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Study of The Relationship between Diabetic Retinopathy, Basal Insulin Therapy (Glargine Or NPH) And Insulin-Like Growth Factor 1 Serum Level

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ABSTRACT

Background: Globally, the leading cause of avoidable blindness is diabetic retinopathy (DR). Diabetes mellitus (DM) type 1 (T1DM) individuals are more likely to develop DR, a microvascular consequence of the disease. As an autoimmune condition that causes insulin insufficiency, T1DM patients need basal insulin therapy throughout the duration of their treatment to achieve optimum glycemic control. An essential growth factor involved in angiogenesis and cell proliferation is insulin-like growth factor 1 (IGF-1). IGF-1 has a strong correlation with DR development, according to a wealth of data. In contrast to the intermediate-acting NPH insulin, insulin glargine is a long-acting insulin analogue that is peak-free and less hypoglycemic. The enhanced affinity of glargine for the IGF-1 receptor has sparked questions regarding its potential involvement in the development of DR. There is ongoing discussion on the connection between IGF-1 blood levels, basal insulin treatment, and diabetic retinopathy.

Objective: We wanted to assess the frequency and severity of DR in T1DM patients on basal insulin treatment (Glargine or NPH) and its relationship with blood IGF-1 levels.

Patients and Methods: A cross-sectional comparative study that included 88 patients conducted at Ain Shams University Hospital, Diabetology Clinic. It was conducted from October 2021 till February 2022. Subjects were divided into 44 T1DM patients on baseline insulin therapy with glargine and Actarapid (Group A) and 44 on insulin NPH and Actarapid (Group B).

Results: Regarding the fundus examination results between the two groups under study, there was no statistically significant difference (P value = 0.429). Serum IGF-1 and diabetic retinopathy did not significantly correlate (P =0.080, mean±SD of serum IGF-1 level in cases with normal fundus 14.8±11 vs. those with diabetic retinopathy 21.3±16.9). Diabetes duration and diabetic retinopathy were statistically significantly correlated (P value <0.05, mean±SD of diabetes duration in patients with DR 17.7 ± 6.9 vs. those with normal fundus 14.6 ± 5.6). The mean ± standard deviation of age in Group B regimen was 28.4 ± 6.7, while in Group A, it was 25.5 ± 4.9. This difference was statistically significant.

Conclusion: There was no statistically significant difference in serum IGF-1 levels between patients with normal fundus or DR, or between individuals on glargine or NPH. In individuals with T1DM, the severity and frequency of diabetic retinopathy are closely correlated with the duration of the condition. There is no discernible difference in the alterations in diabetic retinopathy between glargine and NPH patients receiving basal insulin treatment.

Keywords: DR, Macular edema, Glargine, NPH, IGF-1, T1DM.

INTRODUCTION

Because of its high global incidence and serious late consequences, DM is a medical and social concern [(1)]. Microvascular problems include retinopathy, neuropathy, and nephropathy, whereas macrovascular issues include peripheral artery disease, stroke, and ischemic heart disease [(2)].

Diabetic retinopathy (DR) has been considered a main cause of blindness in working-age individuals [(3)]. In over 90% of cases, visual loss can be avoided with early identification and treatment of DR [(4)].

DR is categorized into four stages: mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). Diabetic macular oedema (DME) is the primary cause of blindness in DR and may happen at any stage of DR [(3)].

The specific biochemical route that causes DR remains unclear [(5)]. Numerous mechanisms have been implicated in DR aetiology. Hypoxia has been considered a significant starting variable. Hypoxia-inducible factor (HIF)-I α and (HIF)-I β activate transcription factors by binding to hypoxia response sites in the vascular endothelial growth factor (VEGF) promoter [(6)].

IGF-1 has recently been linked to the pathogenesis of DR. IGF-1 is the peripheral target hormone for growth hormone (GH), which is nearly related to insulin except that it contains an extension of the A chain called the D domain and its C chains aren't separated [(7)].

The mechanism of PDR development is that vascular endothelial cells, pericytes, glial cells, retinal ganglion cells, and retinal pigment epithelium; all express IGF-1, which in turn induces the production of VEGF in retinal pigment epithelial cells, which participate in retinal angiogenesis [(3)].

The B-subunit contains 80% homology between insulin and IGF-1 receptors. Insulin must be chemically altered (like insulin analogues) or present in high concentrations in order to affect the IGF-1 receptor. Because of its strong affinity for the IGF-1

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receptor, insulin glargine has raised concerns over its potential contribution to the development of diabetic retinopathy [8,9].

We wanted to assess the frequency and severity of DR in T1DM cases on basal insulin treatment and its relationship with blood IGF-1 levels.

PATIENTS AND METHODS

A cross-sectional comparative study that included 88 patients conducted at Ain Shams University Hospital, Diabetology Clinic. It was conducted from October 2021 till February 2022.

Subjects were divided into 44 type 1 diabetic patients on baseline insulin therapy with glargine and Actrapid (Group A) and 44 on insulin NPH and Actrapid (Group B).

Exclusion criteria included patients with ESRD, CLD patients, heart failure, pregnancy, chronic anemia, smoking or alcohol abuse, and patients complaining of ophthalmic disorders, which include glaucoma and optic disc abnormalities.

Complete medical history was taken from all included individuals, emphasizing the duration of DM, insulin taking history (Duration of treatment with basal insulin therapy (Glargine or NPH) for at least 1 year), complications and other comorbidities. Detailed clinical examination comprising pulse, blood pressure measurement, weight, height and BMI (kg/m^2) and fundus examination using Optomed Aurora® IQ handheld fundus camera was done.

Laboratory studies:

Laboratory tests included hemoglobin A_1c (HbA_1c), total cholesterol, triglycerides (TG), LDL, HDL, serum IGF-1. HbA1c was measured by Stanbio Procedure No.0350 "Quantitative colorimetric determination of Glycohemoglobin in blood", Lipid profile (total cholesterol, HDL, LDL, TG) by quantification colorimetric Kit, serum IGF-1 by ELISA Kit.

Ethical approval:

This study has been approved by the Ain Shams Faculty of Medicine's Ethics Committee [No.: FWA 000017585]. Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis:

SPSS, version 20.0, was used for the statistical presentation and analysis of the data included in this investigation. The mean ± standard deviation, and range (minimum to maximum) were used to characterize quantitative data, while frequencies (n) and percentages (%) were used to represent qualitative data. Quantitative factors were compared between groups using the independent t test. The relationship between the qualitative variables was assessed using the chi square and Fisher exact tests. Statistical significance was defined as a P-value of less than 0.05.

RESULTS

Regarding age, there was a statistically significant difference between both groups under study (P value<0.05 with Mean±SD of age in Group B regimen 28.4±6.7 versus Group A 25.5 ± 4.9). However, there was no statistically significant difference between the groups regarding sex, the length of time the patients had diabetes (in years), their vital signs (blood pressure and pulse), their body measurements (BMI and height), or the lab tests (serum IGF-1, HbA1C, and lipid profile) (Table 1).

Table (1): Comparison between the studied groups regarding demographic data and labs findings

		Group A	Group B	Test value	P-value	Sig.
		No.= 44	No.= 44			
Age (years)	Mean±SD Range	25.5 ± 4.9 18 – 38	28.4 ± 6.7 20 – 43	2.330	0.022	S
Sex	Female Male	30 (68.2%) 14 (31.8%)	32 (72.7%) 12(27.3%)	0.218	0.640	NS
Duration of diabetes (in years)	Mean±SD Range	14.3 ± 5.9 6-25	16.7 ± 6.3 6-35	1.823	0.072	NS
Systolic BP (mm Hg)	Mean±SD Range	113.6 ± 10.8 90-130	117.5 ± 15 90-160	1.389	0.168	NS
Diastolic BP (mm Hg)	Mean±SD Range	75 ± 8.5 60-100	77 ± 8.5 50-90	1.128	0.262	NS
Pulse	Mean±SD Range	72.7 ± 11.3 60-100	72.7 ± 12.6 60-100	0.000	1.000	NS
BMI (kg/m^2)	Mean±SD Range	25.6 ± 3.7 21 – 36	27.6 ± 6.6 18 – 47	1.721	0.090	NS
Height (m)	Mean±SD Range	2 ± 0 2-2	2 ± 0.2 1-2	0.000	1.000	NS
Serum IGF-1 (ng/ml)	Mean±SD	18.4 ± 3.6	15.1 ± 2.9	1.150	0.253	NS
HbA1c %	Mean±SD Range	9 ± 2	8.8 ± 1.6	0.358	0.721	NS
Cholesterol total (mg/dl)	Mean±SD	176.8 ± 41.3	176.7 ± 35	0.011	0.991	NS
TGS total (mg/dl)	Mean±SD	118.1 ± 9.6	124 ± 9.6	0.329	0.743	NS
HDL-C (mg/dl)	Mean±SD	45.1 ± 11	48.5 ± 11	1.447	0.151	NS
LDL-C (mg/dl)	Mean±SD Range	108 ± 35.4	103.3 ± 9	0.689	0.492	NS
VLDL-C (mg/dl)	Mean±SD	23.6 ± 4	24.9 ± 5.3	0.355	0.724	NS
CHD-risk	Mean±SD	26.7 ± 5.4	28.3 ± 5.4	0.858	0.393	NS

Group A: patients on insulin Glargine and Actrapid.
Group B: patients on insulin NPH and Actrapid.

Non-significant (NS), significant (S); (†) Independent t test, (#) Chi square test were used. P value < 0.05 is considered statistically significant; BP: blood pressure, BMI: Body mass index.

The results of the fundus examination did not differ statistically significantly across the groups under study (Table 2).

Table (2): Comparison between studied groups regarding fundus findings

		Group A	Group B	Test value	P-value	Sig.
		No. (%)	No. (%)			
Fundus	Normal	33(75)	29(65.9)	8.254	0.496	NS
	Mild NPDR	5 (11.4)	7 (15.9)			
	Mild NPDR and Hypertensive	0 (0)	1 (2.3)			
	Moderate NPDR	2 (4.5)	1 (2.3)			
	Moderate NPDR and macular edema	1 (2.3)	0 (0)			
	Severe NPDR	0 (0)	2 (4.5)			
	Severe NPDR and macular edema	0 (0)	1 (2.3)			
	PDR	3 (6.8)	1 (2.3)			
	Hypertensive retinopathy	0 (0)	1 (2.3)			
	Pigmentary retinopathy	0 (0)	1 (2.3)			
Type of Retinopathy	Normal	33(75)	29(65.9)	2.065	0.429	NS
	Diabetic retinopathy	11 (25)	15 (34.1)			
	other causes	0 (0)	2 (4.5)			

Group A: patients on insulin Glargine and Actarapid.
Group B: patients on insulin NPH and Actarapid.
NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy. Fisher exact test was used. P value < 0.05 is considered statistically significant

The mean ± standard deviation of DM duration in cases with DR was 17.7 ± 6.9 compared to 14.6 ± 5.6 in patients with normal fundus, indicating a statistically significant relationship between the two conditions (P value< 0.05). Serum IGF-1 levels and diabetic retinopathy did not significantly correlate with each other. Patients' demographics (age and sex), body measures (BMI and height), vital signs (blood pressure and pulse), and the results of other laboratory tests (HbA1C and lipid profile) did not statistically significantly correlate with diabetic retinopathy (Table 3).

Table (3): Relation between patients' demographic data, labs findings and fundus findings

		Fundus examination Findings		Test value	P-value	Sig.
		Normal fundus	Diabetic Retinopathy			
Age (years)	Mean±SD Range	26.4 ± 5.4 19-39	28.3 ± 7.3 18-43	1.314	0.192	NS
Sex	Female Male	44 (71%) 18 (29%)	18 (69.2%) 8(30.8%)	0.027	0.871	NS
Duration of diabetes (in years)	Mean±SD	14.6 ± 5.6 6-25	17.7 ± 6.9 6-35	2.209	0.030	S
Systolic BP (mm Hg)	Mean±SD Range	115.5 ± 12.4 90-150	115.8 ± 15 90-160	0.093	0.926	NS
Diastolic BP (mm Hg)	Mean±SD Range	76.3 ± 8.7 50-100	75.4 ± 8.1 60-90	0.453	0.652	NS
Pulse	Mean±SD Range	74 ± 11.5 60-100	69.6 ± 12.5 60-100	1.601	0.113	NS
BMI (kg/m^2)	Mean±SD Range	26.5 ± 5.6 18-47	26.8 ± 4.8 22-36	0.200	0.842	NS
Height (m)	Mean±SD Range	2 ± 0.1 1-2	2 ± 0 2-2	0.000	1.000	NS
Serum IGF-1 (ng/ml)	Mean±SD	14.8 ± 1	21.3 ± 1.9	1.807	0.080	NS
HbA1c %	Mean±SD	9 ± 1.8	8.7 ± 1.7	0.607	0.546	NS
Cholesterol total (mg/dl)	Mean±SD	174.3 ± 41	182.4 ± 29.9	0.011	0.991	NS
TGS total (mg/dl)	Mean±SD	124.6 ± 9.3	112.5 ± 1.4	0.619	0.538	NS
HDL-C (mg/dl)	Mean±SD	46.9 ± 10.2	46.7 ± 11	0.096	0.924	NS
LDL-C (mg/dl)	Mean±SD	102.5 ± 3	113.1 ± 9.6	1.420	.159	NS
VLDL-C (mg/dl)	Mean±SD	24.9 ± 1.2	22.5 ± 3.3	0.611	0.543	NS
CHD-risk	Mean±SD	28.1 ± 5.8	26 ± 5.6	1.065	0.290	NS

Non-significant (NS), significant (S); (†) Independent t test, (#) Chi square test were used. P value < 0.05 is considered statistically significant; BP: blood pressure, BMI: Body mass index.

DISCUSSION

Patients with DR had a statistically significant longer duration of illness than those without DR, according to the current study. This was in line with cross-sectional research that detailed the baseline features of a prospective cohort study of T1DM patients and showed that those without DR developed diabetes for a shorter period of time [(10)]. PDR and maculopathy were also linked to longer duration of type 1 diabetes, according to research by **Esteves *et al.*** [(10)] on 464 T1DM patients.

According to the results of the fundus examination, the patients on glargine and those on NPH did not vary statistically significantly. Similarly, no discernible change in the risk of sight-threatening DR was noticed between matched cohorts in a retrospective cohort study of cases with T2DM who were 20 years of age or older and had recently started therapy with long-acting insulin analogs and intermediate-acting NPH [(11)].

A significant 5-year comparative experiment that was started with 1017 T2DM cases in the United States and Canada and aimed to describe the retinal safety profile of insulin glargine and NPH insulin in individuals with T2DM showed similar results. It revealed no increase in the progression of DR with long-term insulin glargine, which is controversial given the theory that some in vitro studies have suggested that retinopathy (a sign of mitogenicity) may progress more quickly due to insulin glargine's higher binding affinity for the IGF-1 receptor than NPH insulin [(12)].

In contrast, data from 2207 patients who took either NPH or glargine insulin for 28–52 weeks was gathered for a retrospective study of a clinical trial. Using photographic techniques, it showed that insulin glargine had greater ratios of new DME and a > 3-step shift in the course of DR than NPH insulin, and no treatment group experienced optic disc swelling [(13)].

Regarding blood IGF-1 levels, our study found no statistically significant difference between individuals on glargine and those on NPH. Similarly, according to **Varewijck *et al.*** [(14)] IGF-1R activation was observed in the blood of T2DM cases treated with metformin and insulin glargine for 9 months, as opposed to those treated with metformin and NPH insulin. Both groups' total IGF-1 levels were comparable and did not alter while on insulin.

Slawik *et al.* [(15)] conducted a three-week cross-over study in which 42 patients with T1DM and T2DM were compared to NPH and glargine. They found that when patients with T1DM were treated with insulin glargine, their serum IGF-1 concentrations were higher than when they were treated with NPH.

There was insignificant association between serum IGF-1 levels and DR in our investigation. Similarly, **Payne *et al.*** [(16)] carried out a study at the Emory Eye Center to evaluate the connection between DR and serum IGF-1 in individuals with T2DM. Based on their diabetes status and retinal results, 225 participants were divided into 4 groups: no DM, diabetes with no background DR, NPDR, and PDR. Serum IGF-1 levels were measured and the subjects had a dilated fundoscopic examination. The findings demonstrated that there was no discernible variation in blood IGF-1 levels among the research groups and that diabetes participants had comparable serum IGF-1 concentrations to non-diabetics.

In contrast, a two-year research by **Raman *et al.*** [(7)] involved T1DM individuals aged 8 to 25 in order to connect changes in diabetic retinopathy with IGF-1 levels. It was discovered that the patients' IGF-1 levels and the degree of diabetic retinopathy were inversely correlated. IGF-1 levels were considerably lower in patients with severe NPDR and PDR than in those with milder alterations in diabetic retinopathy. Additionally, those with the highest levels of IGF-1 exhibited no alterations in diabetic retinopathy .

Regarding the HbA1C level, our study displayed insignificant difference between subjects with and without DR. This finding is in agreement with **Esteves *et al.*** [(10)] **and Zarghami *et al.*** [(17)] who found no link between blood HbA1C levels and retinopathy.

In contrast, longitudinal observation research revealed that when long-term mean HbA1C rose, the incidence of PDR and persistent macro-albuminuria in individuals with type 1 diabetes rose significantly and happened sooner. It came to the conclusion that the onset of critical problems in type 1 diabetes is closely linked to the long-term weighted mean HbA1C, as determined from diagnosis [(18)].

Regarding the lipid profile, our investigation found insignificant difference between both groups. Similarly, research by **Cetin *et al.*** [(9)] to evaluate the relationship between serum lipids and DR was carried out. It comprised 75 diabetic cases with PDR according on the ETDRS grading system, 55 diabetic cases with NPDR, and 61 diabetic cases without DR (NDR). There was insignificant difference in the mean values of total cholesterol, triglycerides, LDL, HDL, and VLDL between the groups under study or between patients with and without macular edema.

However, according to **Schreur *et al.*** [(19)], individuals with type 1 diabetes who had lower HDL cholesterol and higher total cholesterol levels were at a greater risk of developing diabetic retinopathy.

CONCLUSION

There was insignificant difference in serum IGF-1 levels between patients with normal fundus or DR, or between individuals on glargine or NPH. In subjects with T1DM, the severity and frequency of diabetic retinopathy are closely correlated with the length of the condition. There is no discernible difference in diabetic retinopathy between glargine and NPH patients on basal insulin treatment.

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