National Journal of Health Sciences, **2024,** ***9*****, 271-276**

Research Article

Frequency and Risk Factors of Diabetic Retinopathy in Children having Type-1 Diabetes Mellitus

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Abstract: Background: Diabetic retinopathy is the most prevalent complication and the primary cause of blindness in people with type 1 diabetes mellitus. There are two categories of risk factors: modifiable and non-modifiable for development of diabetic retinopathy.

Objective: To determine the frequency and risk factors of diabetic retinopathy in children having type-1 diabetes mellitus.

Materials and Methods: Children aged 7 to 18 years participated in this cross-sectional study, which was carried out in the National Institute of Child Health's endocrinology department. Clinical, anthropometric, and demographic data of the patients were gathered. To identify diabetic retinopathy, a fundus examination involved examining the optic disc, macula, retinal blood vessels, background, and fundus periphery.

Result: With an average age of 14.07±2.82 years, 157 patients were examined. 88(56.1%) were male and 69(43.9%) were female. Average HbA1C level was 10.10±2.63%. Total 116(73.9%) patients had diabetic retinopathy, of which 103(88.8%) had mild non-proliferative, 10(8.6%) had moderate non-proliferative, 1(0.9%) had severe non-proliferative, and 2(1.7%) had proliferative diabetic retinopathy. Diabetic retinopathy was significantly associated with age group (p=0.025), random blood sugar (p=0.050) and insulin regimen type (p=0.018). Male patients had a lower risk of diabetic retinopathy (OR=-0.497, p=0.069). Individuals with age 14 years or less had a lower probability of developing diabetic retinopathy (OR=0.437, p=0.027). Patients with High HbA1c had more risk to develop diabetic retinopathy (OR=1.314, p=0.003). Patients on basal bolus insulin had a higher risk of developing diabetic retinopathy (OR=2.378, p=0.020).

Conclusion: The results of our investigation showed that a significant portion of the study group had diabetic retinopathy. The most common kind of retinopathy was mild non-proliferative. Males who were less than 14 years old, had a low HbA1c, had the disease for less than ten years, and used regular insulin and neutral protamine Hagedorn (NPH) were less likely to develop diabetic retinopathy.

Keywords: Risk Factors, Diabetic Retinopathy, Type-1 Diabetes Mellitus, Cataract, Secondary glaucoma, Pregnancy.

INTRODUCTION

A class of metabolic illnesses known as diabetes is defined by hyperglycemia brought on by deficiencies in either insulin action or secretion, or both. Diabetes is the third most prevalent chronic illness in children, with autoimmune type 1 diabetes (T1D) accounting for the majority of cases. Diabetes can lead to a number of eye issues, the most serious is diabetic retinopathy (DR), which is associated with a risk of blindness. Other conditions include cataracts and secondary glaucoma [1].

The earliest symptoms of retinopathy typically take months or years to manifest clinically, and even then, the condition may not show any symptoms for some time [2]. It is anticipated that the incidence of DM will continue to rise after showing a consistent growth over the past few decades at all age groups, including younger once [3].

In contrast to the conventional view of DR as an adult consequence of diabetes, a recent investigation of children with T1DM and T2DM found that, after a median follow-up of 3.2 and 3.1 years, 20.1% and 7.2% of the children, respectively, acquired DR [4]. In the pediatric population, the frequency of DR ranged from 2.3% to 57.6% [5]. Proliferative DR was reported in 4.1%, initial DR in 10.7%, and background DR in 26.7% participants of study out of 4172 children with T1D diagnosed at the age of 12 years [6].

A global research comprising 156,090 type 1 diabetics aged 10–21 from 11 different countries revealed an overall DR prevalence of 5.8%, with variations from 0% to 16.2% depending on the nation under observation [7]. The same study discovered a strong positive link between smoking, elevated HbA1c, and hypertension, and the chance of developing DR. It also established a direct substantial correlation between the length of diabetes mellitus and the prevalence of DR [7].

Numerous risk factors, including the length of diabetes, hyperglycemia, hypertension, ethnicity, dyslipidemia, puberty, pregnancy, proteinuria, genetics, obesity, alcohol consumption, inflammation, and endothelial dysfunction, have been linked to the onset and progression of DR. The mechanism of action is poorly understood, and the data is contradictory [8]. One of the primary risk factors for the onset and progression of retinopathy

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is puberty. Patients under the age of ten have a very low chance of developing proliferative diabetic retinopathy [9- 11].

Multiple professional organizations encourage for screening DR [12, 13]. According to the most recent guidelines from the American Diabetes Association, if a young patient has had type 1 diabetes for three to five years and is 11 years of age or older, or has begun puberty, screening for DR with a dilated eye examination is advised [13].

Fundus photography, with or without artificial intelligence-based techniques for point-of-care detection of diabetic retinopathy (DR), serves as an accurate screening tool for DR, is feasible for use among young patients with diabetes, increases adherence to recommended screening, and is cost-effective. These advantages occur even though the gold standard for retinal screening continues to be an ophthalmologist's dilated and thorough eye examination [14-16].

Since diabetic retinopathy does not always result in blindness, every effort should be made to lower the risk of this consequence. In addition to its impact on eyesight, retinopathy has negative societal and economic effects. Hence, the aim of current research is to evaluate the frequency of diabetic retinopathy in type 1 diabetes. The relationship between several risk factors of DR, such as type of insulin and demographics, was also studied.

MATERIALS AND METHODS

This is an observational, cross sectional study conducted at pediatric endocrinology department of the National Institute of Child Health (NICH) from 1st January 2024 till 30th July 2024 (6 months), following inclusion criteria were participated in this cross-sectional study. The hospital's Research and Ethics Committee gave its approval to the research plan (IERB-55/2023). Before enrollment in the study, written informed consent was obtained from the participants.

Using a 95% confidence interval and a 4% margin of error, the OpenEpi sample size calculator was used to determine the sample size based on the 7% [17] frequency of retinopathy in these individuals. A sample size of 157 patients was determined.

Study participants between the ages of 7 and 18 years who were diagnosed with T1D and had the disease for at least 5 years were included. Non-probability consecutive sampling technique was used for sample collection.

Patients provided information on demographic, anthropometric, and clinical characteristics, which was entered into a predesigned questionnaire. Every patient's history of laser therapy, eye surgery, and ophthalmic medication use was obtained. Fundus examination was done by indirect ophthalmoscopy (under sedation if required) or slit lamp bio-microscopy using 90 D noncontact lens, it included the examination of the optic disc, macula, retinal blood vessels, background, and fundus periphery to detect any signs of DR. The International Clinical Diabetic Retinopathy Disease Severity Scale [18], was used for diagnosis and classification of Diabetic Retinopathy. The DR was classified as: no apparent, mild, moderate, severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

STATISTICAL ANALYSIS

The statistical program SPSS (statistical programs for social sciences) version 26.0 was used to examine the data. For quantitative variables such as age, height, weight, BMI, RBS level, and HbA1c (mean value was taken as the average of 5 measures at 3-month intervals [19]), mean and standard deviation were calculated. Calculations were made for the frequency and percentages of several qualitative factors, including gender, diabetes status, insulin usage, and the severity of diabetic retinopathy. The relationship between the qualitative variables was investigated using the Chi-Square test. Odds ratio was estimated using binary logistic regression. P-values that were less than 0.05 were considered statistically significant.

RESULT

A total 157 individuals with an average age of 14.07±2.82 years were investigated. Out of these patients, 69 patients (43.9%) were female and 88 patients (56.1%) were male. The disease (T1D) lasted an average of 7.48±2.68 years. The average height was 148.63±12.93 cm, average weight was 38.22±10.71 kg, and average BMI was 16.97±2.78 kg/m2. The random blood sugar level was 284.00±121.59 mg/dl and the average HbA1c was 10.10±2.63%. It was also observed that 86 (54.8%) of the 157 patients who were investigated were on basal bolus, whereas 71 (45.2%) were on neutral protamine Hagedorn (NPH) and regular insulin therapy. 116 (73.9%) individuals with diabetic retinopathy were included in the study; 103 (88.8%) of these patients had mild non-proliferative DR, 10 (8.6%) had moderate non-proliferative DR, and 1 (0.9%) had severe non-proliferative DR. The proliferative diabetic retinopathy patient rate was 1.7%. The study population's comprehensive descriptive results are shown in Table **1**.

Results mentioned in Table **2** showed that diabetic retinopathy is associated with both clinical and demographic characteristics. Diabetic retinopathy was shown to be substantially correlated with age group (p=0.025), random blood sugar (p=0.050), and insulin regimen type (p=0.018), but not with gender (p=0.066) and length of disease (p=0.887). Regarding HbA1c, the study results discovered a significant mean difference (p-<0.001) among study groups but not for BMI (p=0.111).

Additionally, male patients had a lower risk of diabetic retinopathy than female patients (OR=-0.497, p=0.069) based on uni-variate logistic regression analysis. The odds of getting diabetic retinopathy was lower in those under the age of 14 years than in those above the age of 14 years (OR=0.437, p=0.027). DR was more likely to occur in patients with high HbA1c (OR=1.314, p=0.003). Compared to patients on NPH and regular insulin, those on basal bolus insulin have a greater chance

of developing diabetic retinopathy (OR=2.378, p=0.020). Table **3** presents comprehensive odds, both adjusted and unadjusted.

Table 1. Descriptive Statistics of Demographic and Clinical Parameters of Study Population.

Gender	**n (%)**
Male	88(56.1)
Female	69(43.9)
Age (years)	
Mean± SD	14.07±2.82 (8-17)
≤14 years	76(48.4)
>14 years	81(51.6)
Disease Duration (years)	
Mean± SD	7.48±2.68 (3-15)
≤5 years	37(23.6)
6-10 years	93(59.2)
>10 years	27(17.2)
Random Blood Sugar (mg/dl)	
Mean± SD	284.00±121.59 (69-539)
Normal (<180 mg/dl)	36(22.9)
Impaired (180-200 mg/dl)	7(4.5)
Diabetes Mellitus (>200 mg/dl)	114(72.6)
HbA1c Level (%)	
Mean± SD	10.10±2.63 (5.30-21.6%)
Body Mass Index (Mean± SD)	
Height (cm)	148.63±12.93 (120-175)
Weight (Kg)	38.22±10.71 (20-65)
BMI (Kg/m2)	16.97±2.78 (11.41-26.71)
Insulin Regime Used	
Basal Bolus	86(54.8)
Neutral protamine Hagedorn (NPH) and Regular	71(45.2)
Diabetic Retinopathy	
Yes	116(73.9)
No	41(26.1)
Diabetic Retinopathy Severity (n=116)	
Non-Proliferative diabetic retinopathy	114(98.3)
Mild retinopathy	103(88.8)
Moderate retinopathy	10(8.6)
Severe retinopathy	1(0.9)
Proliferative diabetic retinopathy	2(1.7)

Table 2. Association of Diabetic Retinopathy with Demographic and Clinical Parameters.

	Diabetic Retinopathy n (%)		**p-value**
	Yes	**No**	
Gender			
Male	60(51.7)	28(68.3)	0.066
Female	56(48.3)	13(31.7)	
Age Groups			
≤14 years	50(43.1)	26(63.4)	0.025*
>14 years	66(56.9)	15(36.6)	
Disease Duration (years)			
≤5 years	28(24.1)	9(22)	0.897
6-10 years	69(59.5)	24(58.5)	
>10 years	19(16.4)	8(19.5)	
Random Blood Sugar			
Normal (<180 mg/dl)	22(19)	14(34.1)	0.050*
Impaired (180-200 mg/dl)	4(3.4)	3(7.3)	
Diabetes Mellitus (>200 mg/dl)	90(77.6)	24(58.5)	
HbA1c (mean± SD) #	10.48±2.82	9.02±1.57	0.001*
BMI (mean± SD) #	16.74±2.68	17.60±2.99	0.091
Insulin Regime Used			
Basal Bolus	70(60.3)	16(39)	0.018
NPH and Regular	46(39.7)	25(61)	
Chi-square/fisher exact test was applied. # Independent t-test was applied.			
* Significant at 0.05 levels.			

Table 3. Odds Ratio for Diabetic Retinopathy according to Demographic and Clinical Parameters.

	Non-Adjusted		**Adjusted**	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Age Groups				
≤14 years	0.437 (0.210-0.911)	0.027*	0.529 (0.237-1.180)	0.120
>14 years	Ref		Ref	
Random Blood Sugar				
Normal (<180 mg/dl)	0.419 (0.187-0.939)	0.035		
Impaired (180-200 mg/dl)	0.356 (0.074-1.697)	0.195		

Continue

Continue

Diabetes Mellitus (>200 mg/dl)	Ref			
HbA1c				
HbA1c	1.314(1.101-1.568)	0.003*	1.236(1.027-1.489)	0.025*
Insulin Regime Used				
Basal Bolus	2.378(1.146-4.931)	0.020*	2.311(1.070-4.996)	0.033*
NPH and Regular	Ref		Ref	
Binary logistic regression was applied.				
* Significant at 0.05 levels.				

DISCUSSION

In our study, male patients were slightly more in number than female patients. Almost half of the patients were aged more than 14 years. Most of the patients had disease duration of 6 to 10 years. Majority of them were having high HbA1c. Basal Bolus was mostly used insulin type regimen. High frequency 116(73.9%) of the study's participants had diabetic retinopathy, of which mild non-proliferative was the most observed type. In this study, diabetic retinopathy was significantly associated with, insulin regimen type, and HbA1c level. Further, Females, age more than 14 years, duration of disease more than 10 years, High HbA1c, and basal bolus insulin have a higher risk of developing diabetic retinopathy.

According to published data of multivariate analysis, 6.6% of research participants had retinopathy in a study including 662 individuals. A greater age at evaluation was associated with a higher risk of diabetic retinopathy (DR) in the same research group, where diabetes primarily occurred in adolescence [20]. The results of these studies found that, in comparison to individuals without DR, those who acquired DR had a median duration of diabetes of 7.6 years. Higher age and median HbA1c were associated with retinopathy risks on multivariate analysis. Better glycaemic management can be considered a preventive measure as it lowers the risk of retinopathy. It was also discovered that HbA1c is the sole modifiable risk factor for the development of DR [21, 22].

Retinopathy was discovered in around 50% of teenagers with type 1 diabetes in the early 1990s, this was reiterated according to a cohort study conducted in Australia involving 1604 patients and also mentioned that by the 2000s, that number had dropped to 12%, possibly as a result of aggressive therapy during this time [23]. In a different research study, young individuals with diabetes made up the majority 44 (95.4%) of patients with early retinopathy R1 [24]. A study of 119 study population having diagnosed T1D conducted in UK found that the most of them had early DR [25].

In an Australian research study, children having T1D were examined and observed that children who have T1D at the age of five years or earlier had a longer retinopathy free period than those diagnosed between the ages of five and fifteen years [26]. Of the 265 juvenile diabetics under the age of 20, in the US SEARCH project, 17% of those with T1DM experienced DR on fundus photography [27]. On the other hand, 20% of a sizable cohort consisting of 2240 young individuals had experienced diabetic retinopathy at a younger age (median duration of 3.2 years) [28]. Even though DR can develop due to a number of reasons, HbA1c has been identified as a controllable risk factor. A high HbA1c level was also associated with a greater risk of DR in our study as previously mentioned [29, 30].

In our study, a significant association was found with the type of insulin regimen used (i.e., lower risk of DR in individuals using NPH and regular insulin), though the difference between mean HbA1c of patients using these two insulin regimen type was not much significant, it could be due to its twice daily administration ensuring its greater compliance.

Since there is a significant and strong association between glucose and retinopathy, it is important to focus on strict glycaemic management in patients with type 1 diabetes in order to lower the risk of DR onset and progression.

LIMITATIONS

The study's limitations were its cross-sectional design, which restricted it to relationships that were seen, and its exclusion of any modifiable risk variables that may have shown other risk factors for retinopathy prediction in addition to glycaemic management. This study's limited applicability is also due to its relatively smaller sample size. Because it was done in an urban setting, it is possible that the findings cannot be applied to broader demographics.

CONCLUSION

In conclusion, we discovered that the study population had a significant frequency of diabetic retinopathy. The most common kind of diabetic retinopathy in patients was mild non-proliferative retinopathy. Furthermore, there was a substantial correlation between the HbA1c levels and insulin regimen followed and diabetic retinopathy. Patients who were ≤14 years old, male, had a low HbA1c, were on regular insulin or NPH, had a decreased chance of developing diabetic retinopathy.

AUTHORS' CONTRIBUTION

- **Muhammad Nasir Javed**: Data collection, Data analysis, Article writing.
- **Mohsina Noor Ibrahim**: Supervision and Guidance in data collection.
- **Zubair Khoso, Ikramullah Shaikh** and **Maira Riaz**: Data collection.
- **Versha Rani Rai**: Data collection, Article writing.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

I would like to extend my sincere gratitude and appreciation to the ophthalmology department at Jinnah Postgraduate Medical Centre (JPMC) for their expertise in conducting eye examinations for diabetic retinopathy in our patients. Their commitment and expertise have greatly contributed to the quality of care provided.

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Received: May 09, 2024 Revised: June 21, 2024 Accepted: June 25, 2024