cause of blindness in adults between 20-74 years of age in developed countries. [10] The same pathologic mechanisms that damage the kidneys and other organs affect the microcirculation of the eye. [11] With the global epidemic of diabetes, one expects that diabetes will be the leading global cause of vision loss in many countries. [6,7]

Diabetic Retinopathy is an important cause of visual impairment among persons with diabetes. The prevalence of diabetes is higher in urban areas (11.2%, 95% CI: 10.6–11.8) than in rural areas (5.2%, 95% CI: 4.9–5.4; P < 0·0001),[12] but DR does not show this variation.[13] DR accounted for 1.07% of blindness and 1.25% of moderate to severe visual impairment (MSVI) in 2015.[14]

In diabetic retinopathy, retinal capillaries become occluded, resulting in large areas of retinal nonperfusion and prompting new vessel formation.[15] Improved glycemic control retards the development and progression of retinopathy in both type 1 and type 2 diabetes.[16-18] However, worsening of retinopathy has been reported after rapidly improved glycemic control.[16,19-23] A relationship between the degree of improvement in HbA1c and early worsening of retinopathy was found in the Diabetes Control and Complications Trial (DCCT).[22] In agreement, we found a relationship between the degree of improvement in HbA1c and progression of retinopathy 2 years after the start of insulin therapy in type 2 diabetic patients.[23]

Endocrine and growth factors may also play a role in the pathogenesis of DR. The secretion of growth hormone (GH) is increased in poorly controlled diabetes,[24,25] and DR correlates with the magnitude of GH hypersecretion.[26] A role for pituitary-associated factor in DR was first postulated in 1953, when retinal neovascularization in a diabetic patient was found to regress after postpartum pituitary necrosis.[26] Subsequent controlled clinical trials showed that pituitary ablation could improve DR.[27] Many mitogenic effects of GH are mediated by IGF-1.[28] Merimee et al. [29] found increased serum IGF-1 levels in patients with rapidly accelerating DR, and Chantelau et al. [30,31] reported a relationship between upregulation of IGF-1 and progression of retinopathy in Mauriac's syndrome and in type 1 diabetes.

In a randomized controlled study, Grant et al. [32] showed that the progression to high-risk proliferative diabetic retinopathy (PDR) was diminished in patients treated with ocreotide, a somatostatin analog decreasing the secretion of GH.

With regards to fundus photographies, the international clinical disease severity scale for DR has classified DR into five stages. The first is "no apparent retinopathy". The second stage is "mild non-proliferative retinopathy" (NPDR) characterized by the presence of few microaneurysms. The third stage is "moderate NPDR" which is characterized by the presence of microaneurysms, intraretinal hemorrhages, or veinous beading but reduced compared with "severe NPDR" which is the fourth stage. "Severe NPDR" is characterized by no sign of proliferative diabetic retinopathy" (PDR) but any of the following: more than 20 intraretinal hemorrhages in each of four quadrants, definite veinous beading in two or more quadrants, prominent intraretinal microvascular anomalies in one or more quadrants. The fifth and last stage is "PDR" which is characterized by neovascularization of the disc, retina, iris, and angle; and by vitreous hemorrhage or tractional retinal detachment. Diabetic macular edema (DME) is commonly seen in DR patients. If DME is present, it can be further classified as mild, moderate, and severe depending on the distance of the exudates and thickening from the center of the fovea. [33] Different risk and progression factors for DR have been documented; non-modifiable factors including genetic predisposition, ethnicity, gender, age, duration of diabetes, and modifiable factors including blood glucose, blood pressure, serum lipids and smoking. [4]

The present study was undertaken, as there are no recent studies on the prevalence of DR across all the geographical divisions of India. This makes it difficult to identify where DR screening and treatment programs are most needed. Most of the available estimates of DR are from diabetes clinics, which is subject to bias, limiting their use in planning ophthalmic services for persons with diabetes in the general population. Secondly, often by the time patients seek ophthalmologic examination and treatment, there are significant alterations of the retinal microvasculature. Therefore, it is important for non-ophthalmologists to recognize the importance of eye disease in patients with diabetes so that appropriate referral to eye-care specialists can be a part of their diabetes management program.Furthermore, insulin is the mainstay in the treatment of diabetes mellitus including T2DM as a consequence of the progressive loss of pancreatic beta cell function. [4] Recent insights from prospective studies carried out in developed countries and developing populations from Latin America and Asia have clearly demonstrated an incremented risk of DR with regard to insulin treatment. [4, 34-36] Lastly, few studieshave been done showing association between DR and insulin treatment especially in India which calls for additional largescale,well-designed studies with sufficient data to confirm the findings.

MATERIAL & METHODS

The study was approved from Institutional Ethical Committee. Informed consent was obtained from the

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participant patients. Patient workup format- • HISTORY- A detailed history was taken including - Patient particulars Duration of diabetes Type of diabetic control (insulin,any other) Past glycaemic control (HbA1c values) Any chronic illness (e.g., obesity, renal disease, systemic hypertension, serum lipid levels,) Ocular history (e.g., trauma, other eye diseases, ocular injections, surgery, including retinal laser treatment and refractive surgery). Patients fulfilling the inclusion criteria were divided into two groups on basis of insulin use for treatment. - pts. On insulin - pts. Not on insulin • EXAMINATION- The examination includedVitals Visual acuity (UCVA and BCVA) – using Snellen's chart Anterior segment examination using Slit lamp- to look for corneal transparency, any corneal edema, NVI, iritis. Intraocular pressure (IOP) – using AT Gonioscopy before dilation, when indicated e.g., shallow Anterior chamber angle, Iris neovascularization. Pupillary assessment (any RAPD) Lens transparency to look for any cataract. Thorough fundoscopy, (after pupillary dilation) using – Indirect Ophthalmoscope Slit lamp with 90 D stereoscopic examination was done of - • Posterior Pole • Peripheral retina • Vitreous • Macula • Signs of DR • Optic nerve head neovascularization and/or neovascularization elsewhere • Vitreous or preretinal haemorrhage INVESTIGATIONS – General: Random Blood Sugar Fasting and post prandial blood sugar Fasting lipid profile HbA1C value Serum urea and creatinine Ocular: Fundus photography Fundus Fluorescein Angiography. Optical Coherence Tomography.

Statistical Analysis

Statistical analysis :Qualitative data was represented in the form of frequency and percentage. Quantitative data was represented using Mean ± SD. A p-value < 0.05 was taken as level of significance. Results was graphically represented where deemed necessary. SPSS Version 21.0 was used for most analysis and Microsoft Excel 2010 for graphical representation. Wilcoxion test, Sign Rank Test and Chi Square tests and regression analysis was used for statistical analysis.

RESULTS

In both the groups; males were comparatively more as compared to females. Gender distribution was comparable among both the groups. Mean age among the insulin and non-insulin group was 51.89±6.55 and 55.28±7.61 years respectively. No statistically difference was found among the study groups w.r.t. age distribution. Mean duration of diabetes (in years) among the insulin and non-insulin group was 11.63±4.09 and 8.15±3.58 years respectively. Although mean duration of diabetes (in years) was found to be more in insulin as compared to non-insulin group, but no significant difference was found as p>0.05. Mean BMI (kg/m2) among the insulin and non-insulin group was 27.93±3.12 and 25.70±3.17 respectively. No statistically difference was found among the study groups w.r.t.BMI (kg/m2) distribution. Smoking was revealed in 10.67% and 8% of the subjects in insulin and noninsulin group respectively. Hence smoking habit was not common among the study subjects. Hypertension was reported in 62.67% and 53.33% of the subjects in insulin and non-insulin group respectively. Insulin group: 1 patient with mild NPDR progressed to moderate NPDR, 3 progressed from moderate to severe NPDR and 1 progressed from severe NPDR to mild-moderate PDR. Rest of the patients were stable. Noninsulin group: 1 patient progressed from mild to moderate NPDR, and 1 patientsurge to severe NPDR from moderate NPDR. Rest of the patients were stable. Insulin group: Treatment was given to 9 and 8 cases of mild-moderate PDR and high risk PDR respectively in insulin group. The patients remained stable and disease did not progress further. Non-insulin group: Treatment was given to 4 and 2 cases of mild-moderate PDR and high risk PDR respectively in non-insulin group. The patients remained stable and disease did not progress further. Insulin group: 2 patients with no DR progressed to mild NPDR, 2 progressed to moderate NPDR from mild stage, 2 upsurge to severe NPDR from moderate stage and 2 progressed from severe NPDR to mild-moderate PDR. Rest of the patients were stable. Noninsulin group: 1 patient with no DR progressed to mild NPDR, 1 progressed to moderate NPDR from mild stage, 2 upsurge to severe NPDR from moderate stage and 1 progressed from severe NPDR to mild-moderate PDR. Rest of the patients were stable. Treatment was given to 10 and 8 cases of mild-moderate PDR and high risk PDR respectively in insulin group. The patients remained stable and disease did not progress further. Treatment was given to 4 and 2 cases of mild-moderate PDR and high risk further. Insulin group: 3 patients with no DR progressed to mild NPDR, 3 progressed to moderate NPDR from mild stage, 3 patients each upsurge to severe NPDR from moderate stage and severe NPDR to mild-moderate PDR. Rest of the patients were stable. Noninsulin group: 2 patients from no DR progressed to mild NPDR, 2 progressed to moderate NPDR from mild stage, 2 upsurge to severe NPDR from moderate stage and 1 progressed from severe NPDR to mild-moderate PDR. Rest of the patients were stable. Treatment was given to 12 and 8 cases of mild-moderate PDR and high risk PDR respectively in insulin group. The patients remained stable and disease did not progress further. Treatment was given to 5 and 2 cases of mild-moderate PDR and high risk PDR respectively in non-insulin group. The patients remained stable and disease did not progress further. Insulin group: 3 patients with no DR progressed to mild NPDR, 4 progressed to moderate NPDR from mild stage, 2 patients each upsurge to severe NPDR from moderate stage, 2 severe NPDR to mild-moderate PDR and 1 from mildmoderate PDR

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progressed to high risk PDR. Rest of the patients were stable. Noninsulin group: 2 patients from no DR progressed to mild NPDR, 2 progressed to moderate NPDR from mild stage, 2 upsurge to severe NPDR from moderate stage and 1patient each progressed from severe NPDR to mild-moderate PDR and mild-moderate PDR to high risk PDR. Rest of the patients were stable. Treatment was given to 15 and 8 cases of mild-moderate PDR and high risk PDR respectively in insulin group. One case from mild-moderate PDR progressed to high risk PDR while rest of the patients remained stable and disease did not progress further. Treatment was given to 6 and 2 cases of mild-moderate PDR and high risk PDR respectively in non-insulin group. One case from mild-moderate PDR progressed to high risk PDR while rest of the patients remained stable and disease did not progress further. The frequency of subjects with DME was 29.33% in insulin group and 10.67% in non-insulin group, at baseline, and it increased to 36% and 16% at 6 months interval respectively, with a statistically significant difference. Frequency of DME status was 38.67% in insulin group and 17.33% in noninsulin group, showing a statistically significant difference at 9 months interval.

TABLE-1: Type of diabetic retinopathy at one and three month among the study groups.

Type	Interval							
	One Month				3 Month			
	Insulin		Non-Insulin		Insulin		Non-Insulin	
	N	%	N	%	N	%	N	%
No DR	32	42.67	47	62.67	30	40.00	46	61.33
Mild NPDR	10	13.33	11	14.67	10	13.33	11	14.67
Moderate NPDR	6	8.00	7	9.33	6	8.00	6	8.00
Severe NPDR	9	12.00	4	5.33	9	12.00	5	6.67
Mild-Moderate PDR	10	13.33	4	5.33	12	16.00	5	6.67
High Risk PDR	8	10.67	2	2.67	8	10.67	2	2.67
ADED	0	0.00	0	0.00	0	0.00	0	0.00
Chi Square	4.33				4.79			
p value	0.14				0.09			

TABLE-2: Type of diabetic retinopathy at three and six month among the study groups

Type	Interval							
	3 Month				6 Month			
	Insulin		Non-Insulin		Insulin		Non-Insulin	
	N	%	N	%	N	%	N	%
No DR	30	40.00	46	61.33	27	36	44	58.67
Mild NPDR	10	13.33	11	14.67	10	13.33	11	14.67
Moderate NPDR	6	8.00	6	8.00	6	8	6	8.00
Severe NPDR	9	12.00	5	6.67	9	12.00	6	8.00
Mild-Moderate PDR	12	16.00	5	6.67	15	20	6	8.00
High Risk PDR	8	10.67	2	2.67	8	10.67	2	2.67
ADED	0	0.00	0	0.00	0	0.00	0	0.00
Chi Square	4.79				5.07			
p value	0.09				0.049*			

TABLE-3: Type of diabetic retinopathy at six and nine month among the study groups

Type	Interval							
	6 Month				9 Month			
	Insulin		Non-Insulin		Insulin		Non-Insulin	
	N	%	N	%	N	%	N	%
No DR	27	36	44	58.67	24	32.00	42	56.00
Mild NPDR	10	13.33	11	14.67	9	12.00	11	14.67
Moderate NPDR	6	8	6	8.00	8	10.67	6	8.00
Severe NPDR	9	12.00	6	8.00	9	12.00	7	9.33
Mild-Moderate PDR	15	20	6	8.00	16	21.33	6	8.00
High Risk PDR	8	10.67	2	2.67	9	12.00	3	4.00
ADED	0	0.00	0	0.00	0	0.00	0	0.00
Chi Square	5.07				5.10			
p value	0.049*				0.048*			

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TABLE-4: Type of DME at different intervals

DME	Interval																			
	Baseline				One Month				3 Month				6 Month				9 Month			
	Insulin		Non-Insulin		Insulin		Non-Insulin		Insulin		Non-Insulin		Insulin		Non-Insulin		Insulin		Non-Insulin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No	53	70.67	67	89.33	53	70.67	66	88	51	68.00	65	86.67	48	64	63	84.00	46	61.33	62	82.67
Non Centre Involving	14	18.67	6	8.00	14	18.67	6	8	16	21.33	7	9.33	18	24	8	10.67	20	26.67	9	12.00
Centre Involving	8	10.67	2	2.67	8	10.67	3	4	8	10.67	3	4.00	9	12	4	5.33	9	12.00	4	5.33
Chi Square	4.17				4.02				4.58				5.91				5.80			
p value	0.14				0.18				0.09				0.043*				0.048*			

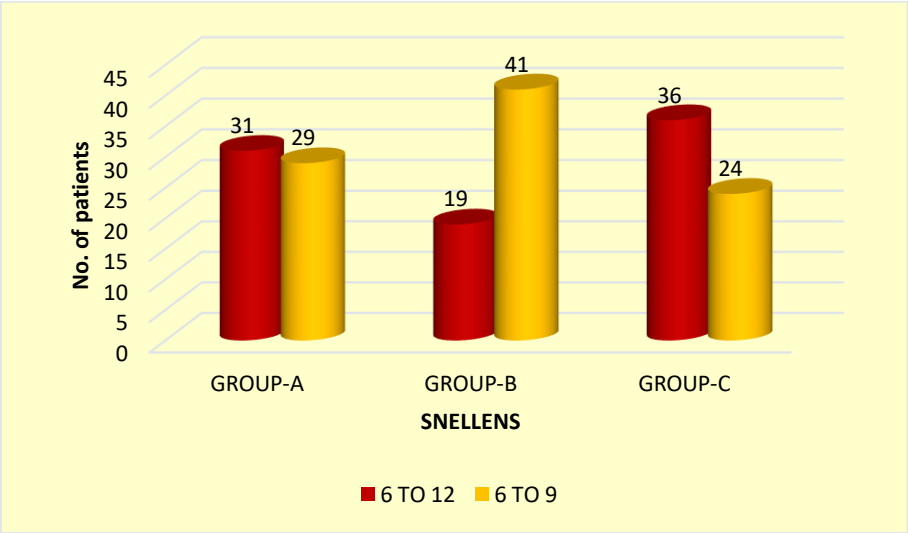

FIGURE-1: SNELLENS of enrolled patients in Group-A, B and C at first follow-up (12 weeks)

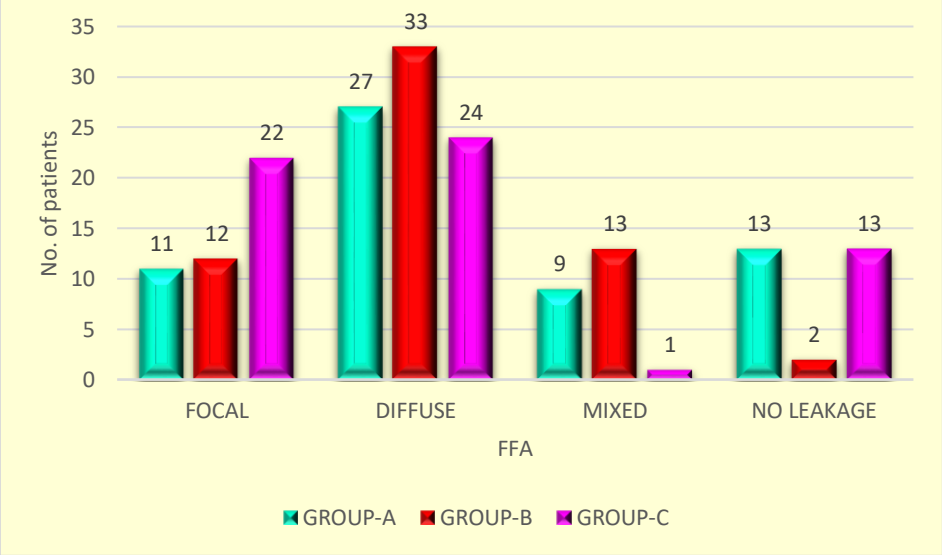

FIGURE-2:FFA of enrolled patients in Group-A, B and Cat first follow-up (12 weeks).

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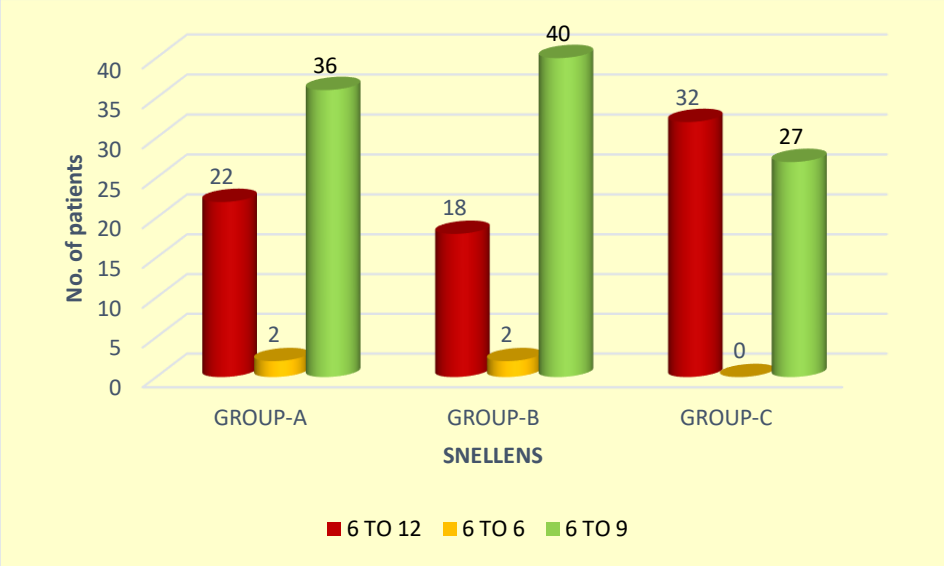

FIGURE-3: SNELLENS of enrolled patients in Group-A, B and C at second follow-up (24weeks).

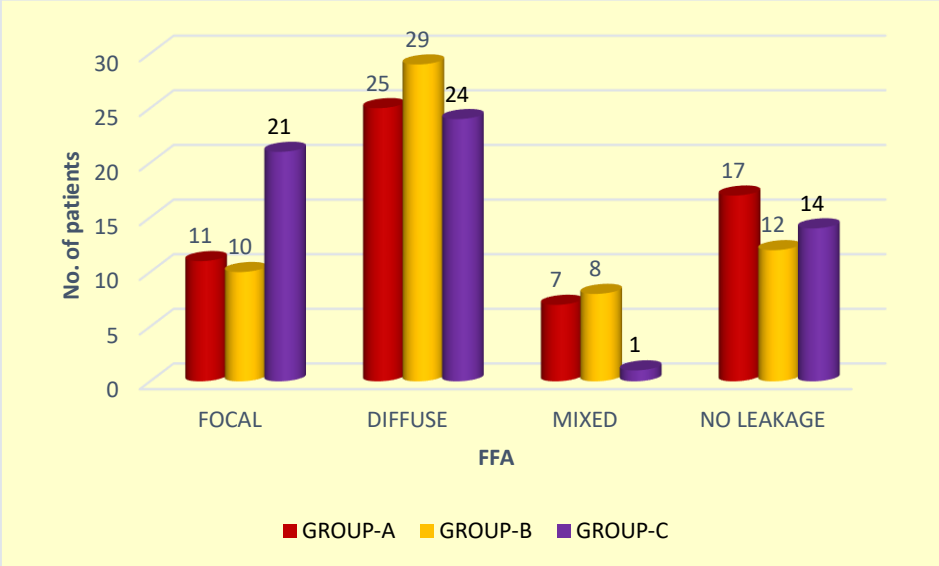

FIGURE-4:FFA of enrolled patients in Group-A, B and C at second follow-up (24 weeks).

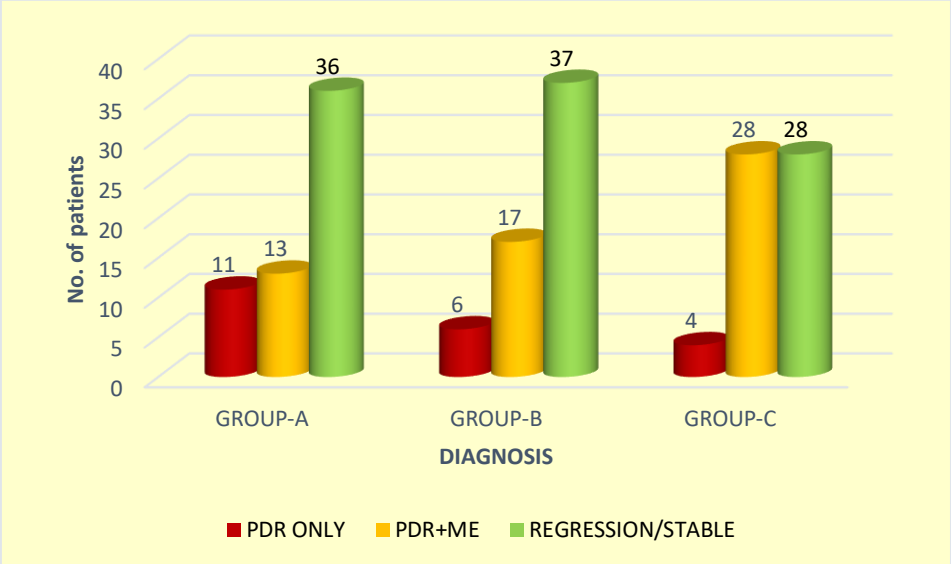

FIGURE-5:DIAGNOSIS of enrolled patients in Group-A, B and C at second follow-up (24weeks).

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DISCUSSION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease leading to multi-systemic complications if left untreated. As its global prevalence increases year by year, it is a significant source of morbidity and mortality worldwide.[4] DR is a disease characterized by microvascular alterations progressively leading to retinal ischemia, retinal permeability, retinal neovascularization and macular edema.[33,] With regards to fundus photographies, the international clinical disease severity scale for DR has classified DR into five stages. The first is "no apparent retinopathy". The second stage is "mild non-proliferative retinopathy" (NPDR) characterized by the presence of few microaneurysms. The third stage is "moderate NPDR" which is characterized by the presence of microaneurysms, intraretinal hemorrhages, or veinous beading but reduced compared with "severe NPDR" which is the fourth stage. "Severe NPDR" is characterized by no sign of proliferative diabetic retinopathy" (PDR) but any of the following: more than 20 intraretinal hemorrhages in each of four quadrants, definite veinous beading in two or more quadrants, prominent intraretinal microvascular anomalies in one or more quadrants. The fifth and last stage is "PDR" which is characterized by neovascularization of the disc, retina, iris, and angle; and by vitreous hemorrhage or tractional retinal detachment. Diabetic macular edema (DME) is commonly seen in DR patients. If DME is present, it can be further classified as mild, moderate, and severe depending on the distance of the exudates and thickening from the center of the fovea.[33] DR is the leading cause of visual impairment and blindness in the populations aged 20–74 years as well as in diabetes patients worldwide. It may affect up to 60% of T2DM patients.Different risk and progression factors for DR have been documented; non-modifiable factors including genetic predisposition, ethnicity, gender, age, duration of diabetes, and modifiable factors including blood glucose, blood pressure, serum lipids and smoking.[4]

Insulin is the mainstay in the treatment of diabetes mellitus including T2DM as a consequence of the progressive loss of pancreatic beta cell function.[4]Insights from prospective studies carried out in developed countries and developing populations from Latin America and Asia have clearly demonstrated an incremented risk of DR with regard to insulin treatment.[4,34] So, the present study was carried out to evaluate it.

The main findings of the present study are as follows:

In present study both the groups, i.e., insulin and non-insulin group males i.e., 68% and 72% respectively,werecomparativelymore as compared to females. Gender distribution was comparable among both the groups

In our study, mean age among the insulin and non-insulin group was 51.89±6.55 and 55.28±7.61 years respectively. No statistically difference was found among the study groups w.r.t. age distribution. Suggesting that age of the subject was not a determining factor for the progression of DR.

Mean duration of diabetes (in years) among the insulin and non-insulin group was 11.63±4.09 and 8.15±3.58 years respectively. Although mean duration of diabetes (in years) was found to be more in insulin as compared to non-insulin group, but no statistically significant difference was found.

Mean BMI (kg/m2) among the insulin and non-insulin group was 27.93±3.12 and 25.70±3.17 respectively. No statistically significant difference was found among the study groups.

Smoking was revealed in 10.67% and 8% of the subjects in insulin and non-insulin group respectively. Hence smoking habit was not common among the study subjects. Hypertension was reported in 62.67% and 53.33% of the subjects in insulin and non-insulin group respectively.No statistically significant difference was found among the study groups.

In present study the frequency of DR was 37.33% in non-insulin group when compared to 57.33% in insulin group at baseline, and it was increased to 44% and 68% after 9 months respectively. Which shows that DR is more common in subjects on insulin therapy when compared to other study group, and rate of progression of disease is more in subjects on insulin therapy

Findings of present study suggest that, there was better improvement in DR status in 9 months interval in non-insulin group when compared with subjects included in insulin group, as subjects with Mild-Moderate PDR in insulin group increased from 12% at baseline to 21% at 9 months interval after treatment, which only showed a slight increase in non-insulin group from 5% to 8% in 9 months interval. And also, subjects with Moderate NPDR remained same in insulin group but reduced by almost 1.5% in non-insulin group, in 9 months' time period. Also, there was a statistically significant difference in insulin and non-insulin group at 6 months and 9 months interval.

The frequency of subjects with DME irrespective of stage was 29.33% in insulin group when compared to 10.67% in non-insulin group, at baseline, and it increased to 36% and 16% at 6 months interval respectively, with a statistically significant difference. This suggest that DME was more common in insulin group subjects when compared to other study group. Similar were the findings at 9 months interval where frequency of DME was 38.67% in insulin group and 17.33% in non-insulin group, showing a statistically significant difference.

CONCLUSION

The results from this study suggest that insulin treatment may be associated with DR, DR severity and DME in T2DM patients belonging to Asian population of a developing country like India. This calls for in-depth analysis of the observed associations

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in the context of large-scale longitudinal studies yielding more accurate estimates and providing a better understanding of the mechanistic link between insulin and DR.Use of insulin was seen to be a risk factor for worsening of retinopathy. Physicians may be needed to emphasize for cautious use of insulin and careful ophthalmic follow-up to be advised when diabetic treatment is changed to insulin in them.Pts. whose retinopathy is already approaching high risk stage, it may be prudent to delay the initiation of intensive insulin treatment until PRP can be completed. Pt. should undergo PRP promptly and close eye monitoring during insulin treatment.Adjunction of insulin sensitizers to any patient on insulin could be beneficial, as dose of insulin needed will be less.For people with DM2 on insulin with no evidence of DR at initial screening, the follow-up schedule could be reduced than 12m.Though our study is small but raises questions about the relationship between retinopathy, and insulin therapy.Smokinghabit was not common among the study subjects. Hypertension was reported in 62.67% and 53.33% of the subjects in insulin and non-insulin group respectively.Better improvement in DR status in 9 months interval in non-insulin group when compared with subjects included in insulin group.There was a statistically significant difference in insulin and non-insulin group at 6 months and 9 months interval.Subjects were given treatment for DR and the disease remain well maintained.DME was more common in insulin group subjects when compared to other study group.

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