RESEARCH PAPER

Glycemic Control and Long-term Complications in Pediatric Onset Type 1 Diabetes Mellitus: A Single-center Experience from Northern India

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Objective: To study glycemic control, mortality and long-term complications in children with type 1 diabetes (T1D).

Design: Cross-sectional study.

Setting: Referral centre at a government teaching hospital.

Participants: Patients with T1D with age ≤18 years at onset.

Methods: We retrospectively collected demographic data from computer records from 1991 to 2015. Prospective study for outcomes was conducted between 2012 and 2016.

Main outcome measures: Mortality rate, glycosylated hemoglobin (HbA1c), and microvascular complication rate.

Results: The proportion of T1D patients (*n*=512) <5 years of age at onset was 18.6% between 1995 and 2004, and 24.2% in 2005-2014 (*P*<0.001). Twenty eight patients had died out of 334 whose living status was known (mortality 1.1 per 100 patient-years over 2549 patient-years follow up). Median (range) HbA1c (*n*=257) was 8.3% (5.1-15.0%). At least one episode of severe hypoglycemia (coma/seizure/inability to assist self) had occurred in 22.8% patients over two years. Hypertension was present in 11.7% patients. Microvascular complications screen in 164 eligible patients [median (range) age 20 (8-45) y and duration of diabetes 9.1 (5-30) y] showed diabetic nephropathy in 3.0%, proliferative retinopathy in 3.6% and LDL cholesterol >100 mg/dL in 34% patients.

Conclusion: The mortality rate and prevalence of hypertension were high, given the short duration of diabetes of the patients. The proportion of patients with age ≤5 years at onset of diabetes has increased at our center.

Keywords: *Hypertension, Microvascular complications, Mortality, Outcome*.

India is home to one of the largest number of children with type 1 diabetes (T1D) in any single country [1]. However, the literature on T1D from India is sparse. Prevalence studies in expatriate Indians residing in UK report a prevalence of T1D in South Asians of 0.54 per 1000 population, compared to 0.99 per 1000 population in the local European population [2]. With regard to the internationally observed rising incidence of T1D, especially in young children, many studies suggest rising incidence rates in expatriate South Asians comparable to those in the local European population.

There are few studies published from India regarding the long-term complications in patients with pediatric-onset T1D [3-6]. India has been witnessing improvement in economic and educational status, with increased availability of diabetes management tools and trained professionals in the last two decades. Therefore, we studied the glycemic status, mortality and long-term complications of pediatric onset T1D patients in our clinic, where patients are looked after by a multi-disciplinary diabetes management team.

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METHODS

We studied all the patients with T1D with age of onset less than 18 years, who attended our outpatient or inpatient facility from January 1991 to June 2015. Diagnosis of T1D was made if polyuria and weight loss were present at onset, obesity with acanthosis nigricans was absent, ketones were documented at any time, or insulin continued to be required for glycemic control beyond one year of diagnosis. Patients with clinical features suggestive of syndromic or monogenic diabetes were excluded. Calcific pancreatic diabetes was ruled out by ultrasonography in all our patients above 15 years of age, as per our departmental protocol.

After clearance from Institutional Ethical Committee of our institute, we collected data from hospital records and case files regarding demographics and the insulin treatment regimen at the time of referral. Between June 2012 and 2016, we prospectively recorded all (at least three glycosylated hemoglobin) (HbA1c) (Bio-Rad, Variant II, Hercules, CA, USA) values available during the previous two-year period, not including the honeymoon period. Subjects with four or more HbA1c in the past two years (≥3 HbA1c values in last one year for recently registered patients) were labelled as being under regular follow-up. We also recorded the number of episodes of severe hypoglycemia during the two year follow-up period, defined by coma, seizures or, in the appropriate age group, a patient's inability to assist oneself in the hypoglycemia management.

Eligibility for long-term complications screening was determined according to American Diabetes Association (ADA) recommendations [7]. Blood pressure was measured 6-monthly at the clinic visits. A persistent elevation of systolic BP above 130/80 mmHg or above 95th percentile for age and height on two occasions in the clinic, corroborated in records by the primary care physician or pediatrician, was considered as hypertension. Diabetic retinopathy (documented by direct ophthalmoscopy) was classified as (*i*) no apparent retinopathy (*ii*) non proliferative diabetic retinopathy (NPDR; mild, moderate and severe) and (*iii*) proliferative diabetic retinopathy (PDR) [8]. An overnight urine sample was tested for microalbumin by radioimmunoassay (Immunotech, Prague, Czech Republic). Persistent microalbuminuria and diabetic nephropathy were defined by standard criteria [7]. Assessment of neuropathy as one of the microvascular complications was not planned in this study.

We made two sets of phone calls and sent two letters to every patient in our database who was not under follow-up, inviting them to attend the clinic and enquiring regarding severe hypoglycemia episodes, and mortality and the circumstances of death.

Statistical analysis: Data were not normally distributed. Mann Whitney U test, Kruskal Wallis test, Spearman's correlation, and Chi square or Fisher's exact tests were performed using the Statistical Package for the Social Sciences (SPSS version 19.0, SPSS, Inc., Chicago, IL, USA). A two-sided $P<0.05$ was considered statistically significant.

RESULTS

The number of new patients with T1D attending our OPD from January 1991 to June 2015 was 512 (male 58%, rural 19%). The proportion of patients with age of onset ≤5 years of age was 18.6 % from 1995 to 2004 and 24.2% from 2005 to 2014 (P<0.001). During 1991 to 2004, only 47% of the patients were on multiple daily injections (MDI) while during the period from 2005 to 2014, 97% of the patients were on MDI, with approximately half on analogue for their basal insulin.

Mortality status was known in 330 (64.5%) patients; 28 out of which had died. Mortality rate was 1.1 per 100 patient-years over 2549 patient years of follow-up. The median duration of diabetes at death was 102 (range 44-278) months. Out of 16 cases in which the cause of death could be ascertained, 10 deaths were directly related to diabetes or its complication. Chronic renal failure due to diabetic nephropathy was the major cause of death (*n*=6) followed by septicemia (*n*=4; two of these also had diabetic ketoacidosis). Among deaths due to causes which may not have been related to diabetes in these particular instances, two patients committed suicide in the third decade of life. Autoimmune hemolytic anemia, tuberculosis, encephalitis and neurocysticercosis with refractory seizures were the cause of death in one patient each.

Of the 257 patients enrolled during the prospective study period, the median HbA1c was 8.3% (5.1-15%) [95% CI; 8.0-8.5%]. Only 29% patients had mean HbA1c ≤7.5%. Patients with regular follow-up had significantly better median HbA1c than those with irregular follow up (***Table* I**), as did patients with higher self/family education. We did not find any statistically significant differences in median HbA1c among patients in the age groups <10 years, 10-18 years and >18 years, or any correlation with duration of diabetes.

Episodes of severe hypoglycemia occurred during the previous two years in 22.8% (95 % CI; 18-28 %) of 217 patients. The rate of severe hypoglycemia associated with coma/seizures was 3.9 episodes per 100 patient-years, and with inability to assist oneself was an additional 10.5 episodes per 100-patient years. The median HbA1c of the group of patients with or without severe hypoglycemia was not significantly different. Rate of severe hypoglycemia did not differ between gender, urban and rural subjects, patients with higher *versus* lower education class in themselves or parents, or with the use of glargine *versus* NPH insulin. The incidence of severe hypoglycemia at least once in the 2-year period in the age groups of <10 year, 10-18 year and >18 year, was 34.8%, 22.2%, 14.6%, respectively. It was significantly higher in the youngest patients ($P<0.001$ between the three groups and each pair of groups). However, there was no significant difference in median HbA1c of patients with severe hypoglycemia across the above mentioned age groups.

TABLE I GLYCEMIC CONTROL IN CHILDREN WITH TYPE I DIABETES (*N*=257)

Comparison groups	*HbA1c (%); Median (range)*
*Regular *vs* Irregular follow-up	8.1 (5.1-14.0) *vs* 8.7 (5.7-15.0)
#Higher (above class 10) *vs* Lower self/family education	8.3 (5.7-15.0) *vs* 8.9 (6.6-14.0)
Rural *vs* urban patients	8.3 (5.7-14.2) *vs* 8.4 (5.7-15.0)
Male *vs* female	8.4 (5.7-15.0) *vs* 8.1 (5.1-15.0)
‡Intermediate-acting (NPH) *vs* long- acting (glargine) insulin	8.7 (5.7-15.0) *vs* 8.3 (5.1-15.0)
Diabetes duration >10 y *vs* ≤10 y	8.0 (6.0-15.0) *vs* 8.4 (5.1-15.6)
Patients with SH episodes *vs* without SH episodes	8.2 (5.8-15.5) *vs* 8.5 (5.1-15.0)
Age groups; ≤10 y, 11-18 y, >18 y	8.4 (5.1-15.0) *vs* 8.6 (5.7-14.2) *vs* 8.0 (6.0-15.0)

*All P values >0.05 except *P<0.001; #P<0.05; ‡Patients receiving the two drugs. SH: Severe hypoglycemia; NPH: Isophane insulin.*

Hypertension was present in 11.7% (95% CI 8.6-16.9 %) of the 257 patients seen prospectively. Patients with hypertension had significantly higher mean age [28.8 (6.6) *vs* 17.8 (7.3) y, *P*<0.001] and mean diabetes duration [16.1 (6.3) *vs* 8.5 (5.7) y, *P*<0.001] *versus* those who did not.

During this 4-year period, 164 patients were eligible for and underwent microvascular complication screen. There was no significant difference in the frequency of any complication in urban *vs* rural and higher *vs* lower education-class patients. Non-proliferative retinopathy was present in 10 patients (6.1%, 7 patients with mild, 2 with moderate and 1 with severe NPDR) and proliferative diabetic retinopathy in 6 patients (3.6%). No patient had blindness. Microalbuminuria was present in 17 patients (10.3%), and 5 patients (3%) had gross albuminuria (***Table* II**).

TABLE II LONG-TERM COMPLICATIONS IN CHILDREN WITH TYPE 1 DIABETES (*N*=164)

Complication	*No.* (%)
Non-proliferative diabetic retinopathy	10 (6.1)
Proliferative diabetic retinopathy	6 (3.6)
Diabetic nephropathy	5 (3.0)
LDL cholesterol (>130 mg/dL)	16 (9.8)
LDL cholesterol (100-130 mg/dL)	40 (24.4)
#Hypertension	30 (11.7)

#257 children screened.

DISCUSSION

Our study provides a comprehensive view of long-term outcomes in patients with type 1 diabetes being cared for by a multidisciplinary team in a public hospital in a developing country. Though it has some drawbacks, it emphasizes the inadequate glycemic control, high rates of severe hypoglycemia and unacceptably high mortality. Our results suggest a greater proportion of younger children presenting with diabetes at our centre in recent years. These data, albeit indirect, are in keeping with world literature showing a rising incidence of T1D, the rise being disproportionately higher in toddlers and preschoolers [9].

Another important finding was the high mortality rate. The ascertainment of living status in only 65 % of the 512 patients registered with us could result in both positive and negative bias. The mortality rate of 1.1 per 100 patient-years in our study was much higher in comparison to the 2008 EURODIAB study (0.5 per 100 patient-years) [10], but comparable to that in other recent large international cohort (1.0 per 100 patient years in Sweden) [11]. These comparisons have to be viewed against the smaller mean duration of diabetes of our cohort (8 years) as compared to 22 years [10], and 20.4 years [11] in those studies, respectively. Better glycemic control being associated with higher formal education and regular follow-up has also been documented by others [12,13]. In contrast, the strikingly poor control in the adolescent age group noticed in world literature [14] was not observed in our patients. We attribute this to the delayed independence for adolescents observed commonly in our country.

The high rates of severe hypoglycemia seen in our patients have also been documented worldwide. In a nationwide study in Brazil [15], severe hypoglycemia was seen in 19.4% patients in the intensive insulin regimen group. A population-based study from Scotland showed a very high incidence of severe hypoglycemia (11.5 per 100 patient-years) with 7.1 % patients requiring emergency medical treatment [16]. In contrast, a lower rate of severe hypoglycemia was noted in a recent report from the Nordic countries, and could be attributed to greater use of insulin pumps. An important finding in our

WHAT IS ALREADY KNOWN?

- Long-term outcomes in type 1 diabetes are not uniform across nations and over the decades.

WHAT THIS STUDY ADDS?

- Glycemic control was not worse in adolescents than at other ages.
- High mortality, and prevalence of hypertension was observed despite a relatively short duration of disease.

study was the significantly higher rate of severe hypoglycemia in younger children, but without a significant difference in mean A1c of patients who had or did not have episodes of severe hypoglycemia, across the age groups, suggesting that liberal glycemic control targets (as per older recommendations) did not protect from severe hypoglycemia. Ceingiz, *et al*. [17] also reported similar results in their study on severe hypoglycemia and DKA in the T1DM Exchange Clinic Registry patients (*n*=13,487).

Data regarding long-term complications in T1D from the Indian subcontinent are limited [3-6,18,19]. We found disproportionately higher rates of hypertension, considering the relatively low median age and duration of diabetes of our subjects. However, reports on subjects with greater duration of diabetes show the prevalence of hypertension to be higher [6, 20-23]. Both over-diagnosis and under-diagnosis can result in alteration of prevalence data of hypertension. Nambam, *et al*. [24] emphasized the issue of under-diagnosis and under-treatment in their study of hypertension in 9362 children participating in the T1DM Exchange Clinic Registry. Therefore, it is vital to record blood pressure at each clinic visit.

Prevalence of microvascular complications has been found to be variable among Indian studies on pediatric onset T1D [3-6, 18]. We also compared our data with the largest database available so far, the Indian Council of Medical Research (ICMR) registry of people with diabetes with young age at onset (ICMR-YDR), phase1 (2006-2011) [25]. The prevalence of retinopathy (3.6%) and nephropathy (3.4%) (*n*=3545) reported were similar. However, with varying durations of diabetes and differences in study design, these studies are not truly comparable with each other. Subjects in most of these studies had a relatively short duration of diabetes. Recent studies from both the United States and the Nordic countries have shown the prevalence of diabetic renal disease to increase with diabetes duration of 20 years to 40 years [26]. It remains to be seen in future studies how Indian patients with longer diabetes duration will fare.

This is the only study from India to have prospectively documented mortality and incidence of severe hypoglycemia. However, we could only contact 65% of all patients registered with us. Those lost to contact had the longest duration of diabetes, and more likely to have suffered microvascular and macrovascular complications in greater numbers.

In conclusion, children at an Indian tertiary-care centre who had access to a multidisciplinary team met glycemic targets only in a third of patients, though median HbA1c was similar to that in recent reports from different regions of the world. Severe hypoglycemia was frequent, especially in the youngest age groups. Mortality was high compared to worldwide literature.

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