

Childhood diabetes mellitus: Recent advances & future prospects

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Diabetes mellitus (DM) is a metabolic disease characterized by absolute or relative insulin deficiency. Absolute deficiency of insulin most commonly results from an autoimmune destruction of insulin producing cells in the pancreas and in general, the term Type 1 DM (T1DM) is used to denote childhood diabetes associated with autoimmunity and absolute insulin deficiency. The term Type 2 DM (T2DM) is used to denote diabetes resulting from a relative deficiency of insulin when insulin secretion is inadequate to overcome co-existent resistance to insulin action on carbohydrate, protein or fat metabolism; T2DM is most commonly associated with the prototypic insulin resistant state of obesity. In the western hemisphere DM is one of the most prevalent chronic diseases in childhood, whereas the incidence of T1DM in developing countries is significantly less than that in the western hemisphere. Epidemiological studies indicate that there is gradual but steady increase in the incidence of both T1DM and T2DM in both developed and developing countries. This review provides an overview of the major advances in our understanding of the aetiology, pathogenesis, and clinical management of DM in children with the focus being on T1DM. Genetic predisposition, environmental causes, and emerging concepts of the pathogenesis of T1DM such as the accelerator hypothesis are discussed. The goals of treating a child with DM are to achieve normal growth and development with prevention of acute and chronic complications of DM. These goals are achieved by co-ordinated care delivered by a multidisciplinary team focusing on insulin administrations, glucose monitoring, meal planning, and screening for complications. Newer insulin analogues ("designer" insulin) and automated methods of delivery via programmable pumps have revolutionized the care of the child with diabetes. Though T1DM cannot yet be prevented, ongoing trials and strategies aimed at modulating the autoimmune response and the burgeoning science of embryonic stem cell biology, and isolating and propagating islet cell progenitor cells are discussed in this review.

Key words Childhood diabetes - glucose monitoring - insulin therapy - MODY

Diabetes mellitus (DM) is a metabolic disease characterized by absolute insulin deficiency, or relative insulin deficiency when insulin secretion is inadequate to overcome co-existent resistance to insulin action on carbohydrate, protein or fat metabolism. Absolute deficiency of insulin can occur in a number of different ways: by an autoimmune destruction of insulin producing cells in the pancreas (Type 1A); by destruction without clear evidence of autoimmunity (Type 1B); by genetic defects that prevent regulated insulin secretion (mitochondrial gene defects, genetic defects in the K_{ATP} channels and their regulatory sub-units); surgical removal; vascular infarcts; crush injuries, *etc.* Some of these genetic defects are milder and may not manifest as limited insulin secretion until there is concomitant resistance to insulin action induced by obesity, pregnancy (gestational diabetes) or other factors. In general, the term Type 1 DM (T1DM) is used to denote childhood diabetes usually associated with autoimmunity and absolute insulin deficiency, even though the deficiency need not be absolute at the clinical outset of the disease. Likewise, the term Type 2 DM (T2DM) is used to denote childhood diabetes associated with obesity and insulin resistance. The term MODY, so-called maturity onset diabetes of youth, is a "milder" form of diabetes caused by specific gene defects that impair insulin secretion. In the western hemisphere DM is one of the most common chronic diseases in childhood. Whereas the incidence of T1DM in developing countries is significantly less than that in the western hemisphere, epidemiological studies indicate that there is gradual but steady increase in the incidence of both T1DM and T2DM in both developed and developing countries. This review provides an overview of the major advances in our understanding of the aetiology, pathogenesis, and clinical management of DM in children with the focus being on T1DM.

Aetiology

Diagnosis and classification: The American Diabetes Association's (ADA) criteria for the

diagnosis of DM were recently revised to include a new threshold for the diagnosis of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). The diagnosis of DM is made on the basis of one of the following criteria¹: (i) Symptoms of hyperglycaemia including polyuria, polydipsia, weight loss plus random plasma glucose concentration >200 mg/dl (11mM). (ii) Fasting (> 8 h fast) plasma glucose > 126 mg/dl (7 mM). (iii) 2 h post prandial glucose >200 mg/dl during an oral glucose tolerance test (OGTT).

Criteria for diagnosing IGT and IFG are a 2 h plasma glucose between 140-200 mg/dl or a fasting glucose between 100-125 mg/dl respectively¹⁻³.

The ADA classification of DM encompasses 4 groups: Type 1, Type 2, other specific types of diabetes, and gestational diabetes. Type 1 DM is further subclassified into Type 1A which is associated with the presence of islet cell autoantibodies, and Type 1B characterized by the absence of such antibodies^{4,5}. Advances in our understanding of the physiology, and molecular and cellular basis for insulin secretion and action have prompted the continued evolution of alternate classifications based on the interaction of β -cell function and insulin resistance⁶:

(i) Diabetes with predominantly insulin deficiency including T1DM, neonatal diabetes, maturity onset diabetes of the young, and mitochondrial diabetes.

(ii) Diabetes and other syndromes with predominantly insulin resistance *e.g.*, leprechaunism, lipotrophic diabetes, and other entities where the resistance cannot usually be overcome by even supra-physiological insulin concentrations. Hence the defect is the inability to perceive the insulin signal (a receptor defect *e.g.*, leprechaunism) or to transduce the insulin signal (a post-receptor defect).

(iii) Diabetes resulting from combined insulin deficiency and insulin resistance: T2DM. In normal

physiology, the product of insulin secretion and insulin sensitivity is a constant, such that insulin resistance is compensated by increased insulin secretion and vice versa. Clinical diabetes only occurs when the product cannot be maintained within normal limits, usually because insulin secretion is inadequate to compensate for the prevailing degree of resistance to insulin action.

T1DM accounts for the majority of cases of diabetes in children. However, in parallel with the increasing incidence of childhood obesity worldwide, the incidence of T2DM is also increasing. Table I summarizes the clinical characteristics that differentiate the various types of diabetes in children⁷. Children with T1DM usually present with a several-week history of classic symptoms of polyuria, polydipsia, and polyphagia and weight loss. Since polyuria may masquerade as occurrence of bed wetting in a child previously toilet trained, a history of polyuria may need to be carefully elicited even if the parent denies on direct questioning the presence of increased

urination during waking hours. Vague lethargy is a common complaint. However, some patients may present without these classic symptoms because of early detection by a family member who has diabetes mellitus and recognizes the symptoms; a high index of suspicion with measurement of glucose in urine and blood can rapidly establish (or refute) the diagnosis. In a lean child presenting with diabetes, the diagnosis of T1DM is presumed unless otherwise proven. In an obese child, differentiating between T1DM and T2DM is essential for rational management. Features such as significant obesity, presence of acanthosis nigricans, negative islet cell autoantibodies or elevated circulating concentrations of C-peptide are in favour of the diagnosis of T2DM. Clinical features including minimal to modest insulin requirement outside the honeymoon period, absence of ketonuria during intercurrent illnesses, a strong family history of non-T1DM, abnormalities of kidneys, eyes, conduction defects in the heart or hearing impairment should prompt the consideration of other types (non-T1DM) of diabetes⁸.

Table I. Characteristics of type 1 and type 2 diabetes in children and adolescents

Characteristic	Type 1	Type 2	MODY
Age at onset	Throughout childhood	Pubertal	Pubertal
Gender	Female = Male	Female > Male	Female = Male
Ethnicity	All (low incidence in Asians)	Native American, African American, Hispanic	Caucasian
Onset	Acute severe; DKA common	Insidious; ketosis less common	Gradual
Obesity	As in population	Common	Uncommon
Acanthosis nigricans	Absent	Present	Absent
Insulin secretion	Decreased/absent	Variable	Variably decreased
Insulin sensitivity	Normal	Decreased	Normal
Insulin dependency	Permanent	Episodic	Infrequent
Pancreatic autoantibodies	70-80% ICA positive 85-98% GAD positive	ICA negative GAD positivity \pm	ICA negative GAD negative
Family history	5-15%	75-90%	100%
Mode of inheritance	Nonmendelian, sporadic	Nonmendelian, familial	Autosomal dominant

MODY, maturity onset diabetes of the young; ICA, islet cell antibody; GAD, glutamic acid decarboxylase; DKA, diabetic ketoacidosis

Source: Ref. 7

Tables II and III summarize syndromes with predominant insulin deficiency and insulin resistance respectively.

Pathogenesis

Type 1 diabetes mellitus: T1DM results from the interaction of genetic and environmental factors that alter the immune system and culminate in destruction of the pancreatic β cell. The 30 to 50 per cent concordance rate in monozygotic twin reflects the role of genetic factors in the aetiology of T1DM^{9,10}. The 50 to 70 per cent discordance in rate of diabetes in identical twins, indicates the significant contribution of environmental factors that must be triggering this disease and about which we seem to know so little. Association studies exploiting unbiased genome-wide analyses have identified a defined number of loci (*IDDM1-18*) that are linked to the causation of T1DM. The most significant susceptibility locus (*IDDM1* locus) is in the HLA class II gene located at 6p21.3. *IDDM1* contributes about 50 per cent of the inherited risk for T1DM. The *HLA-DR* and *HLA-DQ* loci in the class II region have the strongest influence on T1DM risk. *DR3/DR4*, *DR4* homozygosity, *DR3* homozygosity, *DQA1*0301*, *DQB1*0302* (DQ8), *DQA1*0501*, and

*DQB1*0201* (DQ2) haploypes confer a high risk for T1DM with the DR3-DQ2/DR4-DQ8 heterozygous state being associated with the highest genetic risk for T1DM. In contrast, the *DQA1*0102*, *DQB1*0602*, *DRB1*1501* haplotype confers dominant protection from T1DM. Since HLA class II molecules participate in antigen presentation, the mechanism of HLA-influenced susceptibility in T1DM is believed to involve antigen presentation to CD4⁺ cell, thymic selection, and immune responsiveness¹⁰⁻¹³.

Non-HLA loci also play a role in the genetic susceptibility to T1DM. *IDDM2* (*INS-VNTR*, variable number of tandem repeats) located in the insulin gene promoter on chromosome 11p15.5 consists of tandem repeat. Two classes of *INS VNTR* are observed in Caucasians, the short class "I" (26-63 repeats) and the long class "III" (141-209 repeats), while Class II alleles are rare. The Class III allele is associated with higher transcriptional activity of the insulin gene in vitro and it is hypothesized that increased expression of the insulin gene in the thymus results in enhanced negative selection of insulin-specific reactive T cells¹². In contrast, the Class I *VNTR* allele is associated with reduced levels of insulin expression resulting in a less efficient

Table II. Presentation of specific types of diabetes with predominantly insulin deficiency

Disorder related to diabetes	Presentation	Gene/locus	Mode of inheritance
Wolcott-Rallison syndrome	Epiphyseal dysplasia, demineralization of bone, renal impairment, Acute hepatic failure, developmental delay	EIF2AK3/ 2p12	AR
Wolfram syndrome	Progressive optic atrophy, sensorineural deafness DI, truncal ataxia	WFS1/ 4p16.1	AR
TRMA/Roger's syndrome	Thiamine responsive megaloblastic anemia, sensorineural deafness	SLC19A2/ 1q23.3	AR
Mitochondrial mutation	Deafness, myopathy, neurological deficit	Leu-UUR mitochondrial tRNA	Maternal inheritance

TRMA, thiamine responsive megaloblastic anaemia; DI, diabetes insipidus; AR, autosomal recessive

selection of insulin-specific autoreactive T cells. Association studies have demonstrated that Class I allele predisposes to and Class III allele protects against T1DM (Table IV)¹⁴. Recent studies have also demonstrated an association between T1DM and *CTLA4* (cytotoxic T lymphocyte-associated 4, *IDDM12*) located within the 2q31-q33 region. The A6230G single nucleotide polymorphism in the 3' flanking region of *CTLA4* exhibits the strongest association with T1DM¹⁵. *SUMO4* located in the *IDDM5* locus on chromosome 6q25 is believed to play a role in pathogenesis of T1DM via its role in apoptosis of pancreatic β cells¹⁶. Other loci contribute minor effects on the risk of T1DM and include genes such as *VDR* and *PTPN22*. Active vitamin D, $1\alpha,25(\text{OH})_2\text{D}_3$ has immunomodulatory property and can induce cytokine secretion. The *VDR* gene is located on chromosome 12q12-14 and *VDR* polymorphism has been linked to increased risk of developing T1DM¹⁷⁻¹⁹. *PTPN22* is an inhibitor of T cell activation and the 1858T allele is associated with increased susceptibility to develop T1DM²⁰. A

comprehensive list of loci IDDM susceptibility has been recently tabulated by Concannon *et al*²¹.

The 50 per cent discordance rate for the development of T1DM in identical twins reflects the role of environmental factors and their interactions with the immune system. Environmental factors such as virus, dietary factors, and pollutants are implicated in disease pathogenesis. Several viruses have been identified to be associated with the development of T1DM with the strongest evidence linking the rubella virus. Individuals with congenital rubella have a 20 per cent likelihood to develop T1DM in later life²². Infection with enterovirus, cytomegalovirus, coxsackie virus, parvovirus B19, and rotavirus in susceptible individuals have also been implicated to play a role in the causation of T1DM²²⁻²⁴. The mechanism(s) of virus-induced β cell destruction is not fully understood. In certain instances the virus can infect the β cell and cause a direct cytolysis. A virus also can induce an immune response by molecular mimicry, a mechanism that is implicated

Table III. Presentation of specific types of diabetes with predominantly insulin resistance

Disorder related to diabetes	Type of diabetes presentation	Gene/locus	Mode of inheritance
Alstrom syndrome	Short stature, obesity, retinal degeneration, neurosensory deafness, chronic renal involvement, infantile cardiomyopathies	<i>ALMS1</i> gene/ <i>2P13</i>	AR
Bardet-Biedl syndrome	Retinal dystrophy, obesity, hand abnormalities, male hypogonadism, mental retardation renal abnormalities	9 loci	Variable
Leprechaunism	Low birthweight, characteristic facies, acanthosis nigricans nearly total lack of adipose tissue	<i>INSR</i> / 19q13.2	AR
Rabson-Mendenhall syndrome	Acanthosis nigricans, genitomegaly, pineal gland hyperplasia, abnormalities of skeleton, teeth, nails, growth retardation,	<i>INSR</i> / 19q13.2	Sporadic
Type A insulin resistance	Acanthosis nigricans, glycosuria, PCOS, hyperandrogenism	<i>INSR</i> / 19q13.2	AR
Lipoatrophic diabetes	Loss of adipose tissue, hyperlipidemia, hepatomegaly, Acanthosis nigricans	<i>BSC2L2</i> / 11q13	AR, AD

AR, autosomal recessive; AD, autosomal dominant; PCOS, polycystic ovary syndrome

with coxsackie virus B4 that shares sequence homology with the β cell antigen, glutamic acid decarboxylase (GAD65)^{25,26}. Another hypothesis, the bystander hypothesis, posits that viral infection results in stimulation of non-antigen-specific T cells that then release cytokines such as type 1 interferons. Functionally, there are two primary types of effector T4-lymphocytes based on the cytokines they produce, Th1 cells and Th2 cells. Th1-lymphocytes recognize antigens presented by macrophages and function primarily to activate and heighten cell-mediated immunity by producing cytokines such as interleukin-2 (IL-2), interferon-gamma (IFN- γ), lymphotoxin, and tumour necrosis factor- β (TNF- β). In contrast, Th2 lymphocytes recognize antigens presented by B-lymphocytes. They produce cytokines such as interleukins 2, 4, 5, 10, and 13 that promote antibody production. Viral infection has also been proposed to shift the balance between Th1 and Th2 to favour the diabetogenic Th1 cell type which produces IFN- γ . Consequently, IFN- γ upregulates antigen expression on the surface of the β cell and enhances immunity directed against the islet²⁷. It is noteworthy that several case reports have implicated IFN- α treatment as a precipitating factor for the development of autoimmune diseases including T1DM²⁸. The role of noninfectious environmental factors such as exposure to cow milk, breast feeding, soy or wheat product intake, vitamin D intake, and environmental toxins (*e.g.*, nitrite derivatives) in the

pathogenesis of T1DM are the focus of various studies^{29,30}.

Autoimmunity specific to β cells leads to insulinitis and β cell destruction in susceptible individuals. Autoimmunity directed at the β cell involves both cellular and humoral immunity. Islet cell autoantibodies can be detected in 70-80 per cent of patients with newly diagnosed T1DM⁹. These antibodies include islet cell antibody (ICA), glutamic acid decarboxylase antibody (GAD65A), insulin autoantibody (IAA), and protein tyrosine phosphatase antibody (IA-2AA). Prospective studies have established that the appearance of these autoantibodies in the circulation presages by months to years the onset of clinical T1DM. The presence and persistence of autoantibodies at younger age together with the high-risk HLA haplotype increases the possibility of progression to overt diabetes³¹. These antibodies are markers for the presence of the autoimmune process and do not necessarily play a causal role in the destruction of the β cell. The current model for the pathogenesis of β cell destruction in T1DM is that in the early stages of the disease process, in association with MHC class II molecule, pancreatic β cell antigens are presented to CD4⁺ T cell by antigen presenting cells (APC). These APC secrete IL-12 which promote CD4⁺ T cells to secrete IFN- γ and IL-2. The secreted IFN- γ subsequently

Table IV. T1DM susceptibility loci

Locus	Chromosome	Marker	Function
<i>IDDM1</i>	6p21.31-21.32	HLA DR/DQ	Antigen presentation and control of immune responsiveness to islet cell antigens
<i>IDDM2</i>	11p15.5	5'-INS-VNTR	Increased insulin expression in thymus and more efficient negative selection of insulin-reactive T cells
<i>IDDM5</i>	6q25	SUMO4	Nuclear factor (NF)-kappa B regulation, role in apoptosis of pancreatic β cells
<i>IDDM12</i>	2q33.2-33.3	CTLA-4	Negative regulator of T cell activation

Source: Ref. 14

stimulates macrophage or CD8⁺ T cell to release free radical and cytokines such as TNF- α and IL-1 β , resulting in β cell apoptosis³².

The accelerator hypothesis postulates that Type 1 and Type 2 diabetes are actually a single disease distinguished by the rate of β cell destruction and the “accelerator response”. The accelerators have been classified into intrinsic (rate of β cell apoptosis) and acquired (insulin resistance and β cell autoimmunity). This hypothesis posits that a constitutionally high rate of β cell apoptosis is necessary but not sufficient to develop overt diabetes mellitus. Diabetes mellitus results from the interplay of β cell apoptosis and insulin resistance, the first and second accelerator, respectively³³. This theory hypothesizes that insulin resistance associated with obesity will further enhance the rate of β cell apoptosis and by concomitantly increasing the demand on the β cell to make more insulin, obesity will facilitate the development of overt β cell failure and clinical DM. The evidence supporting this hypothesis is the observation that a higher BMI is associated with a younger age of onset of T1DM³⁴⁻³⁶.

Neonatal diabetes mellitus (NDM)

NDM is a heterogeneous group of disorders characterized by hyperglycaemia in the neonatal period that persists for more than 2 wk³⁷. NDM is categorized into transient (TNDM) and permanent (PNDM) based on the duration of insulin dependency, with each category accounting for approximately 50 per cent of NDM³⁸. Recent studies have yielded new insights into the genetic basis for NDM. PDX-1/IPF-1 (pancreas duodenum homeobox/insulin promoter factor) is critical for pancreatic development and the homozygous mutation of PDX-1/IPF-1 results in pancreatic agenesis and ensuing PNDM. Infants with homozygous inactivating mutation of glucokinase gene present with PNDM. Missense mutation of HNF-1 β associated with PNDM is characterized by the presence of renal abnormalities including renal cyst and polycystic dysplastic kidneys. Mutation of the *FOXP3* (Forkhead Box P3) gene results in IPEX

(Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome characterized by PNDM due to islet hypoplasia, enteropathy, infection, thrombocytopaenia, and anaemia. Mutation of the Eukaryotic translocation-Initiation Factor-2 AlphaKinase 3 (*EIF2AK3*) is associated with the Wolcott-Rallison syndrome characterized by PNDM, multiple epiphyseal or spondyloepiphyseal dysplasia, and renal impairment. The most common cause for PNDM is an activating mutation of the *KCNJ11* gene (which encodes Kir6.2, a sub-unit of the ATP-sensitive potassium channel (K_{ATP}) of the β cell. Approximately 40 per cent of infants with this mutation have developmental delay, epilepsy, and dysmorphic features (DEND syndrome)³⁸⁻⁴⁰. In contrast to the *KCNJ11* gene, a minority of patients with NDM have mutations in the *ABCC8* gene that encodes for the SUR1 (sulphonylurea receptor) protein, the other component of the heterotetrameric K_{ATP} channel^{41,42}. Recent reports described the successful use of sulphonylureas to manage NDM patients with mutant Kir6.2 or SUR1 proteins^{39,43,44}. The majority of TNDM cases are associated with uniparental disomy of chromosome 6 with paternal duplication or a maternal methylation defect of 6q24⁴⁵. Two candidate genes at this locus that could play a role in the pathogenesis of TNDM are the *HYMAI* (Hydatidiform Mole-Associated and Imprinted) gene and the *ZAC* (Zinc finger protein regulating Apoptosis and Cell cycle arrest)/also known as *PLAGL1* (Pleomorphic Adenoma Gene-Like1)³⁸⁻⁴⁰. Mutations and variants of these genes, *e.g.*, mutations in *PDX-1/IPF-1* or glucokinase, variants in Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) have been implicated as a cause of T2DM^{44,46-50}.

Maturity-onset diabetes of the young (MODY)

The term “maturity onset” diabetes of the young is a misnomer, since affected patients do not have maturity onset DM with insulin resistance; rather, they have a specific mutation in one of several genes that regulate pancreas formation and/or the secretion of insulin. For this reason, we retain the term MODY, but designate it as “monogenic” rather than “maturity

Table V. Summary of clinical features of MODY

	MODY1	MODY2	MODY3	MODY4	MODY5	MODY6	MODYX
Genetic locus	20q	7p	12q	13q	17 cen-q21.3	2	Unknown
Gene	<i>HNF-4α</i>	Glucokinase	<i>HNF-1α</i>	<i>IPF-1</i>	<i>HNF-1β</i>	NeuroD1	Unknown
Distribution (% of MODY families)	Rare	8-63%	21-64%	Rare	Unknown	Or Beta2 Rare	Heterogeneous? 16-45%
Primary defect	Pancreas/ Liver	Pancreas/ Liver	Pancreas/ Kidney/other?	Pancreas/ Other?	Pancreas/ Kidney/other?	Pancreas/ Other?	Pancreas/ Heterogeneous?
Associated feature	Reduction in serum concen- tration of triglyceride, apoprotein AII, CII and lipoprotein	Reduced birthweight	Reduced tubular reabsorption of glucose	Other?	Glomerulocystic kidneys disease	-	-
Severity of diabetes	Severe	Mild	Severe	Mild?	Mild? (in female carrier)	Unknown	Mild/ Heterogeneous?
Complication of diabetes	Frequent	Rare	Frequent	Rare?	Rare?	Unknown	Unknown
Treatment	Oral hypogly- caemic agent/ insulin	Diet, exercise	Oral hypogly- caemic agent/ insulin	Oral hypogly- caemic agent/ insulin	Insulin	Insulin	Insulin

onset" diabetes of youth. The diagnosis of MODY should be considered in non obese individuals with three or more consecutively affected generations with DM presenting before 25 yr of age. At present seven types of MODY have been described, each caused by mutation in individual genes expressed in the β cell that regulate transcription of the insulin gene or genes encoding enzymes involved in the transport and metabolism of glucose and other proteins requires for normal β cell function (Table V). The most common types of MODY (MODY 3 and 2) are characterized by mild DM⁵¹⁻⁵⁴. Glucokinase is the rate limiting step in glucose metabolism. A heterozygous inactivating mutation of glucokinase gene leads to reduction of glucokinase activity in β cell, resulting in a decrease in glucose phosphorylation and subsequent decline in glucose-stimulated insulin release (MODY 2). Similarly, a heterozygous inactivating mutation in *PDX-1/IPF1* is the cause of MODY 4⁵⁵. Homozygous inactivating mutations in either glucokinase or *PDX-1/IPF1* manifest as neonatal DM⁵⁶⁻⁵⁸.

Management

The goals of treating a child with DM are to achieve normal growth and development with prevention of acute and chronic complications of DM. These goals are achieved by co-ordinated care delivered by a multidisciplinary team, the core of which includes physicians, nursing personnel, diabetes educators, dieticians, social workers and psychologists. For purposes of discussion, the management of DM can be divided into acute management of diabetic ketoacidosis (DKA) and long term treatment of DM.

Acute management: Diabetic ketoacidosis (DKA): The incidence of DKA at the onset of diabetes varies from 15 to 70 per cent in Europe, Australia, and North America⁵⁹. The criteria for diagnosis of DKA are acidosis (venous blood pH < 7.3 or serum bicarbonate < 15 mmol/l), and ketonaemia with total serum ketones (β -hydroxybutyrate and acetoacetate) > 3 mmol/l; the levels of blood glucose are usually

greater than 300 mg/dl. However, hyperglycaemia is not a sine qua non for the diagnosis of DKA. Thus DKA can occur with blood sugar less than 300 mg/dl or even with near normal blood sugar levels; for example, in patients presenting with vomiting and resulting reduced carbohydrate assimilation, with concomitant administration of inadequate dose of insulin^{60,61}.

Management of DKA: The aim of treatment of DKA is restoration of the fluid and electrolyte balance, correction of acidosis and dissipation of ketonaemia, and avoidance of complications of DKA such as hypokalaemia and cerebral oedema. The ADA, Lawson Wilkins Pediatric Endocrine Society (LWPES), European Society for Pediatric Endocrinology (ESPE) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) have published consensus statements on the principles governing management of DKA in children⁶²⁻⁶⁴. The key points in the DKA treatment protocol include the tonicity and the rate of the parenteral fluid administration, early and adequate replacement of potassium losses to avoid hypokalaemia, avoidance of rapid decline in blood glucose concentration, insulin administered intravenously and inadequate dose, and measures to detect clinically significant rise in intracranial pressure which portends the development of cerebral oedema^{60,61}.

Cerebral oedema: Symptomatic cerebral oedema occurs in approximately 0.7-1 per cent of children with DKA^{60,61}. However, recent studies have revealed that ventricular narrowing, an indicator of cerebral oedema, is present in about 50 per cent of children in DKA with 25 per cent of these patients exhibiting various degrees of mental status abnormalities on detailed examination^{65,66}. Therefore, it is likely that cerebral oedema in DKA is more common than previously reported. Children at greatest risk for cerebral oedema are those who are young, especially less than 5 yr and present with high blood urea nitrogen, profound acidosis, high glucose, and low partial pressure of arterial carbon dioxide, all parameters that could reflect the severity of

disease^{65,67,68}. The mechanism(s) of cerebral oedema is not completely understood. A rapid decrease of serum osmolarity (cytotoxic mechanism) due to change of serum glucose, sodium or ketones may precipitate cerebral oedema⁶⁹. Recent studies exploiting state of the art imaging techniques such as contrast-enhanced diffusion magnetic resonance imaging to characterize cerebral blood flow dynamics reveal cerebral hyperperfusion as a prominent finding in DKA suggesting that vasogenic processes, rather than cytotoxic processes may be the primary mechanism responsible for the development of cerebral edema in DKA^{70,71}. Some characteristics of the treatment protocol, such as bicarbonate therapy, administration of hypotonic solution for rehydration, sluggish rise in serum sodium concentration during rehydration, and insulin administration within the first hour of fluid replacement are associated with a higher incidence of cerebral oedema^{67,68,72}. Whether these associations merely reflect the severity of the DKA in these patients or are independent risk factors of cerebral oedema is not clear at this time. The relative low incidence of this complication dictates that it is unlikely that a single medical center will be able to undertake definitive randomized control trials to answer these questions, emphasizing the need for multi-center prospective studies that specifically address these questions. The early recognition of cerebral oedema is critical for prompt treatment. The diagnosis is made by the presence of neurological compromise in patient with DKA using the diagnostic criteria listed in Table VI with two major criteria or one major plus two minor criteria, in conjunction with neuroradiological evidence of diffuse cerebral oedema or focal lesions including subarachnoid or intraventricular haemorrhage⁷³. Treatment of cerebral oedema is directed toward measures to reduce intracranial tension and includes measures such as mannitol (0.25-1.0 g/kg over 20 min and repeated as necessary), reducing the rate of fluid administration, and instituting hyperventilation therapy. Hypertonic saline also has proved effective in some cases of cerebral oedema^{62,74}. Retrospective studies suggest that these measures, instituted promptly, are lifesaving and may avoid neurological sequelae. Heroic measures

such as cerebral decompression via craniotomy may also be indicated in severe cases. In the past, once clinically obvious, cerebral oedema was associated with a mortality of about 70 per cent with only 7-14 per cent of these patients escaping permanent impairment of neurological function⁶⁰. However, with the institution of newer regimens that emphasize the early detection and management of increased intracerebral pressure, the prognosis for complete neurological recovery has significantly improved⁶².

Long term treatment of T1DM: The aims of long term management of T1DM are to avoid the development of chronic micro- and macro-vascular complications of DM. The landmark Diabetes Control and Complication Trial (DCCT) study and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study⁷⁵ have unequivocally established a strong relationship between the levels of HbA1c and the incidence of chronic microvascular complications of T1DM. It is also significant that these studies did not identify a threshold effect, and thus the lower the HbA1c the lower was the risk of developing chronic microvascular complications of DM. The efforts to decrease HbA1c and even consider normalization of

Table VI. Bedside evaluation of neurological status of children with diabetic ketoacidosis (DKA)

Diagnostic criteria:

Abnormal motor or verbal response to pain Decorticate or decerebrate posture, Cranial nerve palsy (especially III, IV, VI) Abnormal neurogenic respiratory pattern (*e.g.*, grunting, tachypnea, Cheyne-Stokes, apneustic)

Major criteria:

Altered mentation/fluctuating level of consciousness, Sustained heart rate deceleration (decline more than 20 per min) not attributable to improved intravascular volume or sleep state, Age inappropriate incontinence

Minor criteria:

Vomiting following initial treatment and its cessation, if present at admission, Headache (recurrent and more severe than on admission), Lethargy or not easily aroused from sleep Diastolic blood pressure greater than 90 mmHg
Age less than 5 yr old

Source: Ref. 73

HbA1c should be tempered against the risk of development of hypoglycaemia. In children, the risk of hypoglycaemia should be weighed against the benefit from intensive treatment since children are especially vulnerable to the long term detrimental effects of hypoglycaemia on brain growth and development⁷⁶⁻⁷⁸. The suggested targets for plasma blood glucose and HbA1c goal for each age group are presented in Table VII⁷⁹.

Blood glucose monitoring: Because the propensity to develop chronic microvascular complications of diabetes is strongly associated with the level of long term glycaemic control, it underscores the critical importance of maintaining blood sugars as near normal as possible. Efforts to achieve euglycaemia entail the unavoidable risk of hypoglycaemia and thus accurate, reproducible, and facile techniques to conduct home blood glucose monitoring is key to the success of all intensive insulin management regimens. Recent advances in enzymology, chemistry, and bioengineering have enabled real time continuous glucose monitoring using techniques such as subcutaneous enzyme-tipped catheter, reverse iontophoresis, or microdialysis to measure glucose from the subcutaneous interstitial fluid compartment^{80,81}. Other non-invasive methods to monitor blood glucose using optical methods such as spectroscopy, polarimetry, and light scattering are

currently under development⁸⁰. The ultimate goal of continuous glucose monitoring techniques is to develop a closed loop system for insulin delivery in a real world practical setting, thereby mimicking the physiological secretion of insulin by the pancreas⁸².

Advances in insulin therapy:

The singular advance in insulin therapy over the past decade has been the development of insulin analogues. These “designer” insulins, in which the insulin molecule has been modified using recombinant DNA and pharmaceutical chemistry techniques, allow for more predictable time course and dose response than native insulin preparations. The recently introduced inhaled insulin is a different class of insulin analogs that seek to deliver insulin in more convenient manner than the traditional subcutaneous route of administration. The overall aim of developing insulin analogues is to mimic the physiological release of insulin during the post-prandial and post-absorptive periods. The ultra-rapidly acting analogues were developed by altering the amino acid sequence of the insulin molecule to enable rapid dissociation into monomers in subcutaneous tissue and consequent entry into the circulation and rapid (within 5 min of administration) action. These insulins serve to mimic the post-prandial release of insulin from the β cells of the pancreas. The advantages of ultra-rapidly acting

Table VII. Age-specific plasma blood glucose and A1C targets for children and adolescents with Type 1 diabetes

Values by age	Plasma glucose gold range (mg/dl)		A1C	Rationale
	Before meals	Bedtime/overnight		
Toddlers and preschoolers (<6 yr)	100-180	110-200	<8.5 % (but >7.5%)	High risk and vulnerability to hypoglycaemia
School age (6-12 yr)	90-180	100-180	<8 %	Risks of hypoglycaemia and relatively low risk of complications prior to puberty
Adolescents and young adults (13-19 yr)	90-130	90-150	<7.5 %*	Risk of hypoglycaemia Developmental and psychological issues

*A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycaemia

Source: Ref. 79

insulins is that compared to regular insulin these insulins enable improved control of post-prandial hyperglycaemia, and in conjunction with the ultra-long acting analogues in basal-bolus regimens, allow for a more flexible life style with less stringent requirements for timing of meal and snacks. These properties generally translate into lower concentrations of glycosylated haemoglobin. Ultra-long acting insulins have prolonged duration of action (approximately 15-24 h) and serve to mimic the post-absorptive release of insulin from the β cells of the pancreas⁸³⁻⁸⁸ (Table VIII).

Basal bolus regimen can be given by multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) which uses only rapidly acting insulin. The advantages of CSII over MDI are decreased number of injections, more flexible life style in timing of meal or snack, and that the basal rate can be adjusted to suit physical activity^{89,90}. An appropriately designed and implemented CSII regimen is associated with reduced nocturnal and exercise-induced hypoglycaemia, minimization of the "dawn phenomenon", and a decrement in HBA1c levels⁹¹⁻⁹³. Many centers now routinely start children with new onset T1DM on a MDI-based basal bolus regimen using a combination of ultra-rapid acting and ultra-long acting insulins.

An innovative approach to insulin administration is noninvasive routes of insulin delivery. Although investigators have tried various routes including nasal, buccal, oral, gastrointestinal, and transdermal, the inhaled route is the one where maximum progress has been made⁹⁴. Inhaled insulin (Exubera[®]) taken before meals in conjunction with a basal insulin injection has been shown to maintain glycaemic control comparable to that of patients taking MDI including patients with T1DM⁹⁵. This route of administration may be especially useful for those patients with significant needle phobia. Whereas initial trials have reported improved patient satisfaction and quality of life, the long term safety and efficacy of inhaled insulin is yet to be established.

Adjunctive therapies to insulin: In some individuals, presently employed treatment regimens do not achieve the desirable degree of glycaemic control. In some of these subjects adjunctive therapy to improve insulin action may help in improving glycaemic control. Adjunctive therapies can be grouped into the following categories based on the mechanism of action⁸⁴: (i) insulin sensitizing agents such as biguanides and thiazolidinediones. The biguanide metformin, has been used in T1DM individuals in whom insulin resistance (generally secondary to obesity) is a marked feature^{96,97},

Table VIII. Insulin analogues

Insulin	Structural change	Onset of action	Peak action	Effective duration (h)
Regular	-	30-60 min	2-3 h	8-10
<i>Rapidly acting analogue:</i>				
Lispro	Lysine- proline conversion in β chain	5-15 min	30-90 min	4-6
Aspart	Aspartic acid for proline substitution in β chain	5-15 min	30-90 min	4-6
Glulisine	Lysine for asparagine substitution in β chain	Rapid	60 min	4
<i>Long acting analogue:</i>				
Glargine	Glycine for asparagines substitution in a chain and a prolonged β chain	2-4 h	No peak	20-24
Detemir	Acylation of lysine in β chain with saturated fatty acid	1 h	90 min	Dose dependent

(ii) medications altering gastrointestinal nutrient delivery (*e.g.*, acarbose and amylin) - these agents serve to decrease post-prandial hyperglycaemia^{84,98} and (iii) other targets of action [*e.g.*, pirenzepine, insulin-like growth factor-1 (IGF-1), or glucagon-like peptide-1]⁸⁴. Many of these agents have been found to be effective in short-term studies with decrease in glycosylated haemoglobin of 0.5-1.0 per cent, lower levels of postprandial blood glucose, and decreased daily insulin requirements^{97,99}. Adverse effects such as poor gastrointestinal tolerability (metformin, acarbose) or potential acceleration of retinopathy (IGF-1) re-emphasize the need for further studies of efficacy, safety, and patient selection before these adjunctive therapies can be routinely recommended for patients with T1DM.

Islet cell transplantation

At present lifelong administration of exogenous insulin is the mainstay of treatment regimens for T1DM. However, innovative treatment protocols aimed at replacing β cells via pancreatic organ transplantation or islet cell transplantation provide a hope for a disease cure. Pancreatic transplantation is indicated in individuals with end-stage renal disease or those with severe metabolic complications in whom the benefits outweigh the risks of surgical procedure and prolonged immunosuppression^{100,101}. However, in children and adolescent who do not have such dire complications, pancreatic organ transplantation is not a practical option. Recent advances in immunosuppressive therapy and transplant biology have enabled patients with T1DM to receive islet cell transplantation. Islet cell transplantation, in which islets cells isolated from pancreas of cadavers are perfused percutaneously into the portal vein, has the advantage of being a minimally invasive procedure compared to pancreas transplantation¹⁰². The regimen that has received a lot of attention in recent years is the so called Edmonton protocol. The salient features of this protocol are the use of adequate islet mass for transplantation by repeated administration of high quality islet cells, and a novel corticosteroid-free antirejection combination of interleukin-2 receptor

monoclonal antibody, sirolimus, and low dose tacrolimus¹⁰². Whereas the 1 yr rate of 80 per cent of patients treated with this protocol achieving euglycaemia and insulin independence represented a significant advancement in DM therapy, longer term follow up has tempered enthusiasm for this strategy. Thus, recent studies have reported that the rate of insulin independence 5 yr post-transplantation is as low as 10 per cent¹⁰⁰. Furthermore, availability of islet cells which is currently only available from cadaveric pancreas is a limiting factor. Concerted efforts are underway in laboratories worldwide to develop alternative sources and strategies to obtain, propagate, and protect transplanted islet cells. These efforts include techniques to encapsulate islet xenografts, exploiting the burgeoning science of embryonic stem cell biology, and isolating and propagating islet cell progenitor cells from adult pancreas or extra-pancreatic source¹⁰³.

Prediction and prevention of type 1 diabetes

Current evidence strongly supports the concept that T1DM results from interactions between environmental and genetic factors. Hence in theory T1DM should be a preventable disease provided the environmental trigger(s) are identified and the temporal sequence of the interaction(s) between the environmental agent and interacting gene(s) characterized. Since the overall risk of developing T1DM in the population at large is relatively small, to be cost-efficient and ethically justifiable it is necessary to target prevention strategies to the cohort at the highest risk. Thus, if prevention strategies are to be successful it is necessary to accurately quantitate the risk for development of T1DM in a given individual. At present prediction strategies involve measurement of autoantibodies in conjunction with genotyping for at risk HLA haplotypes (*e.g.*, DR3-DQ2/DR4-DQ8). The antibodies that are predictive for development of the disease are ICA, IAA, GAD65, and IA-2A/ICA512¹⁰⁴. The presence of two or three of these antibodies represents a predictive value of 50 and 80 per cent respectively for developing the disease within 5 yr¹⁰⁵. The risk of diabetes increases with the

numbers and titres of antibodies and is modified by HLA genotype. In high risk individuals, (*e.g.*, first-degree relatives of type 1 diabetic patients) sequential screening for two antibodies (GAA, ICA, IAA, or ICA512AA) at one time and follow up testing for the remaining antibodies among those who are positive for one of the antibodies yields a sensitivity of 73-99 per cent¹⁰⁶. In the general population, the presence of multiple antibodies (GAD, IA2/ICA512, and insulin) has 50 per cent positive predictive value and 100 per cent sensitivity¹⁰⁷. The interval between the appearance of autoantibodies in the circulation and onset of clinical diabetes could be several years. Assessment of β cell function by first phase insulin response (FPIR) to an intravenous glucose tolerance test (IVGTT) increases the ability to predict the onset of diabetes, especially in individuals with positive autoantibodies and genetic susceptibility. Reduced FPIR (less than 45 mU/ml) with the presence of one antibody signifies a 92 per cent prediction for the development of diabetes. Subjects with genetic susceptibility such as DR3-DQ2/DR4-DQ8 commonly have a low FPIR after seroconversion of autoantibody and in these individuals FPIR might predict time to develop diabetes. In one study, an FPIR less than 50 mU/l was associated with a 85 per cent risk of diabetes within 5 yr¹⁰⁸.

Prevention strategies for T1DM can be classified as either primary prevention or secondary prevention strategies. Primary prevention is the prevention of T1DM prior to the onset of clinical diabetes mellitus. Primary prevention could be in individuals who have either not yet developed autoimmunity to the islet, or prevention after development of islet cell autoimmunity, but prior to development of significant β cell loss, or prevention after onset of β cell loss but prior to onset of clinical manifestation. Secondary prevention seeks to prevent further loss of β cell after onset of clinical disease.

Prevention strategies in individuals without autoimmunity seek to eliminate potential trigger factors. The hypothesis that breast feeding protects against T1DM is supported by some and negated by

other studies. Epidemiological studies demonstrate increase in titres and number of antibodies to cow milk protein in formula fed infants, a finding that has been implicated in increasing the risk for T1DM¹⁰⁹. There is evidence that compared to cow's milk, ingestion of casein hydrolysate formula is associated with decreased incidence of T1DM. In another study consumption of > 0.5 l of cow milk was associated with 3-5 fold increased risk of diabetes in individuals with genetic susceptibility¹¹⁰. The trial to reduce insulin dependent diabetes in the genetically at risk (TRIGR) is a multi-center collaborative study investigating the relationship between breast feeding, the early introduction of cow milk formula and risk of T1DM¹¹¹.

There are several approaches to prevent the disease onset after β cell loss. Immunosuppressive agents such as Cyclosporin A, could delay the onset of clinical diabetes; however, the serious side effects of such regimens pose an insurmountable barrier to routine use of these agents¹¹². Corticosteroids and plasmapheresis do not prevent the development of diabetes¹¹². Nicotinamide, the oxygen-free radical scavenger, was reported to improve metabolic control and prevent disease¹¹³⁻¹¹⁵. However, the European nicotinamide diabetes intervention trial (ENDIT) failed to confirm such a salutary effect¹¹⁶. The active form of vitamin D, $1\alpha,25$ (OH) $_2$ D $_3$ has immunomodulatory actions and prevents development of T1DM in animal models. Individuals with vitamin D deficiency are at a higher risk of developing an autoimmune disorder. Children diagnosed with rickets in the first year of life have a 3-fold increased risk of diabetes, and supplement of vitamin D during pregnancy significantly reduces the risk of diabetes in the offspring. Supplement of vitamin D 2000 U/day has been reported to reduce the relative risk of T1DM (RR of 0.22 with CI of 0.05-0.89)^{117,118}. Insulin is an islet cell autoantigen and is hypothesized to play a causal role in the development of autoimmunity in T1DM. However, despite several trials aimed at determining the effect of either parenteral or oral insulin in preventing T1DM, including the landmark DPT1 trial, to date,

insulin treatment has not been proven to alter the clinical course of diabetes¹¹⁹.

After the onset of disease (secondary prevention), several approaches aim to ameliorate the disease by preventing further β cell damage and thus prolong the honeymoon phase. Methotrexate, anti-thymocyte globulin, oral insulin, BCG vaccine, and Q fever vaccine failed to exhibit protective effects against further decline in β cell function. Other innovative approaches such as Ala-Ala anti-CD3, deglycosylate anti-CD3, oral IFN- γ , heat shock protein peptide, insulin B:9-23, anti-IL2 receptor, and mycophenolate mofetil are the subject of multicenter trials¹¹⁹. In this regard the establishment of a multi-center clinical network (TrialNet; <http://www.diabetestrialnet.org/>) to co-ordinate and facilitate such trials is going to be a significant catalyst in this endeavour. TrialNet is a network of 18 Clinical Centers working in co-operation with screening sites throughout the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand. This network is dedicated to the study, prevention, and early treatment of type 1 diabetes. TrialNet is supported by the United States National Institutes of Health and Department of Health & Human Services, Juvenile Diabetes Research Foundation International, and the American Diabetes Association.

In summary, the syndromes of diabetes mellitus continue to provide new insights into the genetic and biochemical basis of disturbed insulin secretion and action along with specific treatments in some instances such as the use of sulphonylureas in patients with defects in the K_{ATP} channel regulating insulin secretion. T1DM is an autoimmune disease and the most common form of diabetes in childhood. Although this disease cannot yet be prevented, it can be predicted and the ability to predict will facilitate prevention when this becomes possible. Newer insulins and automated methods of delivery via programmable pumps are markedly improving care of the child

with diabetes; a fully “closed loop” system with glucose sensing in real time providing algorithmic control of insulin delivery via a pump is not a distant dream but a likely eventuality in the near future. Modulation of the autoimmune response is increasingly being investigated, islet transplantation is in the early stages as is stem cell therapy. The elusive trigger(s) for T1DM, if and when identified, would permit prevention and a meaningful reduction in the number of new cases of this disease worldwide.

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