Indian J Med Res 144, November 2016, pp 641-644
DOI: 10.4103/ijmr.IJMR_1768_16

Quick Response Code:

# Editorial

## Childhood diabetes mellitus: Advances & challenges

Diabetes mellitus is a common chronic disease in children. Type 1A and type 2 are the two major types of diabetes mellitus (T1DM and T2DM) which account for >95 per cent of cases of diabetes in children. T1DM results from immune-mediated destruction of pancreatic β-cells progressing to absolute insulin deficiency and constitutes the majority of cases of diabetes in children[1]. The incidence of T1DM varies widely with age-adjusted incidences ranging from low of 0.1/100,000 per year in China and Venezuela to as high as 40/100,000 per year in Sardinia and 60/100,000 in Finland[1]. The incidence of T1DM worldwide has been increasing by approximately 2-3 per cent per year for the past few decades. This increase is likely to be multifactorial in origin including higher rates of accurate and complete ascertainment of new cases. Unknown environmental causes must also play a role since genetic alterations in the population cannot explain such secular trends[1]. In India, there are approximately 90,000 children with T1DM[2]. However, these estimates are based on studies in the 1990s restricted to certain regions in India. The Indian Council of Medical Research, New Delhi, India, established the Registry of People with Diabetes with Young Age at Onset (YDR) in 2006[3]. This is an observational, multicentre, clinic-based registry of physician-diagnosed diabetes in individuals below 25 yr of age. The major objectives of YDR are to generate information on the epidemiology of youth-onset diabetes within India.

T2DM, a metabolic disease with insulin resistance as the initial hallmark, commonly associated with obesity, is increasing in prevalence in parallel with the worldwide childhood obesity epidemic[4]. This is especially important in developing countries, which have witnessed a dramatic increase in childhood obesity. The number of at-risk obese children with diabetes lends credence to the current estimates that by 2030, India will have 79-87 million and China will have 42-63 million adults with diabetes[5,6]. These estimates, which arguably are conservative and likely underestimate the problem, highlight the urgency to address the root causes of childhood obesity to blunt this burgeoning epidemic. Additional types of diabetes, such as maturity onset diabetes of the young (MODY), a group of conditions resulting from single-gene defects, account for 2-5 per cent of the diabetes in the population[7]. Neonatal diabetes is an even rarer form of diabetes of childhood with an estimated overall incidence of about 1:100,000 births; its importance lies in the variety of genetic defects in pancreatic organogenesis and insulin synthesis/secretion that have been uncovered and their potential role in more common types of diabetes such as T2DM[8].

T1DM is considered to be a T cell-mediated autoimmune disease resulting in the specific destruction of insulin-producing pancreatic β-cells[1]. A triggering event, likely to be environmental, initiates recruitment of antigen-presenting cells and generation of autoreactive T-cells. These self-reactive T-cells migrate to pancreatic islets to mediate β-cell destruction at a variable but predictable rate through distinct identifiable stages prior to the onset of symptoms[9]. More recent work focused on the study of the pancreatic islet, the site of the β-cell destruction, has offered new insights into the pathogenesis of T1DM. These studies have been made possible largely through the efforts of the National Institutes of Health Integrated Islet Distribution Program, Belgian Beta Cell Bank and the JDRF Network for Pancreatic Organ Donors with Diabetes (JDRF nPOD) programme[10]. These studies suggest that, whereas the classical model may be operative in most cases of T1DM, there are likely to be subtypes of T1DM with different pathogenesis or modifiers[1,11]. Hence, studies indicate that in certain

This editorial is published on the occasion of World Diabetes Day – November 14, 2016.

individuals, the destruction of β-cells is patchy, suggesting a role for additional factors conferring resistance to this autoimmune-mediated destruction in certain β-cells[10]. This finding also correlates with other studies demonstrating the presence of circulating C-peptide, and by inference functioning β-cells, in individuals with long-standing disease[12]. In addition, age plays a significant role with infants and toddlers, exhibiting a more rapid and vigorous β-cell destructive process [1].

The last couple of decades have witnessed significant advances in the management of T1DM. Insulin analogues with ultra-short action (lispro, aspart, fast-acting insulin aspart, and glulisine), long-acting action (glargine, detemir) and the recently introduced ultra-long action (degludec) insulin have allowed for basal-bolus insulin regimens to become the standard of care in children[13]. Basal-bolus regimens can be implemented with injections (syringes or pens) or with insulin pumps. Injection regimens are based on the administration of mealtime (bolus) ultra-short-acting insulin and a once or twice a day (basal) long-acting insulin. Continuous subcutaneous insulin infusion (CSII) therapy is a basal-bolus regimen which uses the insulin pump to administer ultra-short-acting insulin for both mealtime and basal insulin[13]. First introduced in clinical practice in the early 1980s, CSII has become ubiquitous in developed countries with the newer insulin pump models being less intrusive, more user-friendly and offering more flexibility. Self-monitoring of blood glucose (SMBG) using home glucose meters is now the recommended modality for day-to-day monitoring of insulin therapy. Newer meters requiring smaller blood volumes (as low as 0.3 µl), faster results (in seconds) and better accuracy (within 15-20% of reference value) have facilitated the widespread adoption of SMBG in the developed countries. The continuous glucose monitor (CGM), which allows for automated measurement of glucose for every five minutes through an indwelling subcutaneous self-inserted sensor, has resulted in the ability to profile blood sugar levels in real time throughout the day[13]. CGM allows patients to aim for better glycaemic control while decreasing daily blood sugar fluctuations and minimizing the risk of hypoglycaemia. This technology has also been the key to the development of closed-loop mechanical artificial pancreas systems that are being commercially introduced. These systems couple CGM with an insulin pump to allow for automated delivery of insulin with minimal involvement of the patient (*e.g.*, with mealtime announcements of carbohydrate intake). One such system (Medtronic's MiniMed 670G, USA) has been approved by the US Food and Drug Administration for routine clinical use and not just for research[14]. The major impediment to the widespread adoption of these technologies which have been proven to empower patients to achieve meaningful improvement in glycaemic control, is the high cost of these devices. Low cost alternatives need to be developed, especially in the developing countries.

Other experimental therapies being studied include implantation of cells with the ability to secrete insulin in a glucose-responsive manner encapsulated within a protective barrier that shields the cells from the autoimmune process. The implanted cells could be human β-cells derived from stem cells or genetically modified cells such as liver cells (*e.g.*, Melligen cells)[15]. Another strategy being pursued is the development of smart insulin with the ultimate goal of a fully synthetic abiotic pancreas[16]. Efforts in this area include insulin embedded in materials containing glucose oxidase enzyme that results in the release of insulin in response to a drop in pH from the enzymatic conversion of glucose to gluconic acid by the glucose oxidase enzyme. An alternate strategy being explored is to use natural glucose-binding proteins, such as lectins (ConA) polymer, in conjunction with glycosylated insulin, with glucose competing for binding to ConA and thus resulting in glucose-driven equilibrium-releasing insulin from the polymer. The ultimate goal is to develop an insulin regimen that accurately mimics the physiology of insulin release and action - the right type (kinetics) of insulin administered at the right time (preprandial) in the right amount (commensurate with prevailing blood glucose levels) and in the right location (portal circulation). The American Diabetes Association's current glycaemic target for children and adolescents with T1DM is an $HbA_{1c}$ concentration of <7.5 per cent, a target also recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD)[17]. The hope is that with newer advances, it will be possible in future to safely achieve a metabolic and glycaemic profile, indistinguishable from that in the non-diabetic population.

Unlike T1DM for which insulin therapy is essential, T2DM is characterized by insulin resistance and a relative insulin deficiency and hence is amenable to treatment with oral medications that increase sensitivity of tissues to insulin (metformin, thiazolidinediones) or enhance insulin secretion from pancreatic β-cells (*e.g.,* sulphonylureas) or combination

drugs that include both actions. Two drug classes have been developed that target the incretin system: glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 receptor agonists (*e.g*., liraglutide and exenatide) resist degradation by DPP-4 resulting in increased circulating levels of the administered drug[18]. DDP-4 inhibitors (*e.g*., sitagliptin, vildagliptin and saxagliptin) reduce endogenous GLP-1 degradation, thereby maintaining circulating levels of GLP-1 with biological effect. Both these classes of drugs improve glycaemic control with a low incidence of hypoglycaemia because of their glucose-dependent mechanism of action. A new class of oral agents recently introduced are the sodium-glucose co-transporter 2 (SGLT2) inhibitors[19]. SGLT2 is a protein that facilitates glucose reabsorption in the kidney. SGLT2 inhibitors block the reabsorption of glucose in the kidney, increase glucose excretion and lower blood glucose levels. Studies in adults reveal that in conjunction with exercise and a healthy diet, these drugs can improve glycaemic control. Their role in the management of T2DM in children has yet to be established[20]. The current recommendations advise against using these agents in T1DM in children.

The presumed immune aetiology of T1DM is the basis for strategies to prevent T1DM[21]. Primary prevention, defined as actions taken prior to the onset of β-cell-specific autoimmune processes, targets putative environmental stimuli such as cow's milk. Secondary preventions seek to stop the ongoing autoimmune destruction of β-cells so that these strategies target the immune process *per se*. A prerequisite for the implementation of these prevention strategies is accurate and timely identification of children at risk for developing T1DM. Current protocols using a combination of testing for a cadre of circulating autoantibodies and genotyping at the human leucocyte antigen loci are able to accurately stratify the risk for developing T1DM in high-risk populations (first-degree relatives of patients with known disease). However, despite strategies to target candidate environmental triggers such as avoidance of cow's milk or the administration of agents such as niacin, glutamic acid decarboxylase, insulin, anti-CD3 monoclonal antibody (teplizumab), anti-CD20 monoclonal antibody (rituximab) or co-stimulation blocker (abatacept), it has not yet been possible to achieve protection against the development of T1DM or clinically relevant and sustained improvement in β-cell function in children with ongoing β-cell destruction and dysfunction.

In summary, both T1DM and T2DM are now considered diseases initiated by environmental factors in a genetically susceptible host. For T1DM, the environmental trigger(s) is not known, but the sequence of progression leads to marked insulin deficiency which must be replaced. Despite technologies for monitoring glucose in real time, an expanded array of modified insulin preparations and delivery systems such as pumps, including those simulating a closed-loop 'artificial pancreas', control of blood glucose remains imperfect, in part because normal insulin secretion occurs into the portal vein, whereas subcutaneous insulin delivery initially passes through the systemic circulation. For T2DM, the environmental triggers appear to be obesity, the worldwide epidemic of modern living, leading to insulin resistance and unmasking of genetic or acquired defects in the complex machinery of normal insulin secretion which lead to relative insulin deficiency inadequate to overcome the degree of resistance, but which respond to various oral agents. Some of these genetic defects cause autosomal dominant monogenic forms of diabetes and neonatal diabetes syndromes, which account for only 2-3 per cent of childhood forms, but are important to identify for correct management and genetic counselling and for their contribution to develop T2DM when insulin sensitivity declines. These considerations are at the forefront of current research for understanding that may lead to a cure. The 'cure' for T1DM is still far off; the 'cure' for T2DM can be envisioned.

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Received November 1, 2016

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