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REVIEW ARTICLE

Childhood and Adolescent Onset Type 1 Diabetes in India

Anandakumar Amutha, Kalpana Thai, Mohan Viswanathan

ABSTRACT

According to International Diabetes Federation, there are 382 million people with diabetes globally. While the majority of this is constituted by type 2 diabetes, numbers of type 1 diabetes are also increasing. This paper reviews the clinical and epidemiological features and management issues in children and adolescents with type 1 diabetes.

Keywords: Type 1 diabetes, Children and adolescents, Management, Complications, Epidemiology, India.

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INTRODUCTION

Recently, physicians and pediatricians are facing fresh challenges due to new epidemics affecting children's physical and mental health. Earlier, infectious diseases like viral infections, mumps, chicken pox, pneumonia, diarrhea, nutritional deficiencies dominated childhood diseases. Today these are being replaced by noncommunicable diseases like overweight/obesity and diabetes.[1-3]

Diabetes mellitus is one of the commonest endocrine and metabolic diseases of childhood. Till recently, diabetes in children (defined as onset below 12 years) and adolescents (defined as onset between 12 and 19 years) was almost exclusively type 1 diabetes (T1DM) and this has changed, as there is increased recognition of a number of different forms of 'nontype 1 diabetes' in the young. This includes type 2 diabetes (T2DM), maturity onset diabetes of young (MODY), fibrocalculous pancreatic diabetes (FCPD) and diabetes due to genetic disorders. This review will focus exclusively on the epidemiology, clinical profile, management and complications of childhood onset type 1 diabetes with special reference to published studies from India.

Epidemiology

T1DM is a disorder that arises following the autoimmune destruction of insulin-producing pancreatic β-cells.[4] The disease is most often diagnosed in children and adolescents, usually presenting with a classic triad of symptoms, (i.e. polydypsia, polyphagia, polyuria) along with severe hyperglycemia, necessitating the need for exogenous insulin replacement on a lifelong basis.

T1DM probably accounts for 5 to 10% of all diagnosed diabetes. About 40 to 60% of persons with T1DM are younger than 20 years of age at onset, thus making diabetes one of the most common severe chronic diseases of childhood affecting 0.3% of the general population by the age of 20 years and 0.5 to 1% during the lifespan.[5] The worldwide prevalence of T1DM is 0.1 to 0.3%, with 78,000 new cases every year, especially among young individuals (<5 years). Some 79,100 children under 15 years are estimated to develop T1DM annually worldwide.[6]

According to the reports of SEARCH group[7] the incidence of T1DM peaks around the age of 10 years and is highest among non Hispanic Whites followed by non-Hispanic Blacks, Hispanics, Asia and Pacific Islanders and American Indian/Alaskan Natives. The South-East Asia Region (SEAR) has a high prevalence of T1DM in children, with an estimated 77,900 children affected. In 2013, alone an estimated 12,600 children under the age of 15 in SEAR developed T1DM.[6]

India due to its sheer size (1.2 billion people) accounts for most of the children with T1DM in the SEAR. The incidence rate for T1DM in India was frequently used in extrapolation for other countries in the region and therefore the estimates in India are of great significance. In the 1990's, Menon et al[8] had done an overview of childhood onset diabetes mellitus in India. Prevalence of juvenile diabetes (onset below 15 years) among all diabetes hospital/clinic based data was presented and the prevalence ranged from 0.8 to 3.61% during the period from 1964 to 1989.

After a long gap of two decades, this review tries to fulfill the lacunae by presenting the incidence and prevalence/percentage of T1DM reported in India so far in Table 1. In a population based study conducted in South India for a period of 1991 to 1994, the incidence for the 4 year period was 10.5/100,000/year (CI 5.0) for children up to 15 years of age.[9] Similarly, a study from Karnal district in 2008, showed a prevalence of 18.3/100,000 in the 0 to 14 years age group.[10] Clinic based data show that more than 60% of the T1DM patients registered were childhood and adolescent onset T1DM patients.

Etiology and Pathogenesis of T1DM

The precise cause of T1DM is unknown but there are a number of possible contributory factors and some of them were discussed below.

Table 1: Incidence and prevalence/percentage of type 1 diabetes reported in India

Author name	*Place*	*Year or period of study*	*Number of T1DM in children reported and given as % where applicable*	*Total sample studied*	*Age at diagnosis*	*Ref. no.*
Incidence of T1DM						
Bai et al	Chennai	1991		10513	School children	11
Ramachandran et al		1991-1994	10.5/100,000 person-years	IDDM registry	<15 years	8
Kalra et al	Karnal	2008	3.82/100,00 24.22/100,000	Endocrine center registry	0-6 years 5-15 years	10
Prevalence/percentage of T1DM (clinic based)						
Verma IC	New Delhi	1980-84	44 (80.0)	55	5-12 years	12
Venkataraman et al	Chennai	1979-89	126 (7.88%)	160	<20 years	13
Mohan et al		1990	165 (63.9)	258	<20 years	14
Ramachandran et al		1991	0.26/100 (30 children)	116, 486	<15 years	15
Ramachandran et al		2000	617	-	<20 years	16
Kumar et al		1991-2001	8 (0.01%)	70000	≤1 year	17
Mohan et al		2007	286 (65.9%)	434	<16 years	18
Ganesh et al		2003-2007	4 (0.05)	83	≤1 years	19
Poovazhagi et al		1999-2010	350 (81%)	432	<12 years	20
Amutha et al		1992-2009	940 (68.5)	1372	≤19 years	21
Poovazhagi et al		1999-2012	40 (7.9)	506	≤1 year	22
Kota et al	Hyderbad	1997-2011	260	-	10.5 ± 7.2 years	23
Sahay et al		1999-2002	28 (59.6)	47	<20 years	24
Abraham et al	Central Kerala	1985-1989	39 (67%)	58	<20 years	25
Bhadada SK et al	Chandigarh	2002-2008	189	-	10.8 ± 7.3	26
Unnikrishnan et al	Multicentric study	2006-2008	535 (89%)	603	<20 years	27
Bhatia et al	Lucknow	2004	130 (81%)	160	<18 years	28
Balasubramanian et al		10 year period	55 children	-	<20 years	29
Singh et al		1992-1997	83 (57.2)	145	13.8 ± 7.3	30
Samal et al	Cuttack	1983-1988	54 (60%)	90	<15 years	31
Mazumder et al	Kolkata	2004-2006	41 (70.7)	58	<18 years	32
Kumar P et al	Karnataka	1995-2008	134 (43%)	311	9-14 years	33
Zargar et al	Srinagar	1990-1999	84 (90.3)	93	<20 years	34

Genetic Factors

T1DM tends to run in families. Epidemiologic studies have shown that brothers and sisters of children with T1DM have a higher chance of developing the disease (6% in siblings *vs* 0.4% in the general population) among the relatives of T1DM patients, underlying the role of genetic factors as a cause of T1DM.[35] Twin studies of T1DM from a large Finnish cohort of 22,650 twin pairs, 228 of which had at least one twin with T1DM (44 monozygotic (MZ), 183 dizygotic (DZ), and 1 of unknown zygosity), demonstrated a 27.3% MZ pair-wise concordance, and a 3.8% DZ concordance.[36]

Since, the 1970s it has been acknowledged that genes belonging to the human leukocyte antigen (HLA) system on chromosome 6 constitute the most important genetic risk factor.[37-39] The chromosomal locations of these 'diabetes genes' are called inherited susceptibility loci. There are now at least 18 insulin-dependent diabetes mellitus (IDDM) susceptibility loci (IDDM 1 to IDDM 18).[40] HLA make up the human major histocompatibility complex (MHC), which presents antigens to the immune system, but now more than 40 additional loci are known to significantly affect T1D risk.

Recently, genome-wide association studies (GWAS) have been used to identify genetic loci-associated T1DM. In contrast to the traditional methods of using a candidate gene approach, GWAS scans the whole genome for single nucleotide polymorphisms (SNPs) that occur more frequently in people suffering from T1DM. The associated SNPs then are used to mark the susceptibility loci. By using the SNP typing technology, a number of additional susceptibility loci were discovered for T1DM, namely: CLEC16A, CI1QTNF6, UBASH3A, CD226, PTPN2, CTSH, SH2B3, ERBB3, PRKCQ, TAGAP, IL-2RA,

TNFAIP3, BACH2, IL-7R, IL-2, CCR5, IFIH1, IL-18RAP, RGS1, IL-10, IL-19, IL-20, GLIS3, CD69 and IL-27.[41-43]

Viral Infections and Toxins

Epidemics of enteroviral infections in the autumn and winter months are associated with an increase in the incidence of T1DM. Several viruses (e.g. coxsackie B, enteroviruses, rubella, mumps and cytomegalovirus) have been implicated in the etiology of T1DM.[44] Also, T cells target the envelope proteins (VP1, VP2 and VP3) of coxsackie virus B4, but the T cell proliferative response was reduced markedly in T1DM patients compared with control subjects, which eventually results in destruction of beta cells.[45] Possible mechanisms for their effect include molecular mimicry in which the immune response to the infection cross reacts with islet antigens. Alternatively viral infections including those occurring antenatal may have more direct effects on β-cells. Ingestion of the rodenticide vacor is also known to be associated with development of T1DM.

Environmental Factors

Among the various environmental factors, exposure to antigenic substances early in life is thought to contribute to T1DM.[44] Undissolved gluten causes subclinical inflammation of intestinal mucosa, which raises the proportion of aggressive T cells. The functional state of beta cells also plays a role in the pathogenesis of T1DM, and food intake with a high glycemic index increases the insulin demand and forces the beta cell to produce more insulin, which accelerates its destruction. This observation has inspired the 'Accelerator hypothesis', which states that increased weight gain in youngsters might accelerate T1DM development.[46]

Nutrition and Dietary Factors

Breastfeeding appears to provide protection against the risk of developing T1DM.[47] Available evidence to date shows that lack of breastfeeding is a possible modifiable risk factor for the manifestation of both T1DM and T2DM. The benefits of breastfeeding have been attributed to bioactive substances, which promote the maturation of the immune system, reduce insulin resistance, and prevent excessive weight gain during childhood.[48]

Early introduction of cow's milk appears to be a risk factor for the development of T1DM.[49] Many new patients with T1DM have IgG antibodies to bovine serum albumin, a protein in cow's milk with similarities to the islet cell antigen. This protein may stimulate autoantibody production leading to islet cell destruction as a result of molecular mimicry.

Breastfeeding may be viewed as a surrogate for the delay in the introduction of diabetogenic substances present in formula or early childhood diet. Circumstantial evidence suggests a connection between T1DM and consumption of foods and water containing nitrates, nitrites or nitrosamines.[50-52]

Pancreatic β-cell Reserve—C-peptide Assay

It is known that at the time of T1DM diagnosis, 80 to 90% of the pancreatic islet β-cells are destroyed. C-peptide determination[53] is used to better understand the course of T1DM. It was shown that young children with classical ketosis prone insulin dependent diabetes also had residual insulin secretion.[54] Very young children especially those with onset after infections tend to have less C-peptide.

In recent years, C-peptide determinations have gained lot of interest. Efforts to preserve residual insulin secretion have increased dramatically in the last few years.[55] The heterogeneity of diabetes at clinical onset along with the increasing incidence in children and adolescents[56] makes it of interest to test if C-peptide may improve the classification of newly diagnosed children. Katz et al[57] reported fasting C-peptide levels of 0.38 ± 0.37 ng/ml can distinguish T1DM from T2DM with 83% sensitivity. In our study,[21] we found that a combination of clinical criteria and C-peptide criteria is largely helpful for classification of our children with diabetes and this also has been reported by Ludvigsson et al.[58]

Antibodies

Several autoantibodies have been identified in newly diagnosed cases of T1DM. Currently, four major antibodies namely (the 65 kDa form of glutamic acid decarboxylase [GAD65], insulinoma antigen 2 [IA-2], insulin auto, antibodies [IAA] and zinc transporter 8 [ZnT8]) have been shown to be found in T1DM and approximately 94% of all T1DM patients have least one of these antibodies at clinical onset.[59]

Monitoring these autoantibodies is currently the most reliable biomarker in the prodromal phase of T1D, since their appearance typically precedes overt T1D onset for years or even decades.[60,61] This provides a window for therapeutic intervention, and as a measure of treatment efficacy.[62-64] Most important, the prevalence of multiple types of autoantibodies identifies individuals with the highest risk of progression to clinical disease in those in the prediabetes stage of T1DM.

Clinical Features of T1DM

1. Abrupt onset of severe symptoms (polyuria, polydipsia and/or weight loss).

2. Presence of ketosis or ketoacidosis.
3. Severe diabetes with markedly elevated glycated hemoglobin levels (HbA1c).
4. Usually patients are nonobese or even lean.
5. Family history of diabetes in parents is usually absent.
6. C-peptide test shows absence or very low pancreatic β-cell reserve.
7. GAD, IA2, zinc transporter or other islet cell antibodies may be present.
8. Patients require lifelong insulin from time of onset for survival and to maintain good health and for control of hyperglycemia.

Management of T1DM

The basic elements of T1DM management are insulin administration, nutrition management, physical activity, self, monitoring of blood glucose (SMBG), and the avoidance of hypoglycemia. In T1DM, since the pancreas can no longer produce insulin, patients are required to take insulin daily, either by injection or via an insulin pump. Other routes of delivering insulin are currently being investigated.

Children are now being treated with basal bolus regime or an insulin pump. Basal bolus regime – this is the most physiological way of matching the insulin secretion in our body by insulin injections. In this, children receive a basal insulin dose with long acting insulin analog and premeal boluses are given by rapid acting insulin analogs just before meals. The total insulin dosage in children is 0.5 units/kg/day to 1.0 units/kg/day with up to 2.0 units/kg/day during puberty period.[65]

Premeal boluses are calculated more accurately by carbohydrate (CHO) counting, insulin to carbohydrate ratio (ICR) and correction bolus.

CHO counting is a meal planning wherein the patient identifies the CHO in the meal, estimates the total CHO amount in the meal and calculates the insulin to balance the CHO using ICR (insulin to CHO ratio) thereby controlling postprandial glucose levels more accurately. It is done by two methods, CHO exchange (1CHO serving = 15 gm carb portions) and CHO gram counting (food is weighed and CHO is calculated).

Insulin to carbohydrate ratio (ICR) is the amount of insulin required to cover a specified number of CHO grams. This is calculated by 500/300 rule (500/total daily dose of insulin (TDD) for children aged 5 years and above and 300/TDD for preschool children).

Correction bolus is the amount of extra, fast acting insulin added to or subtracted from a bolus to correct a blood glucose that is above or below target (90-140 mg). This is calculated by [(Current blood glucose – Target blood glucose)/insulin sensitivity factor (ISF)]. ISF is how much 1 unit of insulin will lower the blood glucose by. This is calculated by 1500 or 1800 rule (1500/TDD for short acting insulin and 1800/TDD for rapid acting insulin).[66]

Further adjustment of insulin or food intake may be made based on anticipation of special circumstances, such as increased exercise and intercurrent illness. Children on these regimens are expected to check their blood glucose levels (self monitoring of blood glucose) routinely before meals and at bedtime.[67]

Insulin pumps are being more commonly used because of their unique ability to continuously infuse insulin, closely mimicking that of physiological secretion from a normal pancreas. The insulin pump separates the insulin used as background, or basal insulin, from the insulin needed for meal and corrections boluses and therefore insulin can be more exactly matched to the metabolic need achieving better glycemic control. Scientific evidence from published studies have proven added benefit of insulin pumps in improving quality of life and normalizing sugars. The success of insulin pump therapy depends on selection of the right candidate, extensive education, motivation, and implementing the sophisticated programs with skill.[68]

Advantages of Insulin Pump

- Improvement in HbA1c
- Reduction in blood sugar fluctuations
- Reduction in major and minor hypoglycemic episodes
- Reduction in total daily dose of insulin
- Improvement in quality of life.

Disadvantages of Insulin Pump

- Cost of pumps and consumables is beyond the reach of the common individual
- There is a risk of infection if the cannula is not changed once in every 3 days
- Overeating and frequent bolusing could result in weight gain and misuse of an insulin pump
- Improper use of insulin pump boluses can lead to insulin stacking and low sugar.[68]

Complications of Diabetes

Acute Complications

Acute complications of T1DM include diabetes ketoacidosis (DKA), hypoglycemia and infections. An estimated 26% of the patients have at least one episode of severe hypoglycemia within the initial 4 years of diagnosis, with little relation to demographic or socioeconomic factors. The incidence of severe hypoglycemic episodes varies between

6 and 20/100 patient-years depending on age, geographic location and intensity of insulin treatment.[69]

Diabetic ketoacidosis in children continues to be an important cause of morbidity and mortality. Malnutrition also increases the risk of diabetic ketoacidosis-related complications.[70] Boys and girls were equally affected. Newly diagnosed diabetics constituted more than 50% of total DKA admission.[71] Management requires careful replacement of fluid and electrolyte deficits, intravenous administration of insulin, and close monitoring of clinical and biochemical parameters directed toward timely detection of complications, including hypokalemia, hypoglycemia and cerebral edema.[72,73]

Chronic Complications

Long-term complications may be microvascular (retinopathy, nephropathy, and neuropathy) or macrovascular (ischemic heart disease, peripheral vascular disease). Microvascular complications may develop in puberty or early adult hood whereas macrovascular complications affect in later years. The longer the duration of diabetes, the greater the risk of complications which increases significantly following puberty. The risk of developing complications may also be increased by poor glycemic control, hypertension, dyslipidemia and behavior such as smoking in addition to genetic factors.

Background diabetic retinopathy in childhood may rarely progress to proliferative retinopathy later in life. This can be successfully treated in its early stages with laser photocoagulation therapy. Cataracts may also occur in T1DM patients but is very rare under the age of 20 years. The prevalence of retinopathy in adolescents varies from 18 to 47%. More than 90% of patients with T1DM will eventually develop some degree of retinopathy. A pilot study done by SEARCH group estimated, the prevalence of diabetic retinopathy among those with T1DM was 17% which was similar to that reported from Australia [74] with similar duration. The SEARCH for diabetes in Youth study[75] reported a high prevalence of elevated albumin creatinine ratio (22.2%) in youth with T2DM, well over twice the percentage for participants with T1DM (9.2%).

A cohort of 354 patients with T2DM, age of onset between 15 and 30 years (T2DM15-30), were compared with 470 patients with T1DM with a similar age of onset (T1DM15-30) to study the clinical and mortality outcomes. No significant differences were found between T1DM and T2DM with regard to prevalence of retinopathy or renal function assessed by eGFR, but a marked excess of macrovascular disease was found in the T2DM15-30 cohort, with a higher prevalence of ischemic heart disease (12.6 *vs* 2.5%, p, 0.0001), stroke (4.3 *vs* 0.7%, p = 0.002), and the composite end point of any macrovascular disease despite having shorter duration of diabetes and remarkably similar glycemic exposure as T1DM 15 to 30 cohort.[76]

Prevalence of diabetes complications in T1DM reported from India is outlined in Table 2.

Most of the available data are from clinic based studies and the prevalence or percentages represents against their total patients registered from those particular clinics in India. The age ranges studied are usually inconsistent. There is also a lack of uniformity in classification of diabetes types. Some of the adolescents who were originally diagnosed as having T1DM were later found to have T2DM and *vice versa*. Some of the children and adolescents were not able to be classified due to lack of unavailability of GAD antibody and C-peptide assays. Another problem is migration of patients to other centers.

The Indian Council of Medical Research recently set up a national registry of diabetes in the young (onset <25 years of age). This shows that private diabetes centers have

Table 2: Diabetes complications in T1DM reported from India

S. no.	Author name	Year or period of study	Age at onset in years/duration of diabetes in years	Retinopathy n (%)	Nephropathy n (%)	Neuropathy n (%)	Ref. no.
1.	Venkataraman et al	1979-1989	<20 years/ 6 to 9 years	7/126 (5.6%)	5/126 (4%)	19/126 (15.1%)	13
2.	Sharma et al	1991	-	15/35 (42.8%)	-	-	77
3.	Ramchandran et al	2000	≤20 years/ 11-15 years	23/74 (31.1)	16/74 (21.6%)	19/617 (3.0%)	16
4.	Bhatia et al	2004	<18 years/ >5 years	22%	18%	-	28
5.	Unnikrishnan et al	2006-2008	<20 years/ <7 years	27/535 (5%)	29/535 (5.4%)	32/535 (6%)	27
6.	Kumar et al	1995-2008	<25 years	14/166 (8.4%)	20/230 (8.6%)	12/230 (5.2%)	33
7.	Amutha et al	1992-2009	<20 years/ 5-14 years	38/171 (22.2%)	9/183 (4.9%)	5/139 (3.6%)	21

more cases of young-onset T2DM, whereas government hospitals mostly deal with T1DM. This is probably a socioeconomic issue as the free supply of insulin would attract type 1 patients to government hospitals, whereas the more affluent with obesity-related T2DM would visit private diabetes centers.

In spite of a number of studies describing the prevalence, distribution and possible causes of diabetes, many government and public health planners still remain largely unaware of the current magnitude and in particular the increases in young diabetes and its serious complications. Special efforts must be made to collect data, especially in those countries where diagnosis may be missed.

REFERENCES

1. Br Ne M, Hochberg ZE. Secular trends in new childhood epidemics: insights from evolutionary medicine. BMC Med 2013;21;11:226.
2. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911-920.
3. Gluckman PD, Hanson MA, Beedle AS, Raubenheimer D: Fetal and neonatal pathways to obesity. Front Horm Res 2008:36: 61-72.
4. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature 2010;464:1293-1300.
5. Rewers M, LaPorte RE, King H, Tuomilehto J. Trends in the prevalence and incidence of diabetes: insulin-dependent diabetes mellitus in childhood. World Health Stat Q 1988;41:179-189.
6. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation;2013; http://www.idf.org/diabetesatlas.
7. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, Lawrence JM, Liese AD, Liu LL, Mayer-Davis EJ, Rodriguez BL, Standiford D; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the US population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care 2012;35:2515-2520.
8. Menon PSN, Virmani A, Shah P, Raju R, Sethi AK, Sethia S, Bicha RP, Joshi M, Kochupillai N. Ahuja MMS. Childhood onset diabetes mellitus in India: an overview. Int J Diab Dev Countries 1990;10:11-16.
9. Ramachandran A, Snehalatha C, Krishnaswamy CV. Incidence of IDDM in children in urban population in Southern India. Madras IDDM Registry Group Madras, South India. Diabetes Res Clin Pract 1996;34:79-82.
10. Kalra S, Kalra B, Sharma A. Prevalence of type 1 diabetes mellitus in Karnal district, Haryana state, India. Diabetol Metab Syndr 2010;2:14.
11. Bai PV, Krishnaswami CV, Chellamariappan M, Kumar GV, Subramaniam JR. Glycosuria and diabetes mellitus in children and adolescents in south India. Diabetes Res Clin Pract 1991;13:131-135.
12. Verma IC. The challenge of childhood diabetes mellitus in India. Indian J Pediatr 198956 (Suppl) 1:S33-38.
13. Venkatraman S, Suresh K, Sundaram A, Hariharan RS, Madhavan R, Manjula N, Seshiah V. Diabetes in the young: a profile. Int J Diab Dev Countries 1990;10:21-23.
14. Mohan V, Ramachandran A, Viswanathan M. Childhood-onset fibrocalculous pancreatic disease. Int J Diab Dev Count 1990,10:11-16.
15. Ramachandran A, Snehalatha C, Abdul Khader OM, Joseph TA, Viswanathan M. Prevalence of childhood diabetes in an urban population in south India. Diabetes Res Clin Pract 1992; 17:227-231.
16. Ramachandran A, Snehalatha C, Sasikala R, Satyavani K, Vijay V. Vascular complications in young Asian Indian patients with type 1 diabetes mellitus. Diabetes Res Clin Pract 2000;48: 51-56.
17. Kumar SS, Premalatha G, Mohan V. Infantile type I diabetes mellitus (onset less than one year of age) — a report of eight patients. Int J Diab Dev Countries 2003;22:103-106.
18. Mohan V, Revale J, Deepa R. Type 2 Diabetes in Asian Indian youth. Pediatric Diabetes 2007;8:28-34.
19. Ganesh R, Arvindkumar R, Vasanthi T. Infantile-onset diabetes mellitus: a 1-year follow-up study. Clin Pediatr (Phila) 2009; 48:271-274.
20. Varadarajan P, Sangaralingam T. Profile of diabetes mellitus at presentation in children under 12 years of age. Journal of Pediatric Sciences. 2011;3:e94.
21. Amutha A, Datta M, Unnikrishnan R, Anjana RM, Mohan V. Clinical profile and complications of childhood- and adolescent-onset type 2 diabetes seen at a diabetes center in south India. Diabetes Technol Ther 2012;14:497-504.
22. Varadarajan P, Sangaralingam T, Senniappan S, Jahnavi S, Radha V, Mohan V. Clinical profile and outcome of infantile onset diabetes mellitus in southern India. Indian Pediatr. 2013;50:759-763.
23. Kota SK, Meher LK, Jammula S, Kota SK, Modi KD. Clinical profile of coexisting conditions in type 1 diabetes mellitus patients. Diabetes Metab Syndr 2012;6:70-76.
24. Sahay BK, Sahay RK. Type 2 diabetes in the young. Int J Diab Dev Countries 2003;23:51-54.
25. Abraham A, Geevarghese PJ. Young-onset diabetes in central Kerala—A preliminary report. Int J Diab Dev Countries 1990;10:17-20.
26. Bhadada SK, Kochhar R, Bhansali A, Dutta U, Kumar PR, Poornachandra KS, Vaiphei K, Nain CK, Singh K. Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India. J Gastroenterol Hepatol 2011;26:378-381.
27. Unnikrishnan AG, Bhatia E, Bhatia V, Bhadada SK, Sahay RK, Kannan A, Kumaravel V, Sarma D, Ganapathy B, Thomas N, et al. Type 1 diabetes type 2 Diabetes with onset in persons younger than 20 years of age results from an Indian multicenter study. Ann N Y Acad Sci 2008;1150:239-244.
28. Bhatia V, Arya V, Dabadghao P, Balasubramanian K, Sharma K, Verghese N, Bhatia E. Etiology and outcome of childhood and adolescent diabetes mellitus in North India. J Pediatr Endocrinol Metab 2004;17:993-999.
29. Balasubramanian K, Dabadghao P, Bhatia V, Colman PG, Gellert SA, Bharadwaj U, Agrawal S, Shah N, Bhatia E. High frequency of type 1B (idiopathic) diabetes in North Indian children with recent-onset diabetes. Diabetes Care 2003; 26:2697.
30. Singh AK, Bhatia E, Dabadghao P, Bhatia V, Gellert SA, Colman PG. Role of islet autoimmunity in the aetiology of different clinical subtypes of diabetes mellitus in young North Indians. Diabet Med 2000;17:275-280.
31. Samal KC, Tripathy BB, Das S. Profile of childhood-onset diabetes in Orissa. Int J Diab Dev Countries 1990,10:27-34.

32. Mazumder R, Sarkar D, Chowdhury BR, Chowdhury UR, Chowdhury S. Clinical assessment of obesity and insulin resistance in type 1 diabetes subjects seen at a center in Kolkata. J Assoc Physicians India 2009;57:511-514.
33. Kumar P, Krishna P, Reddy SC, Gurappa M, Aravind SR, Munichoodappa C. Incidence of type 1 diabetes mellitus and associated complications among children and young adults: results from Karnataka Diabetes Registry 1995-2008. J Indian Med Assoc 2008;106:708-711.
34. Zargar AH, Bhat MH, Laway BA, Masoodi SR. Clinical and aetiological profile of early onset diabetes mellitus: data from a tertiary care centre in the Indian subcontinent. J Postgrad Med 2001;47:27.
35. Pociot F, McDermott MF. Genetics of type 1 diabetes mellitus. Genes Immun 2002;3:235-249.
36. Hyttinen V, Kaprio J, Kinnunen L, Koskenvuo M, Tuomilehto J. Genetic liability of type 1 diabetes and the onset age among 22, 650 young Finnish twin pairs: a nationwide follow-up study. Diabetes 2003;52:1052.e5.
37. Nerup J, Platz P, Andersen OO, Christy M, Lyngsoe J, Poulsen JE, et al. HL-A antigens and diabetes mellitus. Lancet. 1974;2:864-866.
38. Pociot F, Akolkar B, Concannon P, Erlich HA, Julier C, Morahan G, et al. Genetics of type 1 diabetes: what's next? Diabetes 2010;59:1561-1571.
39. Polychronakos C, Li Q. Understanding type 1 diabetes through genetics: advances and prospects. Nat Rev Genet 2011;12: 781-792.
40. Radha V, Vimaleswaran KS, Deepa R, Mohan V. The genetics of diabetes mellitus. Indian J Med Res 2003;117:225-238.
41. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med 2009;360:1646-1654.
42. Barrett JC, Clayton DG, Concannon P, et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet 2009;41:703-707.
43. Cooper JD, Howson JM, Smyth D, et al. Confirmation of novel type 1 diabetes risk loci in families. Diabetologia 2012;55: 996-1000.
44. Acharjee S, Ghosh B, Al-Dhubiab BE, Nair AB. Understanding type 1 diabetes: etiology and models. Can J Diabetes. 2013;37:269-276.
45. Varela-Calvino R, Sgarbi G, Arif S, et al. T-cell reactivity to the P2C non-structural protein of a diabetogenic strain of coxsackievirus B4. Virology 2000;274:56-64.
46. Buschard K. What causes type 1 diabetes? Lessons from animal models. APMIS Suppl 2011;132:1-19.
47. Borch-Johnsen K, Joner G, Mandrup-Poulsen T, Christy M, Zachau-Christiansen B, Kastrup K, et al. Relation betweenbreast-feeding and incidence rates of insulin-dependent diabetes mellitus. A hypothesis. Lancet 1984;2:1083-1086.
48. Pereira PF, Alfenas RD, Araújo RM. Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. J Pediatr (Rio J) 2013 Oct 16. [Epub ahead of print]
49. Kamal Alanani NM, Alsulaimani AA. Epidemiological pattern of newly diagnosed children with type 1 diabetes mellitus, taif, Saudi Arabia. Scientific World Journal 2013;421569:9.
50. Helgason T, Jonasson MR.Evidence for a food additive as a cause of ketosis-prone diabetes. Lancet 1981;2:716-720.
51. Dahlquist GG, Blom LG, Persson LA, Sandstrom AI, Wall SG. Dietary factors and the risk of developing insulin dependent diabetes in childhood. BMJ 1990;19:1302-1306.
52. Kostraba JN, Dorman JS, LaPorte RE, Scott FW, Steenkiste AR, Gloninger M, Drash AL. Early infant diet and risk of IDDM in blacks and whites. A matched case-control study. Diabetes Care 1992;15:626-631.
53. Heding LG. Radioimmunological determination of human C-peptide in serum. Diabetologia 1975;11:541-548.
54. Ludvigsson J, Heding LG. C-peptide in children with juvenile diabetes. A preliminary report. Diabetologia 1976;12:627-630.
55. Ludvigsson J. Immune intervention at diagnosis-should we treat children to preserve beta-cell function? Pediatr Diabetes 2007;8: 34-39.
56. Soltesz G, Patterson CC, Dahlquist G, EURODIAB Study Group. Worldwide childhood type 1 diabetes incidence—what can we learn from epidemiology? Pediatr Diabetes 2007;8: 6-14.
57. Katz LE, Jawad AF, Ganesh J, Abraham M, Murphy K, Lipman TH. Fasting C-peptide and insulin-like growth factor-binding protein-1 levels help to distinguish childhood type 1 and type 2 diabetes at diagnosis. Pediatr Diabetes 2007;8:53-59.
58. Ludvigsson J, Carlsson A, Forsander G, Ivarsson S, Kockum I, Lernmark A, Lindblad B, Marcus C, Samuelsson U.C-peptide in the classification of diabetes in children and adolescents. Pediatric Diabetes 2012;13:45-50.
59. Wenzlau JM, Hutton JC. Novel diabetes autoantibodies and prediction of type 1 diabetes. Curr Diab Rep 2013;13:608-615.
60. Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. N Engl J Med 1986;314:1360-1368.
61. Marwaha RK, Garg MK, Tandon N, Kanwar R, Narang A, Sastry A, Saberwal A, Bhadra K. Glutamic acid decarboxylase (anti-GAD) and tissue transglutaminase (anti-TTG) antibodies in patients with thyroid autoimmunity. Indian J Med Res 2013;137:82-86.
62. Oling V, Marttila J, Ilonen J, Kwok WW, Nepom G, Knip M, et al. GAD65- and proinsulin-specific CD4+ T-cells detected by MHC class II tetramers in peripheral blood of type 1 diabetes patients and at-risk subjects. J Autoimmun 2005;25:235-243.
63. Kelemen K, Gottlieb PA, Putnam AL, Davidson HW,Wegmann DR, Hutton JC: HLA-DQ8-associated T cell responses to the diabetes autoantigen phogrin (IA-2 beta) in human prediabetes. J. Immunol 2004;172:3955-3962.
64. Pietropaolo M, Towns R, Eisenbarth GS. Humoral autoimmunity in type 1 diabetes: prediction, significance, and detection of distinct disease subtypes. Cold Spring Harb Perspect Med 2012.
65. Bangstad HJ, Danne T, Deeb L, Jarsoz-Chobot P, Urakami T, Hanas R. Insulin treatent in children and adolescents with diabets. Pediator Diabetes. 2009 Sep; 10 Suppl 12:82-99.
66. The Leeds Insulin pump workbook for children and young people, Yorkshire, UK. First Edition 2012:16.
67. Kaufman FR, Halvorson M, Miller D, Mackenzie M, Fisher LK, Pitukcheewanont P. Insulin pump therapy in type 1 pediatric patients: now and into the year 2000. Diabetes Metab Res Rev 1999;15:338-352.
68. Kesavadev J, Das AK, Unnikrishnan R 1st, Joshi SR, Ramachandran A, Shamsudeen J, Krishnan G, Jothydev S, Mohan V. Use of insulin pumps in India: suggested guidelines based on experience and cultural differences. Diabetes Technol Ther 2010;12:823-831.
69. Pinkney JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA. Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. Diabetologia 1994 ;37:70-74.

70. Moulik NR, Jayashree M, Singhi S, Bhalla AK, Attri S. Nutritional status and complications in children with diabetic ketoacidosis. Pediatr Crit Care Med 2012;13:e227-233.
71. Kanwal SK, Bando A, Kumar V. Clinical profile of diabetic ketoacidosis in Indian children. Indian J Pediatr 2012;79: 901-904.
72. Sivanandan S, Sinha A, Jain V, Lodha R. Management of diabetic ketoacidosis. Indian J Pediatr 2011;78:576-584.
73. Ganesh R, Arvindkumar R, Vasanthi T. Clinical profile and outcome of diabetic ketoacidosis in children. Natl Med J India. 2009;22:18-19.
74. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005;146:693-700.
75. Maahs DM, Snively BM, Bell RA, Dolan L, Hirsch I, Imperatore G, Linder B, Marcovina SM, Mayer-Davis EJ, Pettitt DJ, et al. Higher prevalence of elevated albumin excretion in youth with type 2 than type 1 diabetes: the SEARCH for diabetes in youth study. Diabetes Care 2007;30:2593-2598.
76. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, Twigg SM, Yue DK, Wong J. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013;36:3863-3869.
77. Sharma K, Khosla PK, Tiwari HK, Sharma RK, Bajaj JS. Anti-insulin antibodies and retinopathy in juvenile onset type-1 diabetes. Indian J Ophthalmol 1991;39:174-175.

ABOUT THE AUTHORS

Anandakumar Amutha

Research Associate, Department of Epidemiology, Madras Diabetes Research Foundation, Chennai, Tamil Nadu, India

Kalpana Thai

Consultant Pediatric Diabetologist, Department of Diabetology Dr Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India

Mohan Viswanathan

Chairman and Chief Diabetologist, Department of Diabetology Dr Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India

Correspondence Address: No. 613 Conran Smith Road Gopalapuram, Chennai, Tamil Nadu, India, Phone: +91-4443968888 e-mail: drmohans@diabetes.ind.in