Prevalence and Predictors of Diabetic Retinopathy, Its Progression and Regression in Indian Children and Youth With Type-1 Diabetes

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ABSTRACT

OBJECTIVE: There are very few reports on the prevalence of diabetic retinopathy (DR) in children and youth with type-1 diabetes (T1D). Studies have also found very low rates of referral for DR screening in children and youth with T1D. We conducted this study to determine the prevalence of DR, to study the reliability of ISPAD screening recommendations and to identify predictors of DR, its progression and regression in Indian children and youth with T1D.

METHODS: This study included 882 children and youth with T1D. Demographic data, anthropometry, blood pressure, sexual maturity rating, ophthalmological examination (slit lamp for cataract) and biochemical measurements were performed using standard protocols. Fundus images were captured using the Forus Health 3netra classic digital non-mydriatic fundus camera by the same experienced operator. De-identified images were assessed by a senior grader and ophthalmologist (Belfast Ophthalmic Reading Center). Severity of DR was graded as per the UK National Health Service (NHS) DR classification scale.

RESULT: We report 6.4% and 0.2% prevalence of DR and cataract in Indian children and youth with T1D, respectively. All the subjects with DR had early non-proliferative DR. We report that amongst subjects with DR, only 2 subjects were aged less than 11 years and had duration of illness less than 2 years. Presence of hypertension and older age were significant predictors of DR ($P < .05$). Subjects with DR had significantly higher triglyceride concentrations ($P < .05$), of these, 6.9% had progression and 2.9% had regression at 1 year follow up; the change in glycaemic control was a significant positive predictor of progression of DR ($P < .05$). None of the participants included in the study progressed to develop sight-threatening DR.

CONCLUSION: DR is not uncommon in Indian children and youth with T1D, thus screening for DR needs to be initiated early, particularly in older individuals with higher disease duration. Controlling blood pressure and triglyceride concentrations may prevent occurrence of DR. Improving glycaemic control may prevent progression of DR in Indian children and youth with T1D.

PLAIN LANGUAGE SUMMARY

Diabetic retinopathy in Indian children with Type 1 Diabetes

We found that 6.4% and 0.2% Indian children and youth with type-1 diabetes had diabetic retinopathy and cataract respectively. We report that amongst subjects with DR, only 2 subjects were aged less than 11 years and had duration of illness less than 2 years. Thus, International Society for Paediatric and Adolescent Diabetes (ISPAD) screening criteria must be implemented by all centres to avoid missing cases. Presence of high blood pressure, high triglyceride levels and older age were significant predictors of DR. Of the subjects with DR, 6.9% had progression and 2.9% had regression at 1 year follow up; the change in glycaemic control was a significant positive predictor of progression of DR. None of the participants included in the study progressed to develop sight-threatening DR. DR is not uncommon in Indian children and youth with T1D, hence, screening for DR needs to be initiated early, particularly in older individuals with higher disease duration. Controlling blood pressure and triglyceride concentrations may prevent occurrence of DR. Improving glycaemic control may prevent progression of DR in Indian children and youth with T1D.

KEYWORDS: Type-1 diabetes, retinopathy, progression, regression, children

Introduction

Type 1 diabetes (T1D) is the most common form of diabetes in children and adolescents in a majority of countries.[1] India now has the highest estimated number of prevalent T1D cases in the world in people under 20 years of age (229 400).[1] Diabetic kidney disease, neuropathy, retinopathy and macrovascular diseases are long-term vascular complications of T1D. Data on prevalence of these complications from low- and middle-income

countries (LMICs) are scarce. In our previous work, we have reported 13.4%, 47.2% and 4.5% prevalence of nephropathy, dyslipidaemia and metabolic syndrome in children and youth with T1D from our centre in western India.[2-4] However, despite the high prevalence of T1D, there are very limited data on the prevalence of diabetic retinopathy (DR) in Indian children and youth with T1D.

Several studies report variable prevalence of DR. Non-proliferative DR is more common in children and adolescents with T1D. The variation across countries has been reported to be between 0% and 16.2% with some national registries reporting a prevalence of any DR greater than 10%.[5] Further, the risk of progression of DR to vision threatening stages and macular oedema in adolescents with diabetes is higher due to insulin resistance in pubertal years.[6] Various studies have reported low referral rate for DR screening in paediatric diabetes clinics.[7]

The International Society for Paediatric and Adolescent Diabetes (ISPAD) recommends that in children and youth with T1D, screening for DR should be initiated at puberty or from 11 years of age or in patients with a disease duration of 2 to 5 years.[6] This is unlike in type 2 diabetes where screening is advised from the diagnosis of diabetes. Clinical bio-microscopic fundus slit-lamp examination is the most sensitive method to screen for DR. It may also be performed through a mydriatic 7-field stereoscopic retinal photography. The regularity of retinopathy screening may be 2 to 3 yearly if there is no retinopathy at first assessment. It needs to be performed at a higher frequency if there are red-flag features of visual loss. Prompt referral of youth with diabetes with vision threatening retinopathy to an ophthalmologist with understanding in the management of DR is thus suggested.

It is reported that duration of T1D, poor glycaemic control, raised blood pressure and albuminuria play a significant role in development of DR. The progression and regression of DR may occur rapidly with fluctuation in glycaemic control.[8] As most of the studies on prevalence of DR are conducted in developed countries where populations have access to health care facilities and high expenditure on the same, the results of studies conducted in developed countries may not be applicable to LMIC. Further, reliability of the ISPAD guidelines in screening for DR in Indian children has also not been assessed. In an earlier study on dyslipidemia in children and youth with T1D, although ISPAD guidelines suggest screening for dyslipidemia after age of 11 years in children with T1D, the author's group had reported that 11.9% children under 10 years were dyslipidemic.[3,6] We thus conducted this study in children and youth (1-24 years) with the following objectives: (1) To determine the prevalence of diabetic retinopathy in Indian children and youth with T1D, (2) To study the reliability of ISPAD guidelines for screening for DR and (3) To identify predictors of diabetic retinopathy and its progression and regression in children and youth with T1D from India.

Methods

Study design and subjects

This longitudinal, observational study was conducted at a tertiary care hospital in western India. All children and youth with T1D who were examined in the 'Sweetlings' cohort from November 2020 to March 2022 were included in study except those with comorbidities like coeliac disease and hypothyroidism. About 882 participants were examined annually in the above-mentioned study period with paired analysis performed on a total of 343 subjects. The post-hoc power of 0.8 was calculated for logistic regression given ά of .05, sample size of 343 and odds ratio of 2.65 for improvement in glycaemic control categories. At enrolment into the cohort and at 1-year follow up, clinical history and examination, anthropometry and biochemical parameters were evaluated using a medical records-based questionnaire.[4]

Clinical history and examination

Data on age of the study participants, duration of illness, type of insulin regimen and total dose of insulin in units per kilogram body weight per day were collected by paediatricians. Pubertal assessment for sexual maturity was performed using Tanner staging by a paediatric endocrinologist.[9,10]

Blood pressure (BP)

BP was measured by a trained paediatrician on the right arm with the child lying down quietly. The cuff was leak tested prior to commencement of the study. All air was removed from the cuff, the cuff was wrapped snuggly and neatly around the limb to allow 1 finger under the cuff. The cuff was placed 2 to 5 cm above the elbow crease. All the measurements were performed manually with the same oscillometric non-invasive BP (NIBP) device (Goldway™ Multipara Monitor−Model Number GS20). The blood pressure was interpreted based on age, gender and height normative data for Indian children.[11]

Anthropometry

Standing height and weight were measured by a trained paediatrician using a portable stadiometer (Leicester Height Metre, Child Growth Foundation, UK) to the nearest millimetre and an electronic scale to the nearest 100 g. Body mass index (BMI) was computed by dividing weight in kilograms by height in metre square. Subsequently, the height, weight and BMI were converted to *Z* scores using Indian reference data.[12] Waist circumference (WC) and hip circumference were measured with the child standing using a stretch-resistant tape with constant 100 g tension maintained through the use of a special indicator buckle. The tape was applied horizontally above the upper lateral border of right ileum, at the end of expiration and was recorded to the nearest 0.1 cm.[13] The waist-hip ratio

(WHR) was calculated as WC divided by the hip circumference and WC was converted to *Z* score using Indian reference data.[14]

Biochemical measurements

Glycaemic control was evaluated by measuring glycosylated Haemoglobin (HbA1C). A blood sample (5 ml) was collected after overnight fasting of at least 8 hours by a paediatric phlebotomist. HbA1C was measured by High performance liquid chromatography (HPLC, BIO-RAD, Germany). Thyroid stimulating hormone concentrations (TSH) were measured by Chemiluminescent Microparticle Immuno Assay (CMIA). The fasting blood samples were then assessed for lipid profile (total cholesterol, triglycerides and high density lipoprotein cholesterol (HDL-C)) using the enzymatic method and low-density lipoprotein-cholesterol (LDL-C) concentrations were calculated by the Friedewald formula.[15] Microalbumin in spot urine was detected by Immunoturbidimetry, creatinine by Jaffe w/o deproteinization and Albumin/Creatinine Ratio (ACR) by Jaffe method.

Ophthalmic evaluation

Fundus images were captured using the Forus Health 3netra classic digital non-mydriatic fundus camera. For young children (<6 years) we ensured a child-friendly environment and involved parents during the sessions to help children feel comfortable. Multiple images were taken to ensure quality, and the best images were selected. Images were assessed by a senior grader (AS) and ophthalmologist (MQ). Any disagreements between graders were adjudicated by an optometrist (KC) and retinal specialist (TP). Severity of DR was graded as per the UK National Health Service (NHS) DR classification scale (R1– mild, R2– pre-proliferative and R3 proliferative DR).[16] Two main outcomes (at least in 1 eye) were considered: (1) Overall DR Progression (at least 1 step change in DR severity) and (2) Overall DR regression (at least 1 step change in DR severity).

Statistical analysis

All statistical analyses were carried out using the SPSS for Windows software programme, version 26 (SPSS, Chicago, IL, USA). Differences in means were tested using Student's *t* test for parametric data and Mann Whitney *U* test for non-parametric data. Chi-square test and Cramer's *V* were used for correlation analysis of categorical variables. For testing relationships between dichotomous-dependent variables and continuous predictors, binary logistic regression analysis was carried out. $P < .05$ were considered as statistically significant.

Results

Of the 882 records studied, 406 (46%) were boys and 476 (54%) were girls. The mean age of the children in the study group was 12.8 ± 4.7 years and the average duration of diabetes was 5.4 ± 3.9 years. The minimum and maximum age of the participants involved in the study was 1.1 and 24.6 years respectively. The age wise distribution of children was as follows: 316 (35.8%) children were under the age of 11 years and 566 (64.2%) adolescents/youth were above 11 years. About 190 (21.6%) children/youth had disease duration of less than 2 years, 251 (28.5%) had disease duration between 2 and 5 years and the remaining 439 (49.9%) children had disease duration greater than 5 years. The mean HbA1C of study population was $10.1 \pm 2.2\%$. The mean total insulin requirement in our cohort was 1.1 ± 0.3 units/kg/day. 289 (32.9%) children were prepubertal, 269 (30.6%) children were in puberty and 321 (36.5%) children were post-pubertal.

Of the total, 56 subjects (6.4%) had early diabetic retinopathy- mild NPDR (R1). Amongst these 56, 6 subjects (10.7%) had retinopathy in both eyes. Five subjects (8.9%) with diabetic retinopathy had co-existing maculopathy. We also report 2 subjects with cataract (0.2%) from our study cohort. Of these 1 had co-existing coloboma and 1 had bilateral cataract. As seen in Table 1, the subjects with retinopathy were significantly older and shorter. They also had significantly higher blood pressure, triglyceride and very low density lipoprotein (VLDL) concentrations. No significant differences were noted in their insulin requirement and glycaemic control. The median diabetes duration was 5.5 [95% CI: 5.3-7.9] years in patients with retinopathy. The earliest retinopathy that developed in a patient was at the age of 5 years 8 months. We report that amongst subjects with DR, 16.1% (n = 9) had age less than 11 years while 19.6% (n = 11) had disease duration less than 2 years. A total of only 2 subjects with age less than 11 years and duration of illness less than 2 years (3.6%) had DR.

The Cramer *V* showed statistically significant ($P < .05$) correlation of .154 between development of hypertension and retinopathy in children with T1D. The Chi square test showed odds ratio for development of diabetic retinopathy in patients with T1D with hypertension was 4.520 (95% confidence interval: 2.2-9.1) while relative risk of development of diabetic retinopathy in participants with T1D with hypertension was 3.7 (95% confidence interval 2.1-6.6). Binary logistic regression analysis was performed to develop a model to predict occurrence of diabetic retinopathy in participants with T1D with dependent variable as presence or absence of diabetic retinopathy (Table 2). The independent variables used to predict DR were age, glycaemic control, ACR, BMI, hypertension, and triglyceride concentrations. Binary logistic regression analysis showed that age and hypertension were significant positive predictors. Glycaemic control did not have statistically significant relationship with diabetic retinopathy. The model inclusive of all risk factors was significant ($P < .05$) with Nagelkerke R^2 of .097 and correct prediction percentage of 93.6%.

A subset analysis on 343 subjects with 1 year follow-up was performed of which 155 (45.2%) were boys and 188 (54.8%)

Table 1. Comparison of clinical and laboratory findings of subjects with and without retinopathy.

PARAMETER	NO RETINOPATHY (n = 826)	RETINOPATHY (n = 56)
	MEAN ± STD. DEVIATION	MEAN ± STD. DEVIATION
Age*	12.6 ± 4.8	15.5 ± 4.1
Disease duration	5.4 ± 3.9	6.7 ± 5
Birth weight in kg	2.8 ± 0.6	2.8 ± 0.7
Height Z score*	−1 ± 3.7	−2.2 ± 3.9
Weight Z score*	−1 ± 2.6	−2 ± 2.6
Body mass index Z score	−0.4 ± 2	−0.9 ± 1.1
Waist Z score	−1.3 ± 3.7	−1.2 ± 1
Waist to height ratio	0.9 ± 0.1	0.8 ± 0.1
Systolic blood pressure (mm of Hg)*	105.6 ± 13	112.8 ± 14.8
Diastolic blood pressure (mm of Hg)*	64.9 ± 10.5	70.5 ± 10.5
Daily total sleeping time in min	525.5 ± 52.7	506.7 ± 46.1
Insulin requirement (IU/day)	1.1 ± 0.4	1.1 ± 0.4
Biochemical parameters		
HbA1C (%)	10.1 ± 2.2	10.3 ± 2.1
Albumin: Creatinine ratio (µg/mg)	61.3 ± 281.6	138.2 ± 414.4
Haemoglobin (g/dl)	13.3 ± 1.7	13.3 ± 1.8
Cholesterol (mg/dl)*	158.9 ± 34.4	170.6 ± 46
HDL (mg/dl)	49.5 ± 10.8	52.2 ± 13.6
LDL (mg/dl)	92.4 ± 31.5	92.2 ± 47.3
Triglyceride (mg/dl)*	84.8 ± 79.8	131.2 ± 262.1
VLDL (mg/dl)*	16.8 ± 15.1	26.2 ± 52.4

*Statistically significant difference between 2 groups P < .05.

were girls. Of these, 24 (6.9%) had DR progression and 10 (2.9%) had DR regression. None of the participants included in the study progressed to develop sight-threatening DR. Binary logistic regression analysis was performed to develop a model to predict progression of diabetic retinopathy in participants with T1D with dependent variable as progression of diabetic retinopathy (Table 3). Only the improvement in glycaemic control was a significant positive predictor of progression of diabetic retinopathy. The patients with deterioration of glycaemic control had 2.6 times higher risk of progression of diabetic retinopathy. The model inclusive of all risk factors was significant ($P < .05$) with Nagelkerke R^2 of .125 and correct prediction percentage of 93.5%.

Discussion

We report 6.4% and 0.2% prevalence of diabetic retinopathy and cataract in Indian children and youth with T1D respectively. Presence of hypertension and older age were significant predictors of diabetic retinopathy. The subjects with diabetic retinopathy had significantly higher triglyceride and VLDL concentrations. Of subjects with DR, 6.9% had DR progression and 2.9% had DR regression after 1 year. None of the participants included in the study progressed to develop sight-threatening DR. Only improvement in glycaemic control was a significant positive predictor of progression of DR, the patients with deterioration of glycaemic control had 2.6 times higher risk of progression of DR. We also suggest that screening of DR as per ISPAD recommendation must be initiated in children after age of 11 years with duration of illness greater than 2 years.

A study on 156 090 children and adolescents with T1D across 11 countries in 3 continents (Australia, Austria, Denmark, England, Germany, Italy, Luxemburg, Netherlands, Slovenia, United States and Wales) reported an unadjusted prevalence of any DR of 5.8%, varying from 0.0% to 16.2% between countries.[5] Studies from other LMICs like Egypt and Bangladesh report 10.4% and 6.6% prevalence of diabetic retinopathy respectively.[17,18] Similar to the study from Bangladesh wherein 95.4% subjects had early retinopathy (R1), none of our subjects had severe DR.

Older age has been reported to have 1.06 to 1.31 times higher risk of developing diabetic retinopathy[17] which is similar to the current study findings (1.115). A strong association of hypertension with DR has also been reported by other studies (1.12-1.38, $P < .0001$).[6] Increased blood pressure due to effects of increased blood flow may damage the retinal capillary endothelial cells thereby contributing to development of retinopathy in children with T1D.[19]

We report that glycaemic control was not a significant predictor of development of DR ($P > .05$). This may be explained by poor glycaemic control and younger age of subjects in our study as most studies report HbA1C and duration of illness as significant risk factors ($P < .05$) for the development of DR.[6,17] High serum triglyceride concentrations have been reported to have variable association with severity of DR in subjects with T1D. Weber et al found that serum triglycerides were strongly associated with degree of retinopathy in children and adolescents with T1D[20] as opposed to our study where serum triglyceride concentrations were not a significant determinant.

A 20-year study of 1604 adolescents with T1D demonstrated that the prevalence of retinopathy decreased in parallel with a decline in HbA1C and intensification of management.[21] Better

Table 2. Predictors of diabetic retinopathy in Indian children and youth with T1D.

PARAMETERS	B	S.E.	WALD	DF	SIG.	EXP(B)
Age	0.108	0.042	6.533	1	.011	1.115
HbA1C (%)	0.016	0.068	0.058	1	.81	1.016
Albumin:Creatinine ratio	0	0	0.019	1	.891	1
Triglyceride	0.002	0.001	3.426	1	.064	1.002
Hypertension	1.131	0.43	6.914	1	.009	3.099
BMI	−0.011	0.048	0.053	1	.817	0.989

Table 3. Predictors for progression of diabetic retinopathy in children and youth with T1D.

PARAMETER	B	S.E.	WALD	DF	SIG.	EXP(B)
Age	−0.12	0.064	3.703	1	.054	0.884
Gender	0.44	0.468	0.892	1	.345	1.556
Difference in BMI	−0.10	0.065	2.788	1	.095	0.897
Difference in waist circumference	−0.01	0.034	0.103	1	.748	0.989
Difference in diastolic blood pressure	−0.02	0.024	1.082	1	.298	0.976
Glycaemic control	0.97	0.477	4.197	1	.041	2.654
Hypertriglyceridaemia at baseline	−0.62	0.816	0.576	1	.448	0.538
Hypertension at baseline	−0.50	0.727	0.486	1	.486	0.603

glycaemic control was the strongest predictor for decreasing severe retinopathy with time with HbA1C partially explaining the difference in retinopathy.[22] However, another study reports that the use of an insulin pump was associated with lower rates of DR even after controlling for HbA1C concentrations. It suggests that a decrease in glycaemic variability causes improvement in DR rather than reduction in the HbA1C by itself.[23] Interestingly, another study concludes that DR is rare in children regardless of duration and glycaemic control.[7]

The prevalence of early diabetic cataract in children has been reported between 0.7% and 3.4%, the pathophysiology of which is not clearly understood. However, a role of genetics, local factors, nutritional habits, and gender as well as growth and developmental changes in childhood has been suggested.[24]

This study introduces novel insights by specifically examining children's fundus images (including those of very young children), which few studies have previously addressed. To our knowledge, it is the first to investigate the progression of DR in children from a developing country. Additionally, the study includes a comprehensive set of anthropometric measurements and biochemical markers providing a more detailed understanding of the risk factors and progression of DR in this young population. Large sample size and high rate of follow-up are strengths of our study. Longitudinal follow-up of only 1 year and data from a single centre are our limitations. Due to poor glycaemic control of the cohort, the results may not be generalizable to populations with better control. However, to the best of our knowledge, ours is one of the very few studies from an LMIC to report DR in children and young adults with T1D.

Conclusion

In conclusion, ophthalmic complications of T1D are noted in Indian children and youth with T1D and must be screened for as per ISPAD recommendations. Presence of hypertension and older age are significant predictors of diabetic retinopathy. Thus, controlling blood pressure in children and youth with T1D may help in reducing prevalence of DR. The progression of DR may be prevented by improvement in glycaemic control. Future research is needed on diabetic retinopathy in children and youth, particularly by obtaining longitudinal data to gain a better understanding of how diabetic retinopathy progresses among this young group.

Declarations

Ethics Approval and Consent to Participate

Informed consent was signed by parents and assent was obtained from children above 7 years; the study was approved by the Ethics Committee Jehangir Clinical Development Centre Private Limited (EC/NEW/INST/2023/MH/0236), ethical approval dated July 16th, 2020.

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