These guidelines on practical diabetes management in childhood have been written specially keeping in mind the social and economic conditions in which our patients live and we work. Nevertheless, every attempt has been made to refer to international texts and clinical practice guidelines as recent as 2016. The handbook should be useful to pediatricians, pediatric endocrinologists and endocrinologists, diabetologists and physicians, nurse educators, dieticians and counselors.

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TYPE 1 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS IN INDIA

CLINICAL PRACTICE GUIDELINES 2017

INDIAN SOCIETY FOR PEDIATRIC AND ADOLESCENT ENDOCRINOLOGY

PEDIATRIC AND ADOLESCENT ENDOCRINOLOGY CHAPTER
INDIAN ACADEMY OF PEDIATRICS

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2017

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INDIAN ACADEMY OF PEDIATRICS

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PREFACE

The burden of childhood diabetes is increasing year by year in India, as it is in Western countries. However, our basic pediatric training does not provide all the skills essential for the ambulatory chronic care of the child with diabetes. Yet, this is one chronic disease, which, if managed correctly, can help the patient to lead a long and productive life. In recognition of this felt need, the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) and the Pediatric and Adolescent Endocrinology Chapter of the Indian Academy of Pediatrics in 2011 prepared the first edition of practical "diabetes guidelines" for the benefit of pediatricians, physicians, nutritionists, psychologists, diabetes educators and medical students in India. The second edition has been written with an aim to include the newer developments that have taken place in the last five years since the guidelines were first released. This book aims to provide clear practical instructions on how best to look after a patient in the Indian setting.

Childhood diabetes is the only chronic disease in which the patient plays the key role in day-to-day management. Patients have to inject insulin, check blood glucose and plan meals and exercise to match the action profile of insulin. They must be well versed with the prevention and first aid management of hypoglycemia and ketoacidosis. Thus, childhood diabetes cannot be managed merely by providing a prescription; intensive and ongoing *patient education and counseling* are the foundations on which good diabetes care is based. For this reason, patient education forms a constant theme in the background of this book. Special attention has also been paid to psychosocial aspects.

The first edition of this book was devoted only to various aspects of type 1 diabetes mellitus since this is by far the commonest variety seen in pediatric practice. In the second edition, we have included a section on "Type 2 diabetes" which is now becoming increasingly common in the adolescent and young adult population in India, as evident from the ICMR registry. A chapter on "Neonatal diabetes" has been added to make every pediatrician aware of the importance of obtaining *immediate genetic studies* in an infant presenting with diabetes mellitus in the first 6 months of life in order to determine the appropriate line of treatment, as many of these infants can be treated with sulphonylurea compounds and will not require insulin.

It must be noted that there is no "best method" to manage diabetes. The treatment has to be individualized to suit the needs and capabilities of the patient, keeping in mind the level of motivation, intelligence, age of the child and economic situation of the family. The market is flooded with a variety of insulins and insulin administration devices. Diabetes treatment will be needed lifelong; hence there is no point in prescribing insulins or devices that the patient will not be able to

afford for long. A patient can be managed with the older human insulins or with newer insulin analogs; with insulin vials and syringes or insulin cartridges and pen injectors or with the insulin pump, depending on the financial status (besides other factors). The treating doctor must be equipped with the knowledge to make the right choice on a case-to-case basis. Knowing the *economics of diabetes care* would help in deciding what would be most appropriate for a given patient. A chapter on this aspect has been introduced in this edition.

The preparation of these guidelines was entrusted to a team of pediatric endocrinologists and diabetologists from different parts of our vast and diverse country. The team includes those who manage the poor, less literate patients in public hospitals as well as those who deal with the well to do, highly educated patients in the private sector. Each chapter has been written by a single author but incorporates inputs from all members of the writing and editorial group.

The guidelines are divided into 27 chapters, each dealing with a specific aspect of pediatric diabetes. Each chapter is complete in itself and the reader can read the chapters in any sequence. We hope that these guidelines will be read by all those who care for children and that reading the guidelines will result in earlier diagnosis of diabetes and scientific approach to its management, thus ensuring a longer, healthier life for children afflicted with this disease.

Aspi J. Irani
P S N Menon
Vijayalakshmi Bhatia

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INTRODUCTION

Aspi J. Irani

Several excellent guidelines are available for the management of type 1 diabetes mellitus (T1DM) in children and adolescents. These include the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (2014), Australian guidelines (2011), Canadian Diabetes Association guidelines (2013) and the American Diabetes Association (ADA) guidelines (revised in 2016). One may therefore ask – what was the need for publishing the present set of guidelines?

In the year 2011, the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) and the Pediatric and Adolescent Endocrinology Chapter of the Indian Academy of Pediatrics brought out its own "Clinical Practice Guidelines for Type 1 Diabetes Mellitus in Children and Adolescents in India". The ISPAE guidelines have been written keeping in mind the situation prevailing in our country, facilities available in our country, and the constraints under which we work. These guidelines summarize the latest scientific data on the subject and offer suggestions on how best to apply the same for optimum results in the Indian scenario. Since the publication of the first edition, advances in management of T1DM have been taking place at a rapid pace, and hence the editors felt the need to revise and update the guidelines.

T1DM is the commonest metabolic-endocrine disease in children and adolescents. There has been a significant increase in the number of new cases in the past few years, especially in the age group of 1-5 years. There are very few specialized pediatric endocrinologists and pediatric diabetologists in our country. The "adult" diabetologist or endocrinologist manages some patients. The general pediatrician treats most pediatric patients with diabetes. Since a practicing pediatrician in India is not likely to encounter more than a couple of new cases each year, it is not possible for him/her to learn and apply the finer points of diabetes management. These guidelines should serve as a quick and ready reference manual for those caregivers who are not specialized in pediatric diabetes care.

In India, few centers are able to provide a team-based approach for management of diabetes in the pediatric age group. A 24-hour helpline for these patients is virtually non-existent. Little attention is paid to the psychosocial needs of the patients. There are very few diabetes support groups.

Most schools in our country are neither geared for, nor willing to take up, any responsibility for caring for the child with diabetes.

The different types of foods we consume in various parts of our vast country and lack of freely available data on carbohydrate content of our foods poses a major challenge.

The joint family system creates a problem especially with meal planning. The same system, if properly harnessed, can afford parents the benefit of additional support and assistance in managing the child with diabetes.

Poverty, absence of government funding and illiteracy are some of the other important hurdles in the management of T1DM. Misconceptions about the condition, and those affected by it, are rampant. Blind faith in alternative systems of medicine often leads patients to omit insulin therapy, with disastrous results.

Availability of the latest medications and devices for management of diabetes is no longer a problem. The challenge lies in making these available to all classes of patients and ensuring that they are utilized appropriately so as to derive maximum benefit.

For all the above-mentioned reasons, the ideal therapeutic approach may not always be the most practical one to follow. This book on guidelines for diabetes management by the ISPAE has been prepared, keeping these factors in mind.

Four new chapters have been added in the present edition. *The first month after diagnosis of type 1 diabetes mellitus* is a crucial period. Patients and their families have to be helped to overcome the initial shock and denial, and to accept the diagnosis with a positive outlook. At the same time, insulin therapy must be initiated, patients must be trained in basics of diabetes self-management, and preliminary work-up to define the type of diabetes and to look for comorbidities must be undertaken. Families need constant guidance as the phase of metabolic recovery (with high insulin requirements) gradually gives way to the honeymoon phase (with rapidly dropping insulin needs). The quality of care received during this period will have a bearing on the long-term outcome.

T1DM is a lifelong disease and the treatment can be very expensive. Knowledge of *the economics of diabetes care in the pediatric age group* can help the treating physician to choose the best treatment for a given patient, keeping in mind his/her financial status.This chapter will focus on how T1DM can be controlled reasonably well even without the newer expensive medications or gadgets.

Neonatal diabetes mellitus (diabetes with onset in the first six months of life) is unlikely to be T1DM. It needs a special work-up, to distinguish between transient and permanent varieties and to detect as early as possible, with the help of genetic

molecular studies, whether the patient would be sulphonylurea responsive or insulin-dependent. Further, certain syndromes can present with neonatal diabetes. Making a precise diagnosis can improve the outcome by alerting the treating doctor about the appropriate treatment and possible known associations.

Type 2 diabetes mellitus (T2DM) is assuming epidemic proportions *in the adolescent age group* in some parts of the world and is also being encountered in urban India. Every pediatrician needs to be conversant with the primary prevention, early detection (by screening appropriate populations) and management of this disease. Guidelines on pediatric T1DM would be incomplete without a discussion on this variety of diabetes.

2

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Anna Simon

SUMMARY OF RECOMMENDATIONS

- Diabetes mellitus should be suspected in a variety of clinical situations including failure to gain weight, weight loss despite good appetite and recurrent infections, in addition to the classical features of diabetes and diabetic ketoacidosis.
- The revised criteria proposed for diagnosis of diabetes include HbA1c ≥6.5% as a criterion, in addition to plasma glucose levels.
- Even though type 1 diabetes mellitus (TIDM) accounts for most cases in childhood, other types of diabetes are being increasingly diagnosed now.
- Type 2 diabetes mellitus (T2DM) or other etiologies of diabetes should be suspected in the presence of autosomal dominant history, acanthosis nigricans, syndromic features, deafness, optic atrophy, and/or recurrent abdominal pain.
- Insulin-requiring hyperglycemia in the first six months of life is known as neonatal diabetes mellitus (NDM). Approximately half the cases of NDM are transient and resolve spontaneously. The most common form of permanent NDM is due to activating mutations of Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) subunits of KATP channel.

CLINICAL FEATURES OF TYPE 1 DIABETES MELLITUS (T1DM)

- Polyuria, polydipsia, nocturia or secondary enuresis, in association with glycosuria and ketonuria
- Failure to gain weight or weight loss despite increased appetite
- Persisting glycosuria
- Presence of candidial vaginitis or balanitis, or recurrent skin infections
- Diabetic ketoacidosis or rarely hyperosmolar coma

CRITERIA FOR DIAGNOSIS OF DIABETES

The criteria recently proposed by the American Diabetic Association (ADA) for the diagnosis of diabetes are given in **Table 1** below.

TABLE 1. Criteria for the Diagnosis of Diabetes Mellitus (American Diabetes Association [ADA] 2016)

1. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*

OR

2. 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

3. HbA1c ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

**In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.*

T1DM is usually diagnosed with the typical clinical features and random blood glucose (BG) ≥200 mg/dL. When in doubt, re-testing will be helpful to establish the diagnosis. An oral glucose tolerance test (OGTT) should not be performed in children and adolescents if diabetes can be diagnosed using fasting, random or HbA1c criteria. It is rarely indicated in making the diagnosis of T1DM in childhood and adolescence.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are seen in disordered glucose homeostasis and may precede diabetes. IFG and IGT are usually not clinically detected in T1DM, but may occur with T2DM and other forms of diabetes.

- IFG – Plasma glucose 100–125 mg/dL
- IGT – 2-hour post-glucose load plasma glucose 140–199 mg/dL

CLASSIFICATION OF DIABETES MELLITUS

An etiological classification of diabetes in children is given below.

I. Type 1 Diabetes Mellitus (T1DM)

(β cell destruction or insulin deficiency)

A. Immune mediated

B. Idiopathic

II. Type 2 Diabetes Mellitus (T2DM)

(Insulin resistance with variable insulin deficiency)

III. Other Specific Types

A. Genetic defects of β cell function

- MODY 1 (20q12-q13.1, HNF-4α) – neonatal hyperinsulinemia, low triglycerides, sensitive to sulphonylureas
- MODY 2 (7p15-p13, glucokinase) – mild diabetes, impaired fasting BG
- MODY 3 (12q24.2, HNF-1α, TCF-1) – microvascular complications, sensitive to sulphonylureas
- MODY 4 (13q12.1, IPF-1) – rare, mean age at diagnosis 35 years
- MODY 5 (17cen-q21.3, HNF-1β, TCF-2) – variable phenotype, renal cysts, genital anomalies, azoospermia, requires insulin
- MODY 6 (2q32, *NeuroD1*, beta2) – rare, adult onset diabetes
- MODY 7 (2p25, KLF1) – rare, resembles T2DM
- MODY 8 (9q34, CEL) – decreased endocrine and exocrine pancreatic functions
- MODY 9 (7q32, PAX4) – rare, can have ketoacidosis
- MODY 10 (11p15.5, INS) – rare, before 20 years, sensitive to sulphonylureas or insulin
- MODY 11 (8p23, BLK) – rare, more penetrance with increased body mass index (BMI)
- MODY 12 (ABCC8) – similar to HNF-1α/4α MODY
- MODY 13 (11p15, KCNJ11) – rare, variable presentation
- MODY 14 (3p14, APPL1)
- Mitochondrial DNA mutation
- DIDMOAD – Wolfram syndrome (WFS-1/chromosome 4),
- FOXP3 (Xp11.23)
- Others

B. Genetic defects of insulin action

- Leprechaunism
- Rabson–Mendenhall syndrome
- Lipoatrophic diabetes
- Type A insulin resistance
- Others

C. Diseases of the exocrine pancreas

- Cystic fibrosis related diabetes
- Pancreatectomy/trauma
- Fibrocalculous pancreatic disease
- Pancreatitis
- Hemochromatosis
- Irradiation

D. Endocrinopathies

- Cushing syndrome
- Hyperthyroidism
- Acromegaly
- Pheochromocytoma
- Somatostatinoma

E. Drug/chemical induced

- Glucocorticoids
- Cyclosporine
- L-Asparaginase
- Nicotinic acid
- Diazoxide
- Thiazides
- Vacor
- Pentamidine

F. Genetic syndromes with insulin resistance / insulin deficiency

- Prader-Willi syndrome
- Down syndrome
- Turner syndrome
- Friedreich's ataxia

IV. Gestational Diabetes Mellitus

ETIOLOGICAL DIAGNOSIS

Though T1DM is the most common cause of diabetes in childhood and adolescence, there is increasing recognition of the occurrence of T2DM and other rarer genetic forms of diabetes in recent years. The differentiation between T1DM, T2DM, and monogenic forms of diabetes is important for planning the therapeutic strategy.

Type 1 Diabetes Mellitus

T1DM usually presents with polyuria, polydipsia, weight loss and easy susceptibility to ketosis. It is also characterized by the dependence on exogenous insulin to preserve life, the presence of circulating antibodies to cytoplasmic and cell-surface components of islet β cells and its association with certain HLA loci and other autoimmune diseases. In Caucasians, serological markers of an autoimmune pathologic process, including islet cell antibodies (ICA), anti-GAD65, anti-IA-2, anti-IA-2β, or anti-insulin (IAA), and anti-zinc transporter 8 (ZnT8) antibodies are present in > 90% of individuals with T1DM (type 1A). However, the corresponding figures are much lower in Indian studies, therefore the absence of these markers does not rule out T1DM. This antibody negative variety is also called T1DM type 1B.

Clinical and Laboratory Features of Other Forms of Diabetes

The possibility of other types of diabetes must be suspected when there is:

- An autosomal dominant family history of diabetes
- Presence of syndromic features, associated deafness or optic atrophy
- Features of insulin resistance—acanthosis nigricans (AN) or polycystic ovarian syndrome (PCOS)
- Requirement of very little insulin or no insulin even after the honeymoon phase
- History of exposure to drugs toxic to β cells or known to cause insulin resistance (IR)
- Onset below the age of 6 months.

Some of the clinical and laboratory features differentiating the rarer forms of diabetes from T1DM are described below and shown in **Table 2**.

TABLE 2. Differentiation of T1DM, T2DM and Monogenic Diabetes

Characteristic	***Type 1***	***Type 2***	***Monogenic***
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to adolescence	Usually pubertal	Often post-pubertal (except glucokinase) or neonatal
Clinical presentation	Most often acute, rapid	Variable	Variable
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in neonatal forms, otherwise uncommon
Insulin secretion	Decreased/absent	Variable	Variably decreased
Insulin sensitivity	Normal	Decreased	Normal
Insulin dependency	Permanent	Episodic	Variable
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No

Type 2 Diabetes Mellitus (T2DM)

T2DM is a polygenic disease with multiple risk factors. The possibility of T2DM should be considered in children and adolescents:

- Who are obese
- Who have family history of T2DM
- Who have evidence of IR (AN or PCOS)
- Whose fasting insulin and C-peptide levels are normal or elevated.

In an overweight adolescent who had recent onset hyperglycemia without ketosis, it may not be very clear whether the diabetes is type 1 or 2 or MODY. In such cases it may be relatively safer to start treatment with insulin rather than oral antidiabetic agents. There is a place for testing autoantibodies in such situations, even though they are reported to be less prevalent in Indian studies. Once the initial glucotoxicity has settled down, testing C-peptide with simultaneous BG may also be useful.

Maturity Onset Diabetes of the Young (MODY)

These are a group of disorders with a monogenic defect in β cell function. They are important to diagnose as their treatment, natural course, associated features and nature of genetic counseling are different from type 1 or type 2 DM. The clinician should be alerted to the possibility of MODY with the following:

Clinical features which suggest a diagnosis of monogenic diabetes:

- Autosomal dominant pattern of inheritance
- If the patient has very mild hyperglycemia and does not seem to require insulin (i.e., appears like T2DM), but has no obesity or AN, and may have diabetic family members who are not obese.
- Age at onset less than 6 months.

Tests which can give a clue to the presence of monogenic diabetes:

- If the child appears to have T1DM but islet antibodies are negative, particularly at the onset of diabetes, and/or there is evidence of C-peptide production beyond 3 years from the diagnosis of diabetes.
- If the child appears to have T2DM but there is no evidence of IR, and fasting C-peptide is in the normal range.

Specific molecular diagnosis is important for proper management, genetic counseling and testing of family members.

Fibrocalculous Pancreatic Disease with Diabetes (FCPD)

In India, in adolescents, especially those who do not present with ketosis, one must be alert for the diagnosis of FCPD. Some helpful features include:

1) Associated symptoms of pancreatic disease, recurrent abdominal pain and malabsorption

2) Evidence of pancreatic calcification.

Ultrasound of the pancreas is useful, but may not always be diagnostic. The implications of having FCPD include the need to test for exocrine pancreatic function and enzyme replacement in addition to insulin, the occurrence of intermittent episodes of pancreatitis, and an increased risk of pancreatic carcinoma.

DIDMOAD Syndrome (Wolfram Syndrome)

DIDMOAD syndrome is characterized by diabetes insipidus, diabetes mellitus, optic atrophy and deafness. This disease has an autosomal recessive inheritance with the gene mapped on chromosome 4 (*WFS1*). *WFS1* has a role in β cell and neural tissue survival.

Neonatal Diabetes Mellitus

Insulin-requiring hyperglycemia in the first 6 months of life is known as NDM. Most affected infants have intrauterine growth retardation (IUGR) and other clinical features such as polyuria with glycosuria, dehydration, failure to thrive and rarely DKA. More details are given in the Chapter on Neonatal Diabetes.

Neonatal diabetes is classified as:

- Transient - without recurrence
- Transient - with recurrence
- Permanent

Approximately half of the cases are transient which resolve spontaneously. This is often due to delay in maturation of pancreatic β cells. In patients with transient NDM, permanent diabetes may appear later in life.

About 50% of cases are of the permanent form and may additionally present with dysmorphic features, muscle weakness, and epilepsy. The most common form of permanent neonatal diabetes is due to activating mutations of Kir6.2 (*KCNJ11*), SUR1 (*ABCC8*) subunits of KATP channel or mutations of Insulin Promoter Factor-1 (chromosome 7), or *FOXP3* gene. The first 2 forms are responsive to pharmacological doses of the oral sulphonylurea, glibenclamide. The majority of the transient NDM are due to abnormalities of chromosome 6q24.

Other rarer forms of permanent NDM include:

- Pancreatic agenesis (homozygous mutation of *IPF1* or glucokinase gene) – may present with exocrine manifestations like malabsorption.
- IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)
- Wollcott–Rallison syndrome associated with multiple epiphyseal dysplasia, renal and hepatic impairment and ectodermal dysplasia.

Cystic Fibrosis Related Diabetes (CFRD)

With increasing recognition of CF in Indian children, it is important for clinicians to be aware of the entity. CFRD typically presents in adolescence but can occur at any age. Screening for diabetes with OGTT in children with CF should be commenced by 10 years of age. The pathophysiology of CFRD is insulin deficiency and variable IR. The co-existing glucagon deficiency imparts unique characteristics influencing insulin requirement.

Thalassemia

Screening for diabetes with fasting and post-prandial BG should commence from 10 years of age. The pathophysiology is insulin deficiency due to iron deposits in the pancreas, with variable IR.

Stress Hyperglycemia

Stress hyperglycemia is common in children and adolescents and reported in nearly 5% of children presenting to an emergency department. Severe hyperglycemia detected in children with acute infections, respiratory distress, shock, trauma or surgery is usually transient; but may require treatment with insulin, based on close BG monitoring. Stress hyperglycemia by itself is not diagnostic of diabetes. The reported incidence of progression to overt diabetes varies from 0% to 30% and hence it is recommended that such patients be screened for diabetes at regular intervals after recovery.

3

PRINCIPLES AND GOALS OF MANAGEMENT

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- Daily, lifelong insulin injections are essential for the survival of children with type 1 diabetes mellitus (T1DM).
- Medical nutritional therapy, planned physical activity and self-monitoring of blood glucose (SMBG) and ketones are other very important aspects of treatment.
- Hospitalization for initial management and education is required in most, though not in all, newly diagnosed cases.
- Management of childhood diabetes needs a team approach. The patient must have round-the-clock access to a team member.
- Patients and their families must be educated in self-management of diabetes including prevention and first-aid management of diabetes-related emergencies (hypoglycemia and ketosis).
- Psychosocial problems must be anticipated and addressed.
- A childhood and adolescent diabetes support group must be established in each city.
- It is not possible to achieve a normal metabolic milieu, even with the best available treatment. The goals of treatment therefore are to keep the child symptom-free, ensure normal growth and development, with HbA1c as close to the normal range as possible without episodes of hypoglycemia.
- The lower the HbA1c value, the lesser the risk for development/ progression of long-term microvascular and macrovascular complications.
- The therapeutic plan and goals of therapy should be individualized depending on the patient's capabilities, motivation, finances, age, daily schedule and the availability of medical services.
- Regular screening for long-term complications and comorbidities must be undertaken.
- There is no medication other than insulin for control of T1DM, though in selected cases metformin may have some role.
- At present there is no cure for T1DM, but it should be controlled to the best possible extent.

INTRODCTION

Type 1diabetes mellitus (T1DM) is caused by autoimmune or idiopathic destruction of the insulin-producing β cells in the pancreas. Exogenous insulin (available since 1922) is essential for the survival of children and adolescents with T1DM. Prior to the year 1922, T1DM was a fatal disease.

Insulin is available only in injectable form. Inhaled insulin has been re-introduced recently, but is approved only for persons above the age of 18 years; further, it can substitute for short acting (“bolus”) insulin only.

Replacement of the missing hormone, insulin, is only one aspect of management of diabetes in children and adolescents. Equal importance must be given to each of the four "therapeutic pillars” which include:

1. Insulin therapy,
2. Meal planning (medical nutritional therapy),
3. Planned physical activity, and
4. Self-monitoring of blood glucose (SMBG) and urinary or blood ketones.

Diabetes is perhaps the only chronic childhood disease in which the patients (child and family or other caregivers) need to play the key role in day-to-day management. They must be taught about:

1. How to store and inject insulin (including injection sites and site rotation),
2. How to test blood glucose and urine ketones,
3. How to record, analyze and act on the SMBG results,
4. Principles of “healthy eating” and meal planning to prevent swings in blood glucose,
5. How to plan physical activity so as to prevent hypoglycemia, and
6. Details about the prevention, early recognition and first-aid management of the diabetes-related emergencies: ketoacidosis and hypoglycemia.

In a disease requiring active and intelligent participation of the child and family, patient education as well as compliance are most important. Intensive and ongoing education of the patient in self-management of diabetes is essential. Not providing self-care education constitutes substandard care. Ideally this should be supplemented with a round-the-clock telephone "helpline". To ensure patient compliance, attention must be paid to the emotional state of the child and family. Together, patient education and emotional stability constitute the foundation on which the four therapeutic pillars of diabetes management rest.

The patient and family members are invariably in a state of shock and denial at the outset. They are overcome with the feeling of "why us?" and the need to blame a person or event for the diabetes. As there is so much to learn and so much responsibility to shoulder, the parents feel helpless and confused. There is anxiety and worry about the child's future – education, employment, marriage, childbearing, acute and long-term complications of diabetes and the expected lifespan. These emotional upheavals and "unspoken" fears must be anticipated and addressed. Stress must be laid on the strong possibility of a bright future provided diabetes is well controlled.

In order to provide the full range of services, management of childhood diabetes needs a team. The team should include a pediatric endocrinologist or a pediatrician with special interest in diabetes, a dietician, a psychologist, a social worker and a nurse educator. The team should ideally also include senior patients and their family members who can be the best counselors, educators, social workers and above all "role models" for the "new entrants".

Maintaining contact with the patient at regular intervals (preferably with the 24-hour helpline) *per se* improves the level of control. This is possible in our country through telephone, SMS, WhatsApp and e-mail.

A childhood and adolescent diabetes support group should be established in each city. This is useful for group education and counseling. It also enables patients to procure diabetes-related paraphernalia at lower cost on account of bulk purchase. They can help each other by sharing their ideas and experiences. The group can work towards creating informed awareness about this relatively rare disease and securing a fairer deal from schools, colleges, employers, insurance providers and the government.

The medical team must communicate with school authorities to ensure that the child is not treated differently from other children and at the same time the staff members must take care to avoid situations that predispose to hypoglycemia. The staff should be in a position to identify hypoglycemia early and manage the same should the need arise. The child may need the help of the school nurse in case a blood test or insulin dose is required during school hours.

Hospitalization for initial management is mandatory if child is dehydrated, vomiting, breathless, or has abdominal pain or is drowsy (features of ketosis). In patients who are not in ketosis at presentation, the following would be indications for hospitalization:

- The child is below 5 years of age.
- The parents are emotionally disturbed or incapable of administering insulin and checking blood glucose at home.

- The residence is far away from the medical center and/or there are no adequate means of communication.

If hospitalization is required, the child should be managed in the pediatric ward, never in a ward for adult patients. Before discharge, the patient must receive education in basic self-management of diabetes. Patients must be asked to stay in touch with a member of the medical team on a daily basis to guide them safely towards the honeymoon phase.

Ideally one would like to achieve normal blood glucose and a normal metabolic milieu all the time. This is not possible even with the most sophisticated treatment available today. Thus, one should strive to achieve the following arbitrary goals:

1. The child should be leading a normal and happy childhood.
2. The child should be asymptomatic (with no seizures, unconsciousness or confusion due to hypoglycemia, no symptoms of high blood glucose, no weakness or lethargy, no ketoacidosis and no school absenteeism).
3. The child should be growing and maturing normally.
4. The SMBG results and the HbA1c should be within or close to the recommended ideal range for age.
5. The child should remain free of the long-term microvascular and macrovascular complications which are known to impact the quality of survival and shorten the lifespan of patients with T1DM.

The **"Diabetes Control and Complications Trial" (DCCT)** which compared the outcome in two groups of adolescents and adults (a "conventional treatment" group and an "intensified treatment" group) showed that:

1. Those on intensified management had a lower HbA1c (8.1% vs. 9.8%) which in turn resulted in a 50-60% reduction in onset as well as progression of the long-term microvascular complications of nephropathy and retinopathy.
2. There was no lower threshold level of HbA1c below which the complications did not develop. Any sustained improvement in HbA1c was shown to reduce this risk.
3. When individual patients in the two groups were compared, the risk of complications was lower in the "intensified treatment" group, even with identical HbA1c values. The reduced swings of blood glucose may have accounted for this observation.
4. The benefits of intensified management, however, came at the cost of a 3 times higher incidence of hypoglycemia and of weight gain in the intensively treated group.

Later studies, including the **"Epidemiology of Diabetes Interventions and Complications" (EDIC) trial** showed that:

1. Intensified management also lowers the risk of macrovascular complications.
2. The beneficial effects of a period of good control continue to accrue even if the same degree of control is not sustained subsequently.
3. With the newer insulins and monitoring methods which became available after the conclusion of the DCCT trial, the adverse effects of intensified management (hypoglycemia and weight gain) have considerably reduced.
4. It is difficult to achieve the level of control as in the DCCT even though we now have better management tools; this is perhaps because it is not easy to maintain the same level of 24-hour access to medical advice and guidance as was done in the DCCT.

From the DCCT and the EDIC trials it is clear that **one should strive to achieve as perfect a level of control as possible (reflected by the HbA1c) with minimum swings in blood glucose.** A low HbA1c with frequent hypoglycemic episodes is not acceptable.

It must be stressed that **there is no single best way to manage diabetes**. Since patient participation is so crucial, the goals of management must be set, taking into account the level of motivation and intelligence of the patient and the family, their financial status, the child's age, the daily schedule of the child and parents and the availability of medical services.

Thus, the intelligent, rich and motivated patient may opt for the insulin pump or a basal bolus insulin regimen using analogs (3-5 injections a day), perform 5-8 blood glucose tests a day and use a meal plan based on carbohydrate counting. At the other extreme, the underprivileged, uneducated and poorly motivated patient can be managed on two injections a day of premixed insulin with little or no home monitoring and diet instructions covering *"healthy and consistent eating"* and a *"traffic signal diet"*. However, the majority of patients would fall in between these two extremes; they can learn to mix two types of insulins or use the insulin pen, inject 3-4 times a day, test blood glucose 2 (or more) times daily (the time of the tests should be rotated) and use a fixed carbohydrate meal plan. Thus, **the treatment plan must be individualized**.

Regular annual screening for subclinical evidences of microvascular complications, predisposing factors for macrovascular complications and T1DM associated comorbidities must be a part of clinic evaluation. Early detection and prompt remedial action can go a long way in improving the long-term outcome.

Besides insulin, it is possible that **amylin** (another hormone produced by the β cells which regulates postprandial glycemia and glucagon output) may have a role in T1DM management. It has been approved for use in adults with T1DM. Obese adolescents with T1DM and especially those who develop polycystic ovarian disease may benefit from addition of **metformin** to counter the added factor of insulin resistance. No other drugs have so far been proven to play a role in blood glucose control in patients with T1DM, though many oral hypoglycemic agents are being studied for any potential benefit.

Technological advances are set to revolutionize the management of T1DM. **Continuous glucose monitoring systems (CGMS)** are available which record and display subcutaneous interstitial fluid glucose values with trends every 1-5 minutes in real time. **Insulin pumps** with low-glucose-suspend (which suspend insulin delivery when a low glucose threshold is reached) and predictive low-glucose-suspend (which use an algorithm to anticipate hypoglycemia and suspend insulin delivery even before hypoglycemia sets in) and bi-hormonal bionic insulin pumps with dual hormone delivery (automatic glucagon delivery to correct hypoglycemia) can make it easier to achieve good control, minimize if not eliminate hypoglycemia and give considerable flexibility in lifestyle.

A permanent cure for T1DM is not available at present. Several therapeutic modalities, including islet cell transplants and stem cell treatment, are being explored but are still experimental. T1DM is not a curable disease; however, it can and should be controlled to the best possible extent.

4

INSULIN THERAPY

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- Insulin replacement therapy is essential for the survival of children with type 1 diabetes mellitus (T1DM).
- For daily management insulin is injected subcutaneously (SC), two or more times a day. It can be injected with a syringe, a disposable pen, a reusable pen or can be given as a continuous subcutaneous infusion (the insulin pump).
- A combination of short acting human insulin or a rapid acting analog (to provide a "bolus" to cover post-meal glycemia) with an intermediate acting human insulin or a long acting basal analog (for "basal" insulin supply) is essential for day-to-day management. Insulin pumps use only a rapid acting analog for both bolus as well as basal phases. In treatment of DKA only short acting human insulin is used.
- Basal-bolus regimen involves taking 3 or more injections a day, but gives more flexibility of lifestyle and may give better control than the split-mix regimen.
- The choice of the regimen should be based on the assessment of the patient's daily schedule, motivation, capability and financial position.
- The usual dose of insulin varies between 0.5-1.5 units/kg/day according to the stage of diabetes, age and maturation of the child.
- The correct techniques of storing insulin, mixing insulins and injecting insulin should be taught to all patients.
- Hypoglycemia and lipohypertrophy are the two main complications of insulin therapy encountered with the newer preparations. With a little bit of care both can be prevented.

INTRODCTION

Type 1 diabetes mellitus (T1DM) is a hormone deficiency disease and treatment is directed at replacing the chief missing hormone, insulin. Insulin replacement therapy as practiced today is far from being perfect as it is very

difficult to mimic the pattern of endogenous insulin secretion. Exogenously administered insulin first enters the systemic circulation rather than the portal circulation and liver; it is given in a predetermined dose in anticipation of a meal rather than in response to changing glycemia with a meal; it has a long half-life allowing limited flexibility; and the action profile of a given insulin preparation may vary in the same patient from day to day.

All children with T1DM require daily lifelong insulin therapy for survival. Insulin is available only in injectable form. Inhaled insulin (Afrezza) has been approved by FDA, USA in 2014 as a substitute for "bolus" insulin injection, but it is not recommended for the pediatric age group and is not available in India.

DO ALL CASES OF PEDIATRIC DIABETES REQUIRE INSULIN?

Three varieties of diabetes with onset in the pediatric age group may not require insulin therapy:

- *Those presenting with diabetes below 6 months of age:* 30-50% of cases are caused by genetic mutations affecting insulin secretion and may respond to sulphonylurea group of drugs (see Chapter 25 on "Neonatal Diabetes"). After initial stabilization with insulin, molecular genetic studies must be obtained in all cases of neonatal diabetes to decide the long-term management.
- *Type 2 diabetes mellitus (T2DM):* T2DM is now being encountered with increasing frequency in obese adolescents (especially in those with acanthosis nigricans and a strong family history of T2DM). It is treated with lifestyle changes and the oral hypoglycemic agent, metformin. Those who are not metabolically stable at diagnosis (HbA1c >9% and symptomatic) should be given insulin initially and then gradually shifted to metformin over 2-6 weeks after stabilization. (See Chapter 24 "Type 2 Diabetes in Childhood and Adolescence" for more details.)
- *Maturity onset diabetes of the young (MODY):* MODY should be suspected if mild diabetes develops in a pediatric patient with a family history of non-insulin dependent diabetes in at least 2 successive generations with onset below the age of 25 years.

DAILY DOSE REQUIREMENT OF INSULIN

In the management of DKA, a dose of 0.1 unit/kg/hour of short acting insulin given as an intravenous infusion should be appropriate in majority of cases.

After the patient recovers from DKA, the insulin requirement for the first few days may be as high as 2-3 units/kg/day, because of elevated levels of stress hormones, increased appetite and need to restore depleted tissue stores of protein and glycogen.

As the patient enters the honeymoon phase, the dose comes down to 0.5 units/kg/day or lower; some may require virtually no insulin. However, it is preferable to continue with a very small dose once or twice a day. The honeymoon phase lasts for 3-12 months, rarely up to 24 months.

With the onset of the intensification phase (this may happen gradually or it may be abrupt if precipitated by an infection); the requirement rises to 0.7-1.0 units/kg/day in prepubertal children and 1.0-1.5 units/kg/day in pubertal children (on account of the anti-insulin effects of growth hormone and sex steroids).

INSULIN PREPARATIONS AVAILABLE IN INDIA

In India, conventional short acting insulin (regular or soluble) and intermediate acting insulin (NPH) are available. These insulins are manufactured by recombinant DNA technology and are structurally identical to the insulin produced in the human body (as against the animal pancreas extracted bovine and porcine insulins which were used in the past). All available insulins are now highly purified. The intermediate acting *lente* insulin and long acting *ultralente* insulin have been withdrawn from the market and are no longer available.

Insulin analogs (so called "designer insulins") are also available in India. These include the rapid acting "bolus" analogs Lispro, Glulisine and Aspart; the long acting "basal" analogs Glargine and Detemir and the ultra-long acting "basal" analog, Degludec.

Premixed insulins that are available include mixtures of regular with NPH (in the ratio 50:50 and 30:70) and of soluble rapid acting analog with a protaminated suspension of the analog (in the ratio 30:70 or 50:50 in the case of Aspart insulin and 25:75 or 50:50 in the case of Lispro). A 30:70 mixture of Aspart and Degludec is also available. Premixed insulins are convenient to use and eliminate errors in insulin mixing but they have the major disadvantage that the individual components cannot be adjusted in varying amounts or in different directions. Premixed insulins therefore should be used only in those patients who cannot be expected to perform any form of home monitoring.

The time-action profiles of the various insulin preparations are shown in **Table 1**.

TABLE 1. The Time Action Profiles of the Various Insulins available in India

Insulin	*Onset (Hr)*	*Peak (Hr)*	*Duration (Hr)*
Rapid acting analog	0.25	1-2	3-5
Human regular	0.5-1	2-4	6-8
Human NPH	1-3	5-8	12-18
Glargine	2-4	Nil	24
Detemir	1-2	6-12	16-23
Degludec	0.5-1.5	Nil	>24

RAPID ACTING ANALOG VS. REGULAR INSULIN

When compared with regular insulin, the rapid acting analogs have a quicker onset of action, a higher peak effect and a brief "tail" of action. This gives them certain advantages over regular insulin:

1. In view of the *quicker onset of action*, analogs can be injected just before eating. There is evidence to show that the injection can be given even after completion of a meal without significant compromise in efficacy*, though this should not be done routinely*. Regular insulin must be given 20-30 minutes before eating. (This "lag time" would need to be longer if the pre-meal blood glucose [BG] is raised.) Thus, analogs are especially useful in young children who cannot be relied upon to eat after the insulin shot, or in those who have a short lunch break at school and hence must inject and eat immediately. During outings the patient can estimate the type and amount of food or snacks that he/she would be ingesting and then take an appropriate dose of the analog.
2. The *quicker onset when injected subcutaneously (SC)* also makes the analogs the preferred choice in sick day management and in insulin pump though not in management of diabetic ketoacidosis (DKA) when the IV route is used (the time action profile is the same for both varieties of insulins when given IV).
3. The *higher peak action* achieved gives better post-meal glucose control with the analogs.
4. Because of the *shorter "tail" effect* the analogs are associated with lesser risk of hypoglycemia especially at night and there is less need for mid-meal snacks.
5. The absorption of the analogs is more consistent from different injection sites whereas regular insulin is absorbed faster from the abdomen than from the arms or thighs and slowest from the buttocks.
6. Switching to analogs may help in resolution of lipoatrophy when it occurs with regular insulin (this is in any case rare with the use of highly purified "human" insulins).

Although they have several advantages, particularly reduction in incidence of hypoglycemia, long-term studies have shown little change in the HbA1c with use of the analogs. Analogs are 3-6 times more expensive than regular insulin (see **Table 2**). It should be noted that the requirement for basal insulin is higher when analogs are used for pre-meal boluses, since with regular insulin the "tail effect" provides some basal effect.

TABLE 2. Cost of Insulin Preparations Available in India

Insulin	*Cost (In Rupees per Unit)*
Human insulin (in vial)	0.35
Human insulin (in cartridge)	0.75
Human insulin (in disposable pen)	1.30
Rapid acting analog (in cartridge)	1.65
Rapid acting analog (in disposable pen)	2.10
Basal analog, Glargine (in vial)	2.70
Basal analog, Glargine (disposable pen)	2.95
Basal analog, Glargine (in cartridge)	1.80
Long acting basal analog, Detemir (disposable pen)	3.35
Long acting analog, Degludec (disposable pen)	5.40

Note that the long acting basal analogs approved for pediatric use cost 7-10 times more than human NPH insulin. The rapid acting analogs cost 3-6 times more than human regular insulin. Insulin in a vial costs much less than the same insulin in a cartridge (Glargine is an exception) and insulin is most expensive in a disposable pen. Biosimilars of insulin Glargine cost approximately 20 paisa less per unit.

LONG ACTING ANALOGS VS. NPH INSULIN

The long acting analogs (Glargine and Detemir) were developed to address three problems associated with NPH insulin:

1. NPH insulin has a distinct peak of action 6-10 hours after injection. This necessitates ingestion of a snack to prevent late afternoon hypoglycemia and also increases the risk of night-time hypoglycemia. The long acting analogs are relatively peakless hence there is less need for snacks (and therefore reduced chances of obesity) and night-time hypoglycemia is significantly reduced (particularly with insulin Detemir).
2. NPH insulin does not cover 24 hours hence 2-3 injections a day are necessary when it is used as the basal insulin. Glargine covers 24 hours in many children and adolescents though in 20-30% of patients two doses may be needed. Detemir needs to be given twice daily in the majority of children.
3. NPH has a 25-50% or greater variability of action from day to day in the same individual. The long acting analogs have a more consistent time action profile in a given patient.

The long acting analogs however have the following disadvantages:

1. The cost is very high being 7-10 times more than that of NPH.
2. The manufacturer's guidelines state that Glargine, being acidic in pH, cannot be mixed in the same syringe with other insulins. A few studies however

have shown that mixing with rapid acting insulins does not affect the action of either insulin, thus reducing the need for an additional needle prick.

3. Some children experience a burning sensation at the injection site with Glargine insulin.
4. If accidentally injected intramuscularly (IM), the time action curve of Glargine would resemble that of regular insulin (this can cause night-time hypoglycemia if the insulin is given in the late evening.)

Some doubts about the safety of insulin Glargine and its probable association with increased risk of malignancy had been raised in the past. These have now been laid to rest and use of Glargine is considered perfectly safe.

The dose of basal insulin must be reduced by 20% when switching from NPH to Glargine; this reduction in dose is not needed when switching to Detemir.

The newest analog (Degludec) has several potential advantages over Glargine and Detemir. It has a half-life of 25 hours (which is twice that of Glargine) and duration of action of up to 42 hours. It has been shown to reduce insulin requirement and to improve fasting BG while reducing risk of nocturnal hypoglycemia. It can be mixed with short acting insulin. It need not be given at a fixed time each day. Each of these features can be highly advantageous in pediatric patients. It has been safely used in children as young as 1 year of age; however, FDA approval for the age group below 18 years is awaited.

STORING INSULIN

Insulin vials should be refrigerated at 2-8^{o}C. They should never be kept in or near the freezer; should insulin get frozen inadvertently, the vial would have to be discarded. At 2-8^{o}C, the full potency of an unopened vial is retained till the expiry date stated on the vial. A vial in use (after the seal has been punctured) should be used within 4-6 weeks if kept at room temperature**;** if refrigerated it can be used for up to 3 months. Insulin should be brought to room temperature before injecting since cold insulin may be painful.

In households that do not have a refrigerator, insulin should be kept in a cool, dry place away from sunlight and away from other sources of heat (such as the stove). The insulin vial can be put in a plastic bag and after tying a rubber band, stored in an earthenware pitcher or *matka* filled with water (**Fig 1**).

Visual inspection of an insulin vial may provide information about its damage due to improper storage. Regular insulin, the rapid acting analogs, Glargine and Detemir are clear liquids. NPH insulin has a cloudy appearance. If the clear insulin appears cloudy or has particulate matter, it should be discarded. If the cloudy insulin appears thick, discolored, or has solid floating particles, or solid residue at the bottom of the vial, it should be discarded.

Fig 1. Double clay pot (wet sand between the two pots and water on the clay lid keep the interior of the pot cool) system for keeping insulin cool in the absence of a refrigerator *(photograph: courtesy Dr Archana Sarda, Aurangabad).*

Insulin pens in use need not be refrigerated but should be kept in a cool, dry place. Pens should not be stored with the needle attached. The shelf life and viability of insulin in opened cartridges range from 7-30 days, the shorter shelf life is for the cartridges containing premixed insulins. Patients should be advised to refer to the manufacturer's guidelines for precise details.

During travel insulin can be carried in a "cool pack" or in a thermos flask (wrapped in a plastic pouch to prevent direct contact with ice; alternately, the ice can be discarded and the thermos securely capped after it has been cooled). During air travel insulin should never be kept in the check-in baggage.

INSULIN INJECTION: PEN OR SYRINGE?

Insulin can be injected with an insulin syringe or pen. Pens may be disposable or reusable.

In India, insulin in vials may be available in two concentrations (40 IU/mL and 100 IU/mL). It is extremely important to ensure that the insulin syringe has the same number of subdivisions as the strength of insulin preparation in use (i.e. 40 IU syringe for 40 IU insulin vial and 100 IU syringe for 100 IU insulin vial).

Insulin in vials (for use with a syringe) is cheaper (refer to **Table 2**) than the same insulin supplied in cartridges for use in the pen. Syringes are preferred for patients who need to mix two types of insulins in varying proportions and would like to minimize the number of pricks.

Insulin pens are very convenient to use: they do away with the need for carrying insulin vials and filling a syringe before each shot. Injections using the pen are relatively painless. The pen can be carried in the pocket and one merely has to "dial the dose and inject". A half unit pen is also available in India and this is very useful in children with small insulin requirement for fine-tuning of insulin dose.

The needle length for use with insulin pens should be 4 mm in children. When using a syringe the shortest length needle available (6 mm) is to be preferred. This minimizes the risk of IM injection. The 30G-32G in place of 31 gauge thickness needles with insulin syringes and pens are almost pain-free and can be reused (for about 3 injections or till the needle becomes blunt) provided they are handled with clean hands and stored in the refrigerator. The needle should never be cleaned with spirit.

A port with a soft cannula that is inserted in the subcutaneous space (*the i-Port Advance*) can be fixed at the usual sites of insulin injection and kept in place for 72 hours; insulin can be given repeatedly through this port without need to prick the child for each injection. This device is not available in India at the time of writing.

WHO SHOULD ADMINISTER THE SHOT?

Children above the age of 8 years can inject themselves. Self-injection is less painful and psychologically less traumatic for the child. In younger children the parents should administer the shot, while the child can participate in the process of drawing insulin in the syringe. When children and adolescents inject themselves, parental supervision is extremely important to ensure compliance.

It is suggested that all parents must be made to first poke themselves with the insulin syringe in order to make them realize that the injection is not really painful. When children see their parents injecting themselves their fears too are dispelled.

INJECTION SITES

Insulin is injected subcutaneously (SC) in the middle third of the anterolateral thigh, the anterior abdominal wall (leaving out 2 inches on each side of the navel and one inch above the navel) and the upper outer region of the buttocks. The middle third of the lateral aspect of the upper arm is not ideal for the pediatric patient as self-injection is difficult and also because there is little subcutaneous fat in this region.

Insulin is absorbed fastest from the abdomen, then from the upper arms, followed by the thigh region. Absorption is slowest from the buttocks; this would therefore be a good site for injecting basal insulin when the parents give the injection.

SITE ROTATION

The injection area should remain the same for a given time of the day (e.g. if the pre-breakfast dose is being injected in the abdomen, it should not be given in the thigh or buttocks).

Systematic site rotation within the selected area is, however,very important to prevent lipohypertrophy, which is not only cosmetically disturbing, but also leads to erratic insulin absorption.

Within a given area; not more than 2-3 doses should be injected in a month at the same spot. To achieve this, in each area 10-15 spots must be marked in such a way that there is a distance of two fingers width between any two spots. This can be done on a transparent plastic sheet and the spots numbered from 1-10 or 1-15 and again from 15-30 or 10-20 and 20-30.

SEQUENCE FOR DRAWING TWO TYPES OF INSULIN IN THE SYRINGE

The vial of cloudy insulin should be gently rotated between the palms (never shake the vial). This should be done till the suspension is uniform. It is essential to inject air in each insulin vial prior to drawing insulin in the syringe (exception: when in an aircraft, there is no need to inject air). The amount of air injected should equal the dose of insulin to be withdrawn. The vials should be placed on a flat surface when injecting air. Air is injected first in the vial containing intermediate acting insulin and then in the short acting variety. When drawing insulin in the syringe, the vials are held upside down and the short acting insulin is taken first, followed by the longer acting insulin. This sequence must be strictly followed (in case NPH is drawn up first, some of it may enter the vial of regular insulin and convert some of the regular into NPH insulin).

INJECTION TECHNIQUE

The injection is given in the subcutaneous tissue. To prevent IM injection the skin must be pinched up if the child is slim or if the needle length is more than 6 mm. The needle is inserted at an angle of 90^{o} to the surface (45^{0} in a thin child). The needle should be first brought down to touch the skin surface and then slowly allowed to glide in. After injecting one should wait for 10 seconds and then release the pinch before withdrawing the needle; these steps are important to prevent insulin from leaking out from the injection site. The injection site should not be massaged.

Elaborate videos demonstrating the steps in use of various insulin pens can be accessed on the websites of the manufacturers.

DISPOSAL OF SHARPS

Insulin needles should be put in a sharps container or in any strong plastic

bottle that cannot be punctured. The bottle should be tightly capped. When full, a tape should be put over the cap and labeled "sharps". The full container should be taken to the doctor's clinic or the hospitals that are collection centers for biomedical waste. Pens can be discarded (always with cap on) in regular trash.

INSULIN REGIMENS

Insulin is used IV or IM only in management of DKA. For day-to-day management it must be injected SC.

In the management of DKA, only short acting insulin is used. Short acting insulin (or preferably a rapid acting analog) is used alone in the insulin pump (CSII) and for supplements on "sick days".

For routine day-to-day management, patients use either rapid or short acting insulin, together with either intermediate or long acting insulin. The latter insulin alone may rarely suffice in children in the remission phase.

Broadly, there are 2 regimens for giving insulin:

1. *Basal-bolus regimen* in which intermediate or long acting insulin is used as "basal" to suppress hepatic glucose production in the fasting state and rapid or short acting insulin is injected before each major meal to cover post-meal glycemia (the so called "bolus").
2. *Split-mix regimen* in which one type of insulin covers 1 time period.

The basal-bolus regimens should be the preferred choice in all patients as they are more physiological and give greater flexibility.

Basal-Bolus Regimen

The basal-bolus regimen if implemented correctly (with frequent self-monitoring of blood glucose [SMBG], corrective supplemental doses of insulin and carbohydrate counting for pre-meal bolus calculation) can give better control than the split-mix regimens. These regimens use rapid or short acting insulin to cover meals and a long acting analog or NPH to provide basal insulin (to regulate hepatic glucose output in the fasting state). The common regimens in use are:

- *Regular insulin three times a day before each major meal and NPH insulin only at bedtime or preferably pre-breakfast plus bedtime:* 40-50% of the total daily dose (TDD) is given as NPH and 50-60% as regular insulin. 70% of the calculated NPH requirement is given at bedtime and the remaining 30% pre-breakfast. The regular insulin is given in three divided doses in proportion to the carbohydrate content of the meals it is intended to cover.
- *Regular insulin three times a day before each major meal (the doses being distributed as discussed above) and Glargine or Detemir once or twice a day:* 70-80% of children can be controlled on a single dose of Glargine while 20-30% would

require two doses; in the case of Detemir, the majority will need two daily doses.

- *Lispro or Aspart insulin before each major meal or large snack (3-5 doses a day) and either NPH or preferably a long acting analog for basal insulinemia:* It should be noted that the proportion of bolus to basal insulin is lower when the short acting analogs are used since regular insulin itself contributes to basal insulinemia.
- *Continuous subcutaneous insulin infusion (CSII) or the open loop insulin pump:* It has the advantage that it uses only rapid acting analog as a continuous infusion for both basal and bolus doses. Since there is no subcutaneous depot of insulin, there is considerable flexibility. The basal dose too can be varied for different periods of the day (some pumps have provision for programming 48 basal rates through the day, though majority of patients require only four). The bolus can be delivered as a normal bolus, a square wave bolus (for a prolonged meal or a meal with high fat content) or a dual wave bolus (for meals with both rapidly and slowly absorbed carbohydrates and for correcting elevated BG before a meal). The basal insulin infusion can be discontinued during physical activity. Since there is no insulin depot in the body in pump users, mechanical failure of the pump, if undetected, can lead to rapid onset of DKA. Insulin pumps can give excellent control if all other aspects of diabetes self-management (in particular, meal planning with carbohydrate counting, frequent SMBG with corrective insulin supplements) are intensified.

Split-Mix Regimen

In this regimen, one type of insulin is intended to cover one time period: the pre-breakfast short acting covers the period from breakfast to lunch while the intermediate acting works between lunch and dinner; the evening short acting covers the period from dinner to bedtime/midnight while the intermediate acting covers the period from bedtime to pre-breakfast.

- *2 injections regimen:* The patient takes two injections, one pre-breakfast and the other pre-dinner. Generally 2/3rd of the TDD is given before breakfast and 1/3rd before dinner. Each injection is a mixture of rapid or short acting insulin and NPH in the ratio 1:3 for the morning dose and 1:1 or 1:2 for the evening dose.
- *3 injections regimen:* If, on the 2 injections regimen, the BG at 2-3 AM is in the normal range but fasting (pre-breakfast) levels are elevated, stepping up of the pre-dinner intermediate acting insulin to control the pre-breakfast BG may cause nocturnal hypoglycemia. In such cases, it is common to split the evening dose with the short acting being administered before dinner and the intermediate acting delayed to bedtime.

- *1 injection regimen:* This is rarely used, only in the remission phase. A single pre-breakfast injection of intermediate acting insulin *or* short + intermediate acting insulin *or* only a basal analog may give reasonably good control. *A patient should never be started on this regimen*; however as the patient enters the honeymoon phase and insulin requirement drops, the evening shot may become redundant. When on 1 injection, ensure that the blood glucose is in normal range both when the insulin action peaks (late evening) and when the action wears off (pre-breakfast).

It must be noted that the TDD and the distribution of the TDD during the day as indicated in the discussion so far refers to the starting dose. This has to be modified and fine tuned on an ongoing basis with the help of SMBG.

Choice of Insulin Regimen

The choice of regimen would depend on multiple factors: the age of the child, stage of diabetes, financial condition of the family, school timings, motivation of child and parents, and feasibility of giving an afternoon shot and/or multiple shots of insulin.

A basal-bolus regimen should be started at the outset in all patients who can take an afternoon shot of insulin.The split-mix regimens require fewer daily injections (See **Table 3**). However, they are nonphysiological and often associated with high blood glucose levels in the late evening. They may be tried in those children who cannot take an afternoon shot (either because they are in school and the school does not have a nurse or because there is no responsible person at home to give the afternoon shot). Some children may achieve reasonably good control with this regimen if they maintain a fairly constant lifestyle (waking and sleeping hours; school and play and meal timings).

INSULIN SENSITIVITY FACTOR AND INSULIN TO CARBOHYDRATE RATIO

Insulin sensitivity factor is the extent to which the BG is expected to drop (in mg/dL) with 1 unit of regular insulin or rapid acting analog. This factor can be derived by dividing a constant factor (1700 in patients on insulin analogs and 1500 in those on conventional insulins) by the patient's TDD.

The insulin to carbohydrate ratio (or the grams of carbohydrate for which 1 unit of rapid or short acting insulin is needed) is calculated by dividing the constant 500 by the TDD.

Both ratios must be fine tuned on basis of SMBG results.

Intelligent use of these ratios in calculating the pre-meal bolus dose of insulin can help improve the HbA1c significantly.

TABLE 3. Insulin Regimens for Children and Adolescents with T1DM

Common Insulin Regimens	*Pre-breakfast*	*Pre-lunch*	*Pre-dinner*	*Bedtime*
Basal-bolus regimen (using human insulin)	Regular *plus* NPH	Regular	Regular	NPH
Basal-bolus regimen (using a combination of human insulin and analogs)	Regular or rapid acting analog	Regular or rapid acting analog	Regular or rapid acting analog	Glargine* *or* Detemir#
Basal-bolus regimen (using analogs)	Rapid acting analog *plus* Glargine *or* Detemir	Rapid acting analog	Rapid acting analog	Glargine *or* Detemir
Split-mix regimen (2 injections a day)	Regular or rapid acting analog plus NPH	-	Regular or rapid acting analog *plus* NPH	-
Split-mix regimen (3 injections a day)	Regular or rapid acting analog plus NPH	-	Regular or rapid acting analog	NPH

The horizontal columns indicate the time of insulin administration. The vertical rows indicate the insulin regimen and the insulin preparation given at each of the indicated times.

**Though Glargine was originally recommended at bedtime, it can be given at any other (constant) time of the day. Some patients may require two doses of Glargine in a day. Glargine given in the morning may be associated with less nocturnal hypoglycemia.*

#*Most patients would need 2 doses of Detemir in a day.*

COMPLICATIONS OF INSULIN THERAPY

As all insulins available currently are highly purified, the problems of immunoresistance, lipoatrophy and allergy are very rare, unlike in the past. Lipohypertrophy is encountered in patients who do not follow site rotation (see section above). Insulin edema may occur rarely in patients very early in therapy, and is self-limiting.

ROLE OF DRUGS OTHER THAN INSULIN IN T1DM

Metformin acts by suppressing hepatic gluconeogenesis. It may be beneficial as an adjunctive therapy in overweight and obese adolescents with T1DM who have a higher than average insulin requirement.

Pramlintide, an injectable amylin analog, acts by delaying gastric emptying, inducing satiety and reducing glucagon release. It has been shown to lower HbA1c by 0.3 to 0.4%, lower insulin requirement and help in weight control. It is approved by FDA only for adult patients with T1DM.

Acarbose, an inhibitor of intestinal glucosidase can limit postprandial blood glucose rise but has not been proven to offer any added benefit in T1DM patients. Abdominal pain, flatulence and diarrhea and abnormal liver function tests are common adverse effects with the drug.

Injectable *glucagon-like-peptide-1 agonists* and oral *dipeptidyl-peptidase-4 inhibitors* (which act by mechanisms similar to amylin) and oral *sodium-glucose co-transporter 2 inhibitors* (which act by decreasing glucose reabsorption in the renal tubules) are being studied in T1DM patients.

5

NUTRITIONAL MANAGEMENT

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- A dietician with special interest in pediatric diabetes must be an integral part of the diabetes management team.
- Children and adolescents with T1DM do not routinely need a special diet (exceptions are those with obesity, hypertension, hyperlipidemia, nephropathy and celiac disease).
- Caloric requirement is calculated as for any non-diabetic child. Normal growth is the best indicator of caloric sufficiency.
- Meal planning is of utmost importance:
  - To match insulin, exercise and meals,
  - To regulate intake of dietary items that can increase the risk of hypertension, macrovascular and macrovascular diseases,
  - To prevent hypoglycemia especially in relation to exercise and during night hours, and
  - To prevent hypoglycemia and ketoacidosis during intercurrent illnesses.
- Fixed timings and predetermined carbohydrate content for each meal from day to day are necessary for patients on split-mix insulin regimen. They can be given a carbohydrate exchange list to avoid monotony.
- Those on a basal-bolus regimen can have considerable flexibility in their meal timings and content with the intelligent application of carbohydrate counting and insulin to carbohydrate ratio.
- 50-60% of calories should be provided as carbohydrate. Sucrose is not forbidden but is better avoided. Complex carbohydrates and foods with low glycemic index give better postprandial control.
- A high fiber diet may confer some benefit in children above 2 years of age.
- Salt intake should be regulated to reduce the risk of hypertension.

- 30% of calories should come from fats, with restriction of saturated fats to <10% and elimination of trans fats.
- Protein intake should not be higher than that recommended for normal children. Protein restriction is sometimes recommended for patients with microalbuminuria, but is of doubtful benefit.
- Sweeteners may be used if necessary.
- Diabetic snacks are not recommended.
- Routine vitamin and mineral supplementation is not required.
- Instructions on "eating out" must be provided.

INTRODUCTION

A dietician with special experience in pediatric diabetes and carbohydrate counting should be an integral part of the team caring for the patient with T1DM.

IS THERE NEED FOR A SPECIAL DIET?

Children with diabetes do not need a restrictive or special diet. They should be advised to eat all healthy foods in right amounts and avoid eatables, which are considered harmful to health. The entire family should convert to eating only healthy food. The "silver lining in the dark cloud" when a child is diagnosed with diabetes is that the overall health of all other family members would improve if this simple guideline is followed.

A special diet would be needed only in the following situations:

1. If the child is *obese*: calorie restriction.
2. Presence of *microalbuminuria*: protein restriction to the amount recommended for a child of that age group, without diabetes.
3. *Hypertension*: salt restriction.
4. *Hyperlipidemia*: reduce fat intake to 25% of total calories, saturated fat to <7% and increase consumption of monounsaturated fatty acids or MUFA and omega-3 fatty acids.
5. *Celiac disease*: gluten free diet.
6. *Pernicious anemia*: vitamin B12 supplementation, though this may have to be given parenterally.

ROLE OF MEAL PLANNING

Careful meal planning is a must for children and adolescents with T1DM.

Meal planning is necessary for the following reasons:

1. *To ensure normal growth and prevent obesity* (the latter being common in adolescents with T1DM.)
2. *To match food intake (in particular, carbohydrate intake) to the action profile of insulin*. Whenever possible one should try to select an insulin regimen to match the child's preferred eating pattern.
3. *To ensure that the patient eats healthy foods*. The intake of food items that could predispose to hypertension, microvascular and macrovascular diseases must be regulated, as these conditions are more common in T1DM than in the general population. Further modifications in diet would be needed to prevent the progression of these complications if they are detected at an early stage.
4. *To prevent hypoglycemia*, especially at night and in relation to exercise.
5. *To help prevent ketoacidosis or hypoglycemia during intercurrent illnesses*.

DETERMINING CALORIC REQUIREMENT

The caloric requirement of a child with T1DM is calculated as for any non-diabetic child of the same age, weight, gender and race and level of activity. However, it must be kept in mind that the child's appetite and growth are more important determinants of caloric adequacy than any formula.

The caloric requirement is higher than normal soon after diagnosis and after recovery from DKA. This phase lasts till the pre-illness weight has been regained (being the period of catch-up growth after a state of "starvation amidst plenty").

Importance of Growth Plotting

Growth must be plotted on appropriate growth charts once in 6 months.

Inadequate weight gain or weight loss detected on serial growth plotting, would point to the possibility of insufficient caloric intake. Other causes that need to be considered include poorly controlled diabetes, comorbidities including hyperthyroidism, celiac disease, Addison disease, or an eating disorder or an associated chronic illness such as tuberculosis.

Excessive weight gain could be due to overeating with over-insulinization. Other possibilities include hypothyroidism and frequent hypoglycemia with over-correction.

MATCHING INSULIN AND FOOD INTAKE

The meal plan should be finalized in consultation with the patient and parents. The plan should be built around the child's preferred eating habits (timing and type of meals). In order to ensure compliance, changes in the child's pre-illness

meal timings and habits should be made only if they are essential. This is now possible thanks to the more flexible basal-bolus insulin regimens, coupled with frequent SMBG, knowledge of carbohydrate counting and intensive patient education.

Carbohydrates are the chief proximate principals in food that influence blood glucose. Insulin (dose and action) needs to be matched to the carbohydrate intake (rather than calorie content) at each meal. Protein and fat do not have an immediate effect on blood glucose; however, they do contribute to blood glucose rise after many hours of ingestion.

If a patient is on a *split-mix regimen* taking a fixed insulin dose from day to day, the carbohydrate content too should be fixed for a given meal from day to day. Ideally there should be three main meals, two mid-meal snacks to cover the peak hours of insulin action plus a bedtime snack to prevent nocturnal hypoglycemia. The child can be given a sample diet and for each item in the sample diet a list of alternatives with similar carbohydrate and calorie content should be provided. The patient can use this exchange list to avoid monotony in the diet.

If the child is started on a *basal-bolus regimen* (especially with the use of insulin analogs) or on the insulin pump it is possible to have far greater flexibility. Meals can be delayed or even omitted, and the carbohydrate intake at a meal can be varied from day to day. To make this possible, the patient would need to calculate the pre-meal insulin dose to match the anticipated carbohydrate intake at that meal. Patients must be taught the carbohydrate content of common foods and snacks and individualized insulin to carbohydrate ratios must be established for different times of the day.

Insulin to Carbohydrate Ratio

This ratio can be calculated using the formula, 500 (300 for toddlers) divided by total daily dose (TDD) of all insulins taken during the day. The value thus obtained represents the grams of carbohydrate that would be covered by 1 unit of rapid acting insulin. Using this ratio, the patient takes a bolus dose just before eating, after estimating the amount of carbohydrate in the meal. Fine-tuning of this ratio is done by checking the blood glucose before and 2 hours after the meal. If the post-meal rise is not more than 60 mg/dL, the ratio is correct; if it is more, the ratio would need to be revised.

Learning Carbohydrate Content of Common Foods

Patients must initially weigh and measure the foods that they commonly eat. They should be trained to recognize the portion size that represents 15 grams of carbohydrate from the visual impression of the amount of the food item (in

uncooked as well as in cooked form) in a plate as well as in a cup or bowl. For this purpose, they should be supplied with *standardized* measures (food weighing scale, spoons, measuring beakers, *katoris,* cups, bowls and plates). Patients must also be taught how to read and analyze food labels of packaged foods. They should be provided with written material on carbohydrate counting for Indian foods and snacks.

WHAT IS HEALTHY EATING?

Carbohydrates

Of the total calories in the diet 50-60% should be derived from carbohydrates. Carbohydrates are consumed as fruits, vegetables, cereals, legumes (peas, beans or lentils) and milk. The traditional Indian diet is high in carbohydrates. Low carbohydrate diets are not recommended, as carbohydrates are important sources of energy, fiber, vitamins and minerals.

Digestible carbohydrates are classified as starches and sugars. *Starches* are complex carbohydrates; they are slowly digested and absorbed and hence do not produce a rapid or sharp rise in blood glucose. They also contain other nutritional components and fiber. They are consumed in natural or in refined forms; the former should be preferred. *Sugars* (glucose, fructose, lactose and the table sugar or sucrose) occur naturally in foods (fruits, milk, and vegetables) or may be added in manufacturing or before consumption; they produce sharper swings in blood glucose.

Western guidelines recommend that up to 10% of the total calories may be consumed as sucrose so long as it is part of a fiber rich meal, and spaced out through the day. Sucrose provides only "empty" calories, has an adverse effect on dental health, and snacks with sucrose are usually high in saturated fat content as well. Hence, we prefer to advise our patients against adding sucrose to beverages or eating sucrose-containing snacks. Ice creams and chocolates may occasionally be permitted, specifically for the prevention of hypoglycemia before prolonged exercise. The reason for making this calculated concession is that total denial of these tempting items would lead to non-compliance.

Foods that produce slower and lower postprandial blood glucose (PPBG) excursions are to be preferred; these foods are said to have a low *glycemic index (GI).* The GI compares PPBG response to constant amounts of different carbohydrate containing foods. It measures the rise above fasting in BG area in the first 2 hours after ingestion of 50 g of the carbohydrate under study compared with the response to a reference food (glucose or white bread). Foods with a low GI are those that produce lower rise in BG over the first 2-3 hours after ingestion.

- *Low GI foods* include *chapattis* and bread made from whole wheat, Bengal

gram and gram flour, oats, barley, soybeans, kidney beans, peas, lentils, cashew nuts, pasta, noodles, temperate fruits (strawberries, apple, peach, pears, plum, apricots, cherries and oranges), full cream milk and yoghurt.

- *Foods with high GI* include white bread, white rice, puffed rice, *jowar, ragi,* maize, semolina, tapioca, cornflakes, potatoes, tropical fruits (pineapple, papaya, mango and watermelon) and honey.

GI depends on multiple factors other than the type of carbohydrate. These include the style of cooking, state of ripeness, degree of processing and macronutrient distribution of the meal of which the carbohydrate is a part. A recent meta-analysis showed a 0.4% decline in HbA1c with low GI foods as against high GI foods, with some reduction in hypoglycemia episodes.

Fiber

Indigestible carbohydrates present in food are designated as "dietary fiber" or "unavailable carbohydrates". As fiber is not digested, it does not contribute to calories. A fiber intake equal to the child's age in years plus 5 g is known to be beneficial. The traditional Indian diet is naturally high in fiber content.

To increase fiber intake, patients should be advised to consume whole fruits with skin, vegetables, legumes, oats, beans and whole grain cereals.

Soluble fiber improves total and LDL cholesterol levels by binding to bile salts, slows carbohydrate absorption by delaying gastric emptying and thus gives a flatter blood glucose curve and may reduce insulin requirement. Good sources of soluble fiber include dried beans, peas, oat bran, lentils; apples, oranges, pears, plums, bananas, prunes, figs, raisins; and root vegetables.

A high fiber diet is not recommended in children below 2-3 years of age, as they need a calorie-dense diet.

Certain precautions need to be taken when going on a high fiber diet: introduce gradually; step up water intake; anticipate flatulence, abdominal cramps and bloating; and provide supplements of calcium and trace elements, particularly iron and zinc.

Protein

The protein requirement is 2 g/kg at 1 year, 1 g/kg at 10 years and 0.8-0.9 g/kg in adolescence. Protein intake should be 15-20% of the caloric requirement. Higher protein intakes are not recommended.

Proteins from animal sources (fish, milk, egg white, poultry and meat) are of better quality than those from vegetarian sources (soya, beans, and lentils) as they provide all essential amino acids. Proteins from vegetarian sources are accompanied by fiber and complex carbohydrates and contain less of saturated

fat in contrast to those from animal sources which are more likely to be associated with higher salt and saturated fat content. When consuming non-vegetarian sources of protein, skin and visible fat should be removed. Replacement of animal protein with soya protein has been shown, in some studies, to reduce low density lipoprotein (LDL) cholesterol, triglycerides, albuminuria and C-reactive protein (CRP).

If a patient develops microalbuminuria, protein intake in excess of the normal recommendation should not be allowed since increased glomerular perfusion or filtration is a key factor in progression to nephropathy. Microalbuminuria cannot be prevented by consuming a lower than normal protein diet.

Fat

Fats should provide 30% of total calories (35% in infants below 2 years of age). All fats provide the same number of calories (9 calories per g) and contribute equally to weight gain, but some are beneficial to the cardiovascular system while others can be harmful. Hence attention needs to be paid to both the amount and the quality of fat in diet.

Saturated fat consumption should not exceed 10% of the total calories. Higher intakes are associated with increased risk of cardiovascular disease. Saturated fats are the main components of LDL cholesterol. They raise serum total cholesterol (LDL as well as HDL). They are chiefly derived from animal sources including dairy products. They are found in egg yolk, flesh foods, poultry skin and in those fats that are solid at room temperature (coconut oil, palm oil, butter, ghee and cream). Non-vegetarian foods with low saturated fat content are fish, lean meat and poultry without skin and fat. In patients with raised LDL cholesterol, the saturated fat intake needs to be reduced to below 7% of total calories while cholesterol intake should be less than 200 mg per day. Recent guidelines however suggest that dietary cholesterol may not be a major contributor to blood cholesterol levels.

Unsaturated fats are classified as polyunsaturated and monounsaturated fatty acids. They are mainly derived from plant and vegetable sources. These fats have beneficial effects on LDL cholesterol and in the case of monounsaturated fatty acids, also on HDL cholesterol. They help to reduce the risk of cardiovascular disease.

Polyunsaturated fatty acids (PUFA) should make up not more than 10% of calories. These are essential fatty acids, as they are not synthesized in the body. They are classified as omega-6 and omega-3 fatty acids. Both have cardioprotective effects especially by reducing pro-inflammatory markers and raising the anti-inflammatory markers of atherogenesis. Omega-6 PUFAs reduce LDL cholesterol while omega-3 PUFAs lower serum triglyceride.

Omega-6 PUFA is found in various oils used in cooking (safflower, sunflower, soya, cottonseed, corn, canola, peanut and sesame) and in pulses, vegetables, cereals, nuts, seeds, eggs and poultry. Most diets provide adequate amounts of this fatty acid.

Omega-3 PUFA is not found in foods as freely as omega-6 fatty acids. Cold water fatty fish (mackerel, salmon, sardine, herring and tuna) are good sources and their intake would be particularly beneficial if the patient has high triglyceride levels. For the vegetarian, flaxseeds, walnuts, soybean, canola oil, kidney beans, tofu, broccoli, spinach, cauliflower, and Chinese cabbage are good sources of omega-3 fatty acids.

Monounsaturated fatty acids (MUFA) are the healthiest fats. They should make up 10-20% of the total calories. They are found in olive, canola, groundnut, peanut, sesame, rice-bran and mustard oils and in almonds and avocados. A diet using monounsaturated fat, rather than carbohydrate, to lower saturated fat intake gives better postprandial blood glucose levels with equivalent lowering of LDL cholesterol; however it may cause undesirable weight gain and does not significantly improve HbA1c levels.

Trans fatty acids are produced by heating liquid vegetable oils in the presence of hydrogen (partial hydrogenation) to make them less liquid. They are found in processed foods, commercially prepared fried fast foods and bakery products. They not only raise LDL cholesterol but also lower HDL cholesterol, making them even more dangerous than saturated fats. There is no documented beneficial role for them in the human body. Patients must be told to avoid any product containing "hydrogenated oil" or "partially hydrogenated oil".

It should be borne in mind that focus on carbohydrate counting may lead to a higher consumption of carbohydrate free foods, most of which, unfortunately, are high in saturated fats and cholesterol.

Salt

Children with T1DM are more likely than non-diabetic children to develop hypertension. At the same time, they are more likely to consume higher amounts of salt as the stress is on a "non-sweet" diet. It would be prudent to restrict salt to 2 g per 1000 calories. Further restriction may be indicated if hypertension sets in.

Patients should be advised to restrict canned or packaged foods, baked products, pickles, *pappad,* sauces, and Chinese food. They can use flavor enhancers such as herbs, lemon juice, vinegar, spices, onions, tamarind, and green pepper.

Vitamin and Mineral Supplementation

Studies have documented that vitamin D deficiency may be associated with significantly reduced insulin sensitivity and higher insulin requirement. Repletion

of vitamin D has been shown to improve diabetes control. It is important to look for and correct vitamin D deficiency in all patients with diabetes. At the same time, an adequate intake of calcium, in the form of low fat dairy products, is essential.

Routine provision of other vitamins and minerals is not indicated except in patients who are on a restrictive diet, or have celiac disease, pernicious anemia or achlorhydria.

Potassium supplementation is important for patients recovering from DKA till they reach the pre-DKA weight.

Diabetes puts body tissues under increased oxidative stress. However, there is no evidence that increasing consumption of antioxidants improves health outcomes. Fresh fruits and vegetables are good natural sources of anti-oxidants.

Sweeteners

Sweeteners are classified as nutritive and non-nutritive. Of the nutritive sweeteners, fructose contains calories similar to sucrose but with a lower GI; fructose has a GI of 29 as against 69 of sucrose. However, fructose may have an adverse effect on serum lipids and hence its use as a replacement for sucrose in the diet is not recommended. The sugar alcohols such as xylitol, sorbitol and mannitol contain half the number of calories found in sucrose and have a better GI. They are considered safe, though in excess, they may cause diarrhea.

Nutritive sweeteners are included in diabetic snacks. Diabetic snacks have no role in dietary management of T1DM, as sucrose is no longer considered "out of bounds". Further, these snacks are often high in calories and saturated fat content.

The non-nutritive (artificial) sweeteners are virtually calorie-free. These include aspartame, sucralose, stevia, saccharin and acesulfame potassium. All are fairly safe in amounts recommended by the American Diabetic Association, but most children can do without them.

PREVENTION AND MANAGEMENT OF HYPOGLYCEMIA

All children with diabetes must carry a plastic pouch with 3-4 teaspoons of powdered sugar or glucose for prompt ingestion in case of symptoms of hypoglycemia. Children must also carry a fruit or a few biscuits with them when in school or college; in case for some reason there is a delay in returning home for a meal. (See Chapter 10 "Hypoglycemia" for more details.)

Patients must be instructed on the importance of ingesting a snack prior to unaccustomed (not part of daily schedule) physical activity; approximately 1.0-1.5 g carbohydrate per kg body weight for 60 minutes of exercise. This snack

should provide a readily absorbable form of carbohydrate plus a sustained supply of carbohydrate for prolonged activity. (See Chapter 9 "Physical exercise" for more details.)

An additional bedtime snack to prevent delayed post-exercise hypoglycemia after intense evening exercise is also important. The role of the nocturnal snack cannot be over-stressed, as the frequency of hypoglycemia is highest at night in sleep. The bedtime snack should have a low glycemic index with protein and fat in addition to starch to cover the long hours of fasting during sleep.

MEAL PLANNING ON "SICK DAYS"

When the child is unwell, anorexia may lead to hypoglycemia while elevated levels of the counter-regulatory hormones can cause hyperglycemia and even ketoacidosis. Meal planning plays an important role in preventing both hypoglycemia and ketoacidosis during intercurrent illnesses. (See Chapter 13 "Sick Day Management" for more details.)

If the illness is accompanied with the appearance of ketones and a blood glucose level above 180 mg/dL, the child should be coaxed to have plenty of salty liquids to compensate for polyuria, prevent dehydration, and replace salt loss in urine.

On the other hand, if blood glucose is below 180 mg/dL, with presence of ketones in urine or blood the patient should be encouraged to have sweet liquids to prevent hypoglycemia while insulin administration can be continued to correct the ketosis.

On sick days small, frequent meals and cool liquids of child's choice are better accepted and tolerated.

PERIODIC REVIEW AND REINFORCEMENT OF MEAL PRESCRIPTION

Children and adolescents with T1DM should visit a dietician once in 6 months as meal requirements may change rapidly on account of fast growth, puberty and frequent changes in activity and school schedules in this age group. Patients should periodically weigh foods to have a better concept of portion sizes.

ROLE OF SELF-MONITORING OF BLOOD GLUCOSE (SMBG)

SMBG plays an important role in fine-tuning the meal plan. This tool should be used by the patient to study the effects of various foods and physical activities on blood glucose levels in different situations and to periodically revise their insulin to carbohydrate ratios. Experience gained from SMBG is the best guide for perfecting the meal plan.

DIET IN INFANTS AND TODDLERS

In the first 6 months of life, exclusive breastfeeding or a humanized infant formula is recommended. After 6 months, weaning foods in the form of cereals and pulses, fruits, vegetables and meats should be gradually introduced.

After 9 months of age, the rate of weight gain and consequently the appetite decline significantly, causing parental anxiety. Parents must be informed that this is natural. Further, they must be counseled that babies at this age are negativistic by nature and so forced feeding or coaxing may prove counterproductive, leading to food refusal and a difficult behavioral problem.

Small, frequent meals should be offered. Toddlers eat best by imitation and hence the infant above 9-12 months should be made to sit with the mother (if not the entire family) to eat. Toddlers are attracted by the appearance of the food; hence decorating the meal well can go a long way in improving compliance. Meal times should be pleasant. Toddlers cannot resist temptation: unhealthy snacks and junk foods should therefore not be kept in the house ("out of sight is out of mind") and under no circumstances should these be offered as rewards. Bottle-feeding or breastfeeding should never be used to put the toddler to sleep (See Chapter 22 "Diabetes in Toddlers" for more details).

EATING OUT

Children and particularly adolescents will need to eat out periodically under peer pressure (if not personal choice). The dietician must check with the patient and the family the eating-houses that are likely to be frequented and then guide them on the most appropriate items to order at each such place and the carbohydrate content of those meals or snacks. With knowledge of the carbohydrate content of the eatables and using the child's individual insulin to carbohydrate ratio it is possible to ensure that the blood glucose is not adversely affected when eating out.

COMPLIANCE WITH THE MEAL PLAN

Compliance with the meal plan is difficult to achieve. There is often a huge gap between knowledge and its implementation. This is due to various factors: individual, social and environmental, which must be carefully addressed. These factors include faulty cooking and eating habits of the family, emotional state of the child, forced feeding by parents, exposure to television advertisements, food faddism, peer pressure when eating away from home, sharing of food or snacks in school, frequent parties, unrealistic "standardized" diet prescriptions and an eating disorder to mention a few. Appropriate counseling of the parents, siblings and in a joint family, the grandparents, is necessary. Informing the school authorities about the dietary needs of the child (not missing a meal and additional snack before unaccustomed activity) is essential.

Patients must be helped to identify and overcome barriers to healthy eating. Maintaining and analyzing a diet diary can serve as an eye opener for detecting and correcting flaws in eating habits. Parents should be encouraged to set time bound goals for improvement in meal habits; positive reinforcement must be provided when these goals are met.

SPECIAL DIABETIC SNACKS

Diabetic cookies, pies, cakes, and candies mislead the diabetic patient into believing that decreasing sucrose or sugar intake is all that is needed to regulate blood glucose levels. Most of the "diabetic" snacks are high in calories and fat – they belong to the times when sucrose was forbidden. They have no role in modern nutritional management of T1DM.

6

HOME MONITORING

M. Vijayakumar

SUMMARY OF RECOMMENDATIONS

- Self-monitoring of blood glucose (SMBG) is the best method for good glycemic control and should be practiced in all children with diabetes.
- SMBG measurement should be done at 4-6 times a day and include measurements before major meals (breakfast, lunch and dinner) and at bedtime.
- It should also be done 2 hours after meals and during night hours (12.00 AM – 3.00 AM) in some situations for better control.
- It should be monitored before and after exercises, during sick days and during hypoglycemic episodes.
- Inadequate monitoring results in increased incidence of long-term complications like retinopathy, nephropathy and neuropathy.
- Insulin doses and carbohydrate intake should be adjusted based on SMBG results.
- Patients and caregivers should record each reading in a logbook and should bring it in the clinic visit regularly.
- Blood/urine ketones should be measured whenever the child is sick or blood sugar levels are above 250 mg/dL.

INTRODUCTION

The greatest revolution in this decade in the management of childhood diabetes is the invention of newer techniques to measure blood glucose (BG) levels and the empowering of patients and their caregivers to modify the treatment based on BG tests done at home. Various studies have established an inverse correlation between frequency of self-monitoring of blood glucose (SMBG) and HbA1c values. The newer glucometers are based on glucose oxidase-based electrochemical methods, and are very accurate (within 5-10% of laboratory standards), fast and require only a small amount of blood (0.1 mL). Previous home monitoring tools such as urine sugar measurements are unreliable and are no longer recommended.

IMPORTANCE OF REGULAR BLOOD GLUCOSE MONITORING

- Each BG reading provides vital information regarding the glycemic status in response to insulin received, food consumed and the exercise done by the child.
- Decisions can be taken regarding adjustment of insulin dose, food pattern and exercise.
- Good glycemic control reduces the risk of long-term complications such as retinopathy, nephropathy and neuropathy as well as macrovascular complications.
- Insulin dose can be adjusted during illness.
- Acute complications such as hypoglycemia and its response to treatment can be assessed more effectively. This is particularly useful in children with hypoglycemia unawareness.

Measuring HbA1c is not a "replacement" for SMBG (as some people believe), because SMBG provides a more real-time feedback of glycemic status and can identify hypo- or hyperglycemia at any point of time. HbA1c levels on the other hand reflect the mean blood glucose level of the past 2-3 months.

TIMING OF BLOOD GLUCOSE TESTING

In ideal situations, daily pre- and post-feed BG levels during breakfast, lunch and dinner plus daily bedtime BG measurements and occasional (1-2 times a week) nighttime measurements should be done to get an accurate glycemic status (**Table 1**). At least four BG tests daily are required for a reasonable assessment. These should be scheduled before breakfast, before lunch, before dinner and at bedtime. Occasionally additional BG testing may be required 2 hours after meals and during late night. Ideally testing 2 hours after breakfast and lunch should be encouraged daily or as often as possible, taking into account compliance, motivation, affordability and cooperation by school authorities. Importance must be given to hesitation on the part of the child to test at school and appear different from his or her peers, especially if the child expresses such concerns. Having said that, many adolescents in Indian schools do test and/or take insulin injections without any difficulty. Therefore, the onus is on the medical fraternity to increase awareness and decrease compromise. Late night testing should be encouraged as often as possible but at least weekly. Each result has its own importance in diabetic control.

TABLE 1. Ideal Recommendations for SMBG

- Four times per day, before each major meal and at bedtime.
- 12.00 Midnight – 3.00 AM once in 1-2 weeks.
- Postprandial samples (2 hours after food) to be done whenever necessary.
- Additional tests: When hypoglycemia is suspected, before and after exercise, and during illness.

Each high pre-meal BG value indicates how much additional regular/rapid insulin is to be taken on that occasion; high (or low) post-meal values help us alter future regular/rapid insulin doses. The post-meal BG is to be used for adjusting the dose of the preceding pre-meal bolus insulin (e.g. if post-breakfast BG is high, increase the pre-breakfast bolus insulin). If the post-meal BG is in the target range but the following pre-meal BG is high then the basal insulin for that section of the day needs to be adjusted (e.g. if post-breakfast BG is normal but pre-lunch is high then the basal insulin for that section of the day is to be stepped up).

Pre-breakfast BG testing is probably the most important of all measurements. It reflects the glycemic control at night. This value is closely related to the amount of basal insulin given at night. If the pre-breakfast (fasting) BG is high, one must look at the 2-3 AM value before making any dose adjustments**.** If the latter is also high, then the basal insulin that covers the night hours needs to be increased. If, however the 2-3 AM BG is low, then either the basal insulin needs to be reduced or an additional bedtime snack of low glycemic index (GI) is required or, in case the basal insulin happens to be NPH insulin, it should be shifted to bedtime (rather than pre-dinner, if that is the case) so that its peak is delayed.

Results of pre-lunch and pre-dinner BG levels are controlled by morning and pre-lunch doses of regular insulin respectively. This value is also affected by the morning dose of basal insulin like NPH. Further, this value will be affected by the evening outdoor activities. Timing and amount of evening snacks (usually taken by our children after returning from school) also affects this value. Bedtime testing is important to know the effect of rapid acting/regular insulin given before dinner. This value is also important in children who develop nocturnal hypoglycemia. If bedtime BG values are low (< 80 mg/dL), extra snacks should be given to prevent hypoglycemia at night and ideally late night testing should be again done.

In our country, the gap between morning regular insulin and pre-meal blood test at lunch is usually about 6-8 hours, and by that time, the effects of both

morning regular and basal insulin might have vanished from action. Similarly, the gap between the lunch and pre-dinner glucose reading is about 6 hours. Hence in such situations, pre-lunch and pre-dinner values have to be managed by altering the dose of basal insulin. Another practical problem we often face is that, intake of school snack will be less. Hence, in such case, additional regular insulin before evening snack (between 4.00 and 5.00 PM) as soon as the child arrives from school is recommended.

In a motivated patient, we can go for pattern adjustment of BG at regular intervals with the help of a member of the medical team. Insulin supplements or corrective supplements (based on the 1800 and 1500 rules) should be taught to all affected children who understand the concepts and can apply it reliably. This method usually applies to those who follow a fixed carbohydrate meal plan.

For the more intelligent and motivated patients who use carb counting (including those on continuous subcutaneous insulin infusion, CSII), insulin supplements are very important. The pre-meal BG is used for calculating the corrective supplement (using the insulin sensitivity factor) and the pre- and post-meal BG levels together are analyzed to fine-tune the insulin sensitivity factor (ISF) and the insulin to carb (IC) ratio.

Blood glucose should be monitored when the child "feels" hypoglycemic and should be repeated after treatment to see whether he/she had improved. Frequent monitoring should be done before and after exercise. During sick days frequent monitoring is required to prevent hyperglycemia leading to diabetic ketoacidosis (DKA) or a hypoglycemic episode.

It is not possible to make longer-term change in insulin doses with a single BG reading. The pattern of BG levels is more important rather than individual values for long-term changes. The main obstacles for multiple readings are multiple pricks and especially in our country, cost of the strips. We may have to compromise with less frequent BG estimations. For reducing the risks of long-term complications, both fasting and postprandial glucose levels are important. If HbA1c is high, the fasting BG level is a better indicator, but if HbA1c levels are approaching the normal level (<7.3%), post-feed level is a better indicator of glycemic control. If HbA1c is high, we may need to target fasting and pre-meal BGs first; if HbA1c is approaching optimal values, then we must turn our attention to post-meal BGs also, to detect swings in BG readings and bring out undetected midnight lows.

PRECAUTIONS WHILE USING BLOOD GLUCOSE METERS

- Check whether the glucometer is working properly by the use of control solutions.

- Check the unit in which the result is expressed in the meter. The readings may be in mmol/L or mg/dL. Use the appropriate conversion factor (1 mmol/L= 18mg/dL).
- Use a meter with its matching strips.
- Always see whether expiry date is over.
- Some meters require to be coded before using each batch of strips. This is because of the batch-to-batch variation in the chemicals used. The meter reading will be inaccurate if the coding is not done. Some meters do not require coding as they come precoded.
- Strips should be discarded after use.
- Do not keep the strip at high (> 90^0) or low temperature (frozen).
- Hematocrit affects the reading. High hematocrit (slower diffusion leading to slower reaction rate) results in low reading and vice versa.
- Meters should be brought to the clinic during each visit for calibration.
- Ideally meters should read within the 10% of a reference laboratory value. It is to be noted that plasma glucose value is 10-15% higher than the whole blood glucose level.

PRECAUTIONS TAKEN BEFORE BLOOD TESTING

- Hands should be washed with warm water (in addition to cleaning the hands it will also increase the local blood flow) and air-dried.
- Alcohol wiping is less preferred because alcohol will interfere with the chemical reaction and give faulty results.
- Place the finger on the table before pricking (otherwise the child will withdraw the fingers resulting in an inadequate prick).
- Side of the fingers should be used. Fingertip is more painful.
- Do not use the same fingertips always. Rotate the fingers every time.
- Other sites including upper arm, forearm, and fleshy pad at the base of the thumb, back of the calf can be used, but the results are not reliable. Alternative sites are usually slower to reflect a falling BG level; hence it is preferable to use fingertips when hypoglycemia is suspected.
- Change the lancet after using it three times or when it is blunted and dispose it safely in a sharps box or an improvised sharps box like a powder or shampoo bottle.
- Do not share lancets.

DOCUMENTATION OF THE BLOOD GLUCOSE LEVELS

Always document:

- The timing of blood test.

- When (how many hours before) was the last meal taken and what were the amount and type of food or drink taken?
- The amount of insulin (both basal and bolus) administered.
- The activity done by the child (playing, walking, running etc.)

The child should be provided a logbook to enter these details in a tabular format. The patterns of BG readings are more important than individual values. Hence an honest recording of all the results done at a specified time is very important. An example of a logbook is given below (**Fig 1**).

Fig 1. Example of a logbook to be used for recording SMBG, insulin dose, carb count and other details

Name:						**Age:**		**Weight:**		**Insulin dose:**		
Date	*Breakfast*			*Lunch*			*Dinner*			*Bedtime*	*Night*	*Other*
	Pre-feed	Post-feed	Carb/ Insulin	Pre-feed	Post-feed	Carb/ Insulin	Pre-feed	Post-feed	Carb/ Insulin	Carb/ Insulin		

This is the ideal method of keeping a logbook but is not done in many situations. Routinely checking pre-meal and bedtime glucose reading with post-meal and night-time BG measurements as and when required is a good alternate option. In many children 4-6 BG testing per day is not practical due to financial constraints or due to various other reasons. Hence 2-3 SMBG measurements per day by rotating the time of BG measurement is another option once the child is stabilized. An example of such a strategy is given below (**Fig 2**).

Fig 2. An example of rotating 3 tests per day SMBG

Days	***Breakfast***		***Lunch***		***Dinner***		***Bed time***	***Carbs***	***Insulin dose***
	Pre-feed	Post-feed	Pre-feed	Post-feed	Pre-feed	Post-feed			
Monday	√	√					√		
Tuesday			√	√			√		
Wednesday	√				√	√			
Thursday	√	√					√		
Friday			√	√			√		
Saturday	√				√	√			
Sunday	√	√					√		

If the strips are very scarce, testing 4-5 readings on a particular day in a week can be tried. But the results are not satisfactory.

HOW TO ADJUST THE INSULIN DOSE?

If the BG levels are always outside the target limits, in the absence of exercise or abnormal diets to explain this variation, insulin dose should be changed. A guideline for adjusting the insulin dose is given below.

- If the fasting BG is high, the evening dose of long acting insulin is increased by 10-15% (or additional fast acting insulin coverage for bed time snacks).
- If the pre-lunch BG levels are high, morning dose of fast acting insulin/NPH/ Glargine is increased by 10-15% or better still, a regular or rapid insulin dose with school snack is encouraged.
- If pre-dinner BG levels are high, the noon dose of fast acting insulin/basal insulin is increased by 10-15% or a small dose of fast acting insulin can be encouraged with evening snack especially in adolescents.
- If bedtime BG levels are high, night dose of fast acting insulin is increased by 10-15%.
- Similarly, reduction in insulin dose can be made if the corresponding BG levels are below the target range.

Some tips about SMBG values are given below:

- If the SMBG values are consistently high, the patient requires more insulin.
- If the values are consistently low his/her insulin doses should be reduced.
- If the readings are erratic (high some times and low sometimes) his/her insulin dose, method of storage and administration, food intake or his/her activity may be inconsistent and need a detailed evaluation or counseling.

The target indicators of optimal glycemic control using SMBG levels are given in **Table 2.**

URINE GLUCOSE TESTS

Urine glucose testing is more economical, easier and is a painless procedure but it has many limitations. This test will be positive only if BG levels exceed the renal threshold (180 mg/dL). Hence we cannot identify low BG values and cannot predict hypoglycemia. Moreover, the test result reflects the glucose levels of the past 1-2 hours because it will take few hours for the urine to be stored in the bladder after getting filtered from the kidneys. SMBG levels on the other hand give you an instantaneous result of BG status.Children with renal disease may give abnormal results. This test is useful only when BG monitoring is not

TABLE 2. Target indicators of glycemic control (Modified from ISPAD Guidelines 2011)

SMBG Values	Ideal mmol/L *(mg/dL)*	Optimal mmol/L *(mg/dL)*	Suboptimal (Action suggested) mmol/L *(mg/dL)*	High-risk (Action required) mmol/L *(mg/dL)*
Fasting or pre-prandial plasma glucose	3.6–5.6 *(65–100)*	5–8 *(90–145)*	>8 *(>145)*	>9 *(>162)*
Post-prandial plasma glucose	4.5–7.0 *(80–126)*	5–10 *(90–180)*	10–14 *(180–250)*	>14 *(250)*
Bed time plasma glucose	4.0–5.6 *(80–100)*	6.7–10 *(120–180)*	<6.7 or 10–11 *(<120 or >180-200)*	<4.4 or >11 *(<80 or >200)*
Nocturnal plasma glucose	3.6–5.6 *(65–100)*	4.5–9 *(80–162)*	<4.2 or >9 *(<75 or >162)*	<4.0 or >11 *(<70 or >200)*
HbA1c %	< 6.5	< 7.5	7.5 – 9	>9

affordable; it does provide some pattern for modifying the treatment. Hence this can be utilized in resource-poor settings even now. Some important points to note while monitoring with urine glucose are as follows:

- If the urine sugar tests are always positive (indicating that BG >180 mg/dL), insulin doses can be increased and a reduction in carbohydrates can be advised.
- If the urine sugar levels are persistently low and the child is getting frequent sickness (probably hypoglycemic episodes) insulin doses can be reduced and an increase in carbohydrates can be advised.

MEASUREMENT OF KETONES

Methods for ketone should be taught to the children/caregivers and the necessary instruments should be kept with them. The building up of ketones in the blood leads to diabetic ketoacidosis (DKA). This will happen particularly when the child is ill. Early detection of ketones and administration of additional insulin can prevent DKA. Till recently, urine ketone (acetoacetate) measurement was the only option. Now, strips for home blood ketone (β-hydroxybutyrate) measurements are also available, to be used in the BG meter itself. Urine ketone tests are less specific compared to blood tests.

A sick child with labored breathing, vomiting with hyperglycemia and ketonuria/ketonemiahas impending DKA and needs emergency hospitalization.

Table 3 lists the indications for ketone testing at home.

TABLE 3. Indications for Ketone Testing

- If the pre-feed BG levels are > 240 mg/dL or post-feed BG levels are > 300 mg/dL (or a random BG> 250 mg/dL).
- If the child is sick, febrile, or having nausea or vomiting, polyuria, abdominal pain, rapid breathing even if the BG levels are not high.

If the child has DKA or his/her blood glucose levels are not controlled, ketone body measurements are advised at least twice a day. Daily testing is not needed once the child has achieved euglycemia. **Table 4** provides a comparison of blood ketone levels and urine ketone measurements and appropriate interventions.

TABLE 4. Comparison of Blood Ketone Levels and Urine Ketone Measurements

Blood ketones (mmol/L)	*Urine ketones*	*Suggested intervention*
< 0.6	Negative	No treatment is required.
0.6 – 1.5	Small to moderate +	Drink extra fluids containing carbohydrates. Additional dose of fast acting insulin if BG level is > 180 mg/dL.
1.6–3	Large ++	High risk of DKA. Take extra rapid acting insulin and drink extra fluids. Consult diabetic clinic.
>3	Very large +++	Child has DKA. Child needs inpatient care.

CONTINUOUS GLUCOSE MONITORING (CGM)

Devices measuring subcutaneous interstitial fluid glucose levels constantly (every 1-5 minutes) give valuable information regarding patient's glycemic status. Blood glucose targets can be preset, so that an alarm will alert the patient when the glucose levels fall below or above the targets. The CGM instrument consists of a glucose sensor (a tiny electrode, which is inserted under the skin and measures glucose levels in the interstitial fluid), a transmitter and an external monitor for viewing the glucose levels. Some insulin pumps have built-in CGM. The glucose sensor is inserted with a needle, which is removed after the glucose sensor is in place. (Details of continuous glucose monitoring are dealt in detail in the Chapter 17 on CGM.)

GLYCOSYLATED HEMOGLOBIN (HBA1c)

Glucose molecules get attached to hemoglobin molecule irreversibly and form glycosylated hemoglobin (HbA1c). HbA1c reflects the blood glucose status over the last 12 weeks and is the most useful investigation tool to assess the metabolic status of the child. There is a good correlation with HbA1c levels and chronic microvascular complications. A target of < 7.5% is suggested for children (<18 years) with diabetes. (The details are provided in the Chapter 8 on Laboratory monitoring of type 1 diabetes).

7

CLINIC MONITORING

Anna Simon

SUMMARY OF RECOMMENDATIONS

- Clinic visits for a child with diabetes should consist of meetings with a team, not just a doctor.
- The diabetes management team consists of a pediatric diabetes specialist, diabetes educator, dietician, psychologist and social worker. In India, many teams may be incomplete due to lack of trained personnel.
- History should include aspects of schooling, sports, social issues and diabetes knowledge, as well as aspects of diabetes care particularly hypoglycemia.
- Examination should include assessment of growth and puberty, in addition to examination for diabetes-related long-term morbidity.

INRODUCTION

Children and adolescents with type 1 diabetes mellitus (T1DM) should be routinely cared for by an experienced multidisciplinary team consisting of:

- A pediatric endocrinologist or diabetologist or a pediatrician with special interest in diabetes,
- A diabetes nurse-educator,
- A dietician and
- A social worker.

The team would benefit by the addition of a clinical psychologist or psychiatrist. Experienced parents of children with diabetes and elder (grown-up) childhood onset diabetes patients might help the team in counseling.

Coordinated effort by this multidisciplinary team is essential to achieve the treatment goals of:

- Satisfactory biochemical control,
- Maintaining growth and development,

- Preventing acute complications,
- Preventing or delaying late onset complications and
- Ensuring emotional stability of the child and the family **(Fig 1.)**

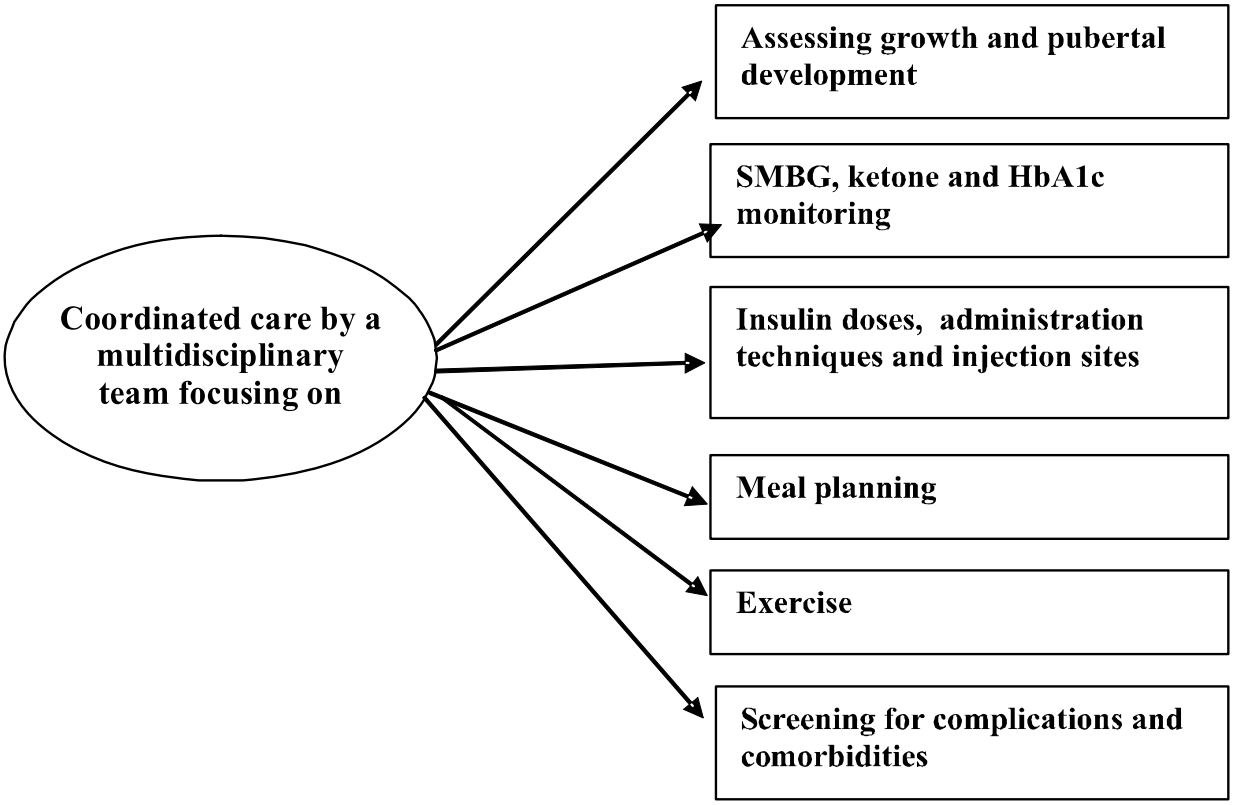


Fig 1. Multidisciplinary Team Care for Diabetic Children

Clinic monitoring essentially comprises of 2 components:

- 2-3 monthly clinic visits:
  - Aiming at assessing glycemic targets and goals and
  - Addressing diagnosed comorbidities and complications
- Annual reviews:
  - Screening for complications and associated comorbidities.

2-3 MONTHLY CLINIC VISITS

Frequent regular follow-up visits every 2-3 months are important for achieving the targets planned with therapy. Clinic visits may have to be more frequent during the first few months following diagnosis. Also the details of SMBG can be communicated to the physician or diabetes nurse-educator every two weeks by telephone, email or fax for assessing adequacy of insulin dosing schedule and if required dosage adjustments.

History

The clinical assessment begins with eliciting history regarding the following:

- General well-being.
- Any recent events disturbing the child's lifestyle.
- Reviewing the results of self-monitored blood glucose ((SMBG) estimations done daily or at least a minimum of 3-4 consecutive days of monitoring every fortnightly.
- Review of insulin therapy with particular attention to adequacy of insulin, injection technique and rotation of injection sites.
- Review of dietary behavior and exercise.
- Any experiences of hypoglycemia, and its causes, such as skipping of meals, uncovered exercise and missed snack. Suspect hypothyroidism, celiac disease or adrenal insufficiency with unexplained hypoglycemia or requirement for reduction in insulin dosage.
- Any failure to gain weight, weight loss, polyuria or polydipsia.
- Review of any associated medical condition especially other autoimmune disorders such as thyroid disease, celiac disease or adrenal insufficiency.
- Review of any symptom suggestive of long-term complications.
- Underlying psychopathology: features of depression, over-eating and altered sleep rhythm.

PHYSICAL EXAMINATION

Growth

Exact measurement of height, weight and pubertal assessment is an integral part of the examination. Height and weight should be monitored carefully and plotted on a growth chart at least twice a year. It is important to use population specific percentile charts and also take mid-parental height into account. (http://iapindia.org/Revised-IAP-Growth-Charts-2015.php is the link to the 2015 Indian Academy of Pediatrics growth charts.) Any deviation from the normal should be identified early and appropriate remedial measures should be undertaken.

Adequate insulin concentrations are required to maintain the GH/IGF-1 axis and promote growth. Children on current management strategies of multiple daily injections (MDI) and insulin pumps exhibit better growth. Poor glycemic control may result in poor linear growth, inadequate weight gain, delayed puberty and delayed skeletal maturation. Other causes of poor weight gain could be an eating disorder, or an associated chronic disease such as tuberculosis, celiac disease

or Addison disease. Conversely, excessive insulin therapy associated either with overeating or with frequent hypoglycemia can result in excess weight gain. Monitoring weight gain is therefore important in planning insulin doses.

Persistent insulin deficiency and poor control of diabetes can lead to Mauriac syndrome characterized by stunting, hepatomegaly with steatosis and delayed puberty.

Pubertal Assessment

Pubertal assessment is an essential part of the clinic monitoring as important hormonal, metabolic and psychological changes occur in puberty which impact on the management of T1DM. The decline in insulin sensitivity requires appropriate readjustment and redistribution of insulin doses to maintain glycemic targets. Psychosocial changes must be monitored and supportive therapy and appropriate referral has to be provided when required.

Blood Pressure

Blood pressure (BP) measurement using an appropriate size cuff and with the patient seated and relaxed should be part of every diabetes physical examination. Hypertension is defined as systolic or diastolic BP >95th centile for age, gender and height percentile, measured on three separate occasions. Children with hypertension should be evaluated for renal functional status and urinary albumin excretion. Therapy with lifestyle modification and ACE inhibitors such as enalapril should be instituted for those diagnosed with hypertension.

General and Systemic Examination

This should focus on insulin injection sites, palpation of the liver, elicitation of the deep tendon reflexes (DTR) and sensations, foot inspection, thyroid gland palpation, limited joint mobility (LJM) and fundus examination. Limited joint mobility occurs due to stiffening of soft tissues due to glycosylated collagen in longstanding diabetes, leading to contracture of small or large joints and waxy skin. It is best elicited by the 'prayer sign', wherein the patient is unable to appose the fingers completely when the hands are folded as in prayer (**Fig 2**). LJM is regarded as a harbinger of chronic microvascular and macrovascular complications of diabetes.

Lipodystrophy

Lipoatrophy is rarely seen nowadays with the use of human insulin, but has been reported with the use of insulin analogs. Lipohypertrophy can occur due to poor rotation of injection sites, reusing needles and with a longer duration of diabetes. Insulin absorption can be unpredictable and erratic from these sites. Avoidance of the affected sites for 2-3 months will promote resolution of the lipohypertrophy.

Fig 2. Folded hands showing inability of the fingers to appose closely, also called the 'prayer sign' *(photograph: courtesy Dr Anju Virmani)*.

Refractive Errors

Transient refractive errors can occur with larger changes in blood glucose levels.

ANNUAL AND PERIODIC REVIEWS

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that annual review for long-term complications should commence from the age of 11 years after 2 years duration and from the age of 9 years after 5 years duration. The American Diabetes Association (ADA) recommends it annually after 5 years duration, after the age of 10 years.

Screening for Associated Autoimmune Disorders

This is recommended at diagnosis and thereafter every 1-2 years or whenever the clinical assessment demands.

Autoimmune Thyroid Disease

Deceleration of height velocity, delayed puberty or a goiter may point towards hypothyroidism. The diagnosis of hypothyroidism is confirmed by elevated TSH

and low free T4 levels. Anti-thyroid antibodies (anti-thyroid peroxidase and/or anti-thyroglobulin) are usually demonstrable in the serum. (See Chapter 8 for details.)

Subclinical hypothyroidism needs close follow-up for evolution into frank hypothyroidism or rarely resolution of the subclinical state. Rarely Graves' disease or transient hyperthyroidism with Hashimoto thyroiditis may also occur in children with T1DM.

Celiac Disease

Celiac disease is often asymptomatic or may present with gastrointestinal symptoms such as intermittent or chronic diarrhea, abdominal pain, anorexia or flatulence. Increase in hypoglycemic events and decreasing insulin requirement are often seen with undiagnosed celiac disease. Poor weight gain, growth retardation, symptoms of malabsorption and concurrent iron deficiency are common with celiac disease. Screening for celiac disease with antibodies to tissue transglutaminase should be done at the time of diagnosis and every 2-3 years thereafter. (See Chapter 8 for details.)

Primary Adrenal Insufficiency

Primary adrenal insufficiency occurs rarely. Addison disease must be suspected in patients with frequent hypoglycemia, decreasing requirement of insulin, increasing skin pigmentation, weight loss or electrolyte imbalance.

Vitiligo

This is rare. Vitiligo, an autoimmune disease characterized by white patches commonly on exposed areas of skin (rarely on mucus membrane and retina) is not life-threatening or physically damaging; but the cosmetic changes may affect psychological well-being of the affected child.

Long-term Complications

Nephropathy

The earliest sign of diabetic nephropathy is microalbuminuria. Microalbuminuria is defined as the persistent urinary excretion of albumin in the range of 30-300 mg/day. Microalbuminuria if treated early, can prevent or even reverse progression of renal disease. The presence of microalbuminuria calls for improved glycemic control, attention to normalization of BP and lipid profile, and treatment with ACE inhibitors.

Retinopathy

Assessment of retinopathy should be done by an ophthalmoscope through dilated pupils by an experienced ophthalmologist. Stereoscopic fundus photography and fluorescein angiography are more sensitive in detecting

background or proliferative retinopathy. The presence of only microaneurysms denotes mild non-proliferative diabetic retinopathy (NPDR); the addition of hemorrhages and hard exudates (protein and lipid leakage) denotes moderate NPDR and severe NPDR is characterized by greater numbers of hemorrhages with venous beading and intraretinal microvascular abnormalities (IRMA). Proliferative diabetic retinopathy (PDR) is present if soft exudates (ischemic areas) and new vessel formations are seen. In addition, maculopathy is given a different staging irrespective of retinopathy and is characterized by exudation and microaneurysms in central retina. Maculopathy is not common in children and adolescents.

If significant retinopathy is present, more frequent reviews by the ophthalmologist is necessary. Risk factors for diabetic retinopathy include longer duration of diabetes, poor metabolic control, presence of microalbuminuria, hypertension, abnormal lipid profile and higher BMI. Interventions should include improving glycemic control and addressing associated risk factors. Laser therapy should be considered for proliferative retinopathy or maculopathy.

Cataracts

Clinical examination of the eye for cataracts should be done soon after diagnosis.

Neuropathy

Neuropathy is rare in children and adolescents with T1DM. The most common neuropathic complication with diabetes is generalized sensorimotor polyneuropathy, which occurs insidiously, first manifesting as sensory loss and later motor weakness. A history of paresthesia, numbness or persistent pain and examination of light touch with graded microfilaments will help in diagnosis.

Macrovascular Disease

Hypertension and atherosclerosis are major risk factors for macrovascular disease. It is important to regularly screen and maintain BP in the normal range (<120/80 mm Hg or <90th percentile for age, gender and height). If persistently >130/80 mm Hg (or >95th percentile), antihypertensive treatment is started. Lipid profile should be performed at onset, after BG control, if there is family history of hypercholesterolemia, and at age 10 years, if there is not. Thereafter, if the result is normal, it should be repeated after 5 years. Treatment with a step 2 AHA (American Heart Association) diet should be started if hypercholesterolemia is detected and statins are to be considered if needed, beyond the age of 10 years.

Foot Care

At every clinic visit, an evaluation of the feet should be performed for corns, calluses and abrasions. Examination of the footwear and socks of the patient

should be performed. This helps reiterate the messages for preventive care for the foot and healthy habits, which the patient and family must always practice at home (**Table 1**).

TABLE 1. Patient Instructions for Preventive Foot Care

1. Wash your feet daily with soap and water. Examine your feet daily to look for cracks or wounds. Be aware that if you have decreased sensation due to neuropathy, you will not feel pain even if you have a wound, therefore a visual examination on a regular basis is very important.
2. If your skin is dry, apply a moisturizing cream. Do not apply spirit.
3. If your feet get sweaty, use talcum powder but do not let it get caked between your toes.
4. While cutting your toenails, be very careful not to injure your skin. Do not cut the nails very close to the skin; cut them with a square end rather than round, so that the corner of the toe is not injured.
5. Do not let your foot get too close to a room heater during winter.
6. ***Do not walk barefoot, even at home.*** Wear shoes that are comfortable, not tightly fitting. Use cotton socks without tight elastic.
7. Treat any wound immediately. Wash with clean plain water or *Savlon*, dry and then cover with a sterile dressing pad if possible or else a clean cotton cloth. Visit the doctor immediately. If this is not possible, apply a simple ointment like *Neosporin*. *Do not apply iodine, Betadine, Mercurochrome or carbolic acid.* Do not use *Band-Aid* or other sticky material, or any warm fomentation. Give rest to your foot.

CONCLUSIONS

Time and space must be provided for individual consultations with the nurse-educator, dietician and social worker during every clinic visit. Every visit is an opportunity for continuing and reinforcing diabetes education.

Each clinic visit should be concluded by outlining an individualized plan incorporating school timings, eating habits, cognitive ability and emotional maturity.

The plan should contain the following:

- Reiteration of treatment goals.
- Agreement or revision of insulin dose, meal plan and exercise schedule.
- New treatment for any associated conditions or complications.
- Appointment date for next consultation.

8

LABORATORY MONITORING

Anna Simon

SUMMARY OF RECOMMENDATIONS

- Glycosylated hemoglobin (HbA1c) is the single most important laboratory monitoring test for a child with type 1 diabetes mellitus (T1DM).
- Thyroid disease and celiac disease should be screened for.
- Microvascular and macrovascular complications screen includes microalbuminuria and lipid profile.

HEMOGLOBIN A1c (HbA1c)

Measurement of HbA1c every 3 months prior to the clinic visit is an excellent method to judge adequacy of insulin therapy. HbA1c best correlates with the mean blood glucose level over the previous 8 to 12 weeks and this value needs to be interpreted in the context of self-monitored blood glucose (SMBG) readings and clinical findings. HbA1c along with SMBG helps to determine the requirement for insulin adjustment. The aim is to keep the HbA1c as close to normal as possible without high glycemic variability. Targets for HbA1c are to be given with careful attention to avoid severe hypoglycemia. Based on DCCT results and other studies, the general goal is to keep the HbA1c in all patients <7.5%, but a realistic goal for infants and toddlers would be between >7 and <8.5%.

Physicians should be aware of the potential interferences like hemoglobinopathies, which may affect HbA1c values. HbA1c values that are inconsistent with the clinical presentation should be investigated further.

CONTINUOUS GLUCOSE MONITORING (CGM)

In an occasional patient with poor glycemic control, 6 to 14 days of continuous glucose monitoring is very useful for planning management, as this will allow the study of the effect of food, exercises and insulin timing on glucose levels (See Chapter 17 for more details.)

URINE FOR MICROALBUMINURIA

Microalbuminuria is defined as the persistent urinary excretion of albumin in the following range:

- Albumin excretion rate (AER) between 20-200 μg/min or AER 30-300 mg/ 24 hr,

- Albumin concentration 30-300 mg/L (early morning sample), and/or
- Albumin/creatinine ratio 30-300 mg/g (spot urine).

If a microalbumin report is abnormal, the screening should be repeated twice more within the next 3 to 6 months; 2 out of the 3 reports should be abnormal to classify the result as persistent microalbuminuria. Microalbumin measurement should not be done during an acute illness or fever, urinary infection, menses, or after vigorous physical exercise. It should also not be done during poor glycemic control and hyperlipidemia.

Screening for microalbuminuria should be done annually, should start from 10 years of age, or at onset of puberty if this is earlier, with 2–5 years diabetes duration as per recommendations of the International Society for Pediatric and Adolescent Diabetes (ISPAD 2014).

The presence of microalbuminuria calls for improved glycemic control, attention to normalization of blood pressure and lipid profile and treatment with ACE inhibitors if necessary. Microalbuminuria if treated early can prevent or even reverse progression of renal disease.

SERUM LIPIDS

Screening for fasting lipid profile should be performed in all children with T1DM aged over 10 years. If there is family history of hyperlipidemia, testing should be performed from the age of 2 years. If normal, the tests should be repeated every 5 years.

The normal values for lipids are given in **Table 1** below. Hyperlipidemia should be managed by strict glycemic control, dietary intervention (weight reduction, if obese and reduction of saturated fat intake) and an exercise schedule. Treatment with a statin may be considered (at age > 10 years) if the LDL cholesterol remains >160 mg/dL despite the above measures; or is >130 mg/dL in the presence of other risk factors for cardiovascular disease. There is limited experience with fibrates, bile acid sequestrants and nicotinic acid in children.

TABLE 1. Target Levels for Serum Lipids in Children

Lipid	*Target*
LDL cholesterol	<100 mg/dL
HDL cholesterol	>40 mg/dL
Triglyceride	<150 mg/dL

SCREENING FOR ASSOCIATED AUTOIMMUNE CONDITIONS

Thyroid Disease

Up to 20% of patients with T1DM have positive anti-thyroid antibodies (anti-

thyroid peroxidase and/or anti-thyroglobulin antibodies) and 2-5% with T1DM develop autoimmune hypothyroidism or subclinical hypothyroidism. Hypothyroidism usually manifests by deceleration of growth, pubertal delay, goiter, poor glycemic control or unexplained hypoglycemia.

Anti-thyroid antibodies are checked at the time of diagnosis and if positive, patients require screening for hypothyroidism yearly or whenever clinical suspicion arises. If the test is positive, anti-thyroid antibodies need not be repeated. Elevated serum TSH and low free T4 levels confirm the diagnosis of hypothyroidism.

Screening of thyroid function with TSH is to be done every 2 years in asymptomatic patients without a goiter or in patients who are negative for autoantibodies.

Hyperthyroidism is less common and can occur as the hyperthyroid phase of Hashimoto thyroiditis or Graves disease.

Celiac Disease

Celiac disease occurs in 1-10% of children and adolescents with diabetes. It is usually associated with unexplained hypoglycemia or a reduction in insulin requirement. It should also be suspected when there is poor growth, poor glycemic control, iron deficiency anemia or gastrointestinal symptoms. Celiac disease can often remain asymptomatic.

Screening for celiac disease with IgA antibodies to tissue transglutaminase (tTGA) should be done at the time of diagnosis and every 2-3 years thereafter. Total IgA levels also should be routinely done or alternatively when tTGA is negative, to exclude an IgA deficiency. Endomysial IgA levels can also be used to screen for celiac disease. The specificity and sensitivity of endomysial IgA is similar to that of tTGA (>90%). If antibodies are positive, a small bowel biopsy is necessary to confirm the diagnosis. Gluten-free diet should be advised in these patients and inputs from the gastroenterologist and dietician will be beneficial.

9

EXERCISE AND PHYSICAL ACTIVITY

Anna Simon

SUMMARY OF RECOMMENDATIONS

- Physical activity should be considered as an important aspect of management of type 1 diabetes mellitus (T1DM).
- Regular physical activity has been demonstrated to improve glycemic control, physical fitness and muscle strength and psychological well-being. Children participating in sports or programmed exercises should be supervised and should have access to sweetened drinks and snacks.
- Extra caution should be taken when undertaking solo sports or events in water (or mid-air).
- Blood glucose (BG) levels should be monitored before, during and after physical activity.
- Do not inject insulin into a site that will be heavily involved in muscular activity.
- Extra carbohydrate intake and/or reduction of insulin dosage may be necessary; previous experience and BG monitoring will help to determine the appropriate adjustments required with diet and insulin therapy.
- A general recommendation is that for every hour of moderate to intensive sport or physical activity, 1.5 g/kg of an extra serving of carbohydrate should be consumed.
- Extra carbohydrates should be taken if BG is <100 mg/dL at bedtime and check BG at 3.00 AM as well.
- Strenuous physical activity should be avoided if BG concentration is >250 mg/dL, especially if ketones are present. This will require insulin supplementation as well.

INTRODUCTION

The management of type 1 diabetes mellitus (T1DM) focuses on insulin therapy, planned diet, physical activity and monitoring therapy. Physical activity is not just organized sports; it includes walking, playing, dancing and other activities of daily living. The benefits of physical activity in people of all age groups

with chronic diseases are well-known and accepted. Physical activity, by improving known risk factors for atherosclerosis (obesity, hypertension and hypercholesterolemia) will benefit patients with diabetes who are at increased risk for macrovascular disease.

The major benefits of physical activity in diabetes can be listed as follows:

- Decreases blood glucose (BG) levels.
- Reduces insulin dosage.
- Increases insulin sensitivity.
- Controls blood pressure and increases cardiovascular function.
- Improves lipid profile.
- Promotes psychological well-being.

In contrast to the effect of exercise on type 2 diabetes mellitus (T2DM), which is indisputably positive, exercise and physical activity should be carefully factored into the management plan in T1DM. Though there are definite physical and psychological benefits, the occurrence of acute complications such as hypoglycemia with physical exercise is common with T1DM. An understanding of the metabolic changes occurring with physical activity in T1DM is necessary to individually modulate insulin therapy and diet plan before and after exercise to avoid these complications.

METABOLIC AND HORMONAL RESPONSES DURING PHYSICAL ACTIVITY IN T1DM

1. Influence of Exercise on Glucose Metabolism

There is increased blood flow to the muscles during exercise to facilitate the increased demand for oxygen, energy substrates and carbon dioxide removal. This increased glucose demand activates complex hormonal responses involving insulin and the counter-regulatory hormones (glucagon, cortisol, growth hormone [GH] and catecholamines).

2. Subverted Physiological Regulation of Insulin

The lack of endogenous insulin secretion makes children with T1DM totally different from non-diabetic children. In children with T1DM, the peripheral insulin concentration depends on the dose and type of injected insulin, site of the injection and time elapsed after the injection. Thus physiological suppression of insulin is not achievable in T1DM.

3. Blunted Response of Counter-Regulatory Hormones

Several studies have also demonstrated a blunted counter-regulatory

hormonal response to exercise in patients with T1DM.

COMPLICATIONS DURING AND AFTER PHYSICAL EXERCISE IN T1DM

1. Exercise Hypoglycemia

This is the most common and important complication with physical activity in T1DM and is defined as BG levels <70 mg/dL. During exercise, there is increased peripheral glucose uptake and also an increased absolute or relative concentration of insulin. Excessive insulin absorption due to the increased blood flow through muscles during exercise, especially if the injection is into the working muscle aggravates the over-insulinization. Exercise also causes increased insulin sensitivity, which can persist for up to 24 hours and predispose to late hypoglycemia.

Factors predisposing to the occurrence of hypoglycemia include:

- Low glycemic trends/previous hypoglycemia,
- Exercising during the peak insulin action,
- Long duration or high intensity sports,
- Aerobic exercises tend to decrease BG both during and after the exercise,
- Anaerobic exercises cause a transient initial rise in BG (first 30-60 minutes) followed by hypoglycemia,
- Injection into working muscle, leading to enhanced absorption,
- Intake of inadequate food or food with low glycemic index before exercise, and
- Autonomic involvement.

Late-onset hypoglycemia, which develops 5-24 hours after exercising, is mainly due to:

- Increased insulin sensitivity and
- Depletion of muscle and liver glycogen stores.

2. Exercise Hyperglycemia and Ketosis

This occurs mainly in poorly controlled T1DM performing high intensity exercises. The BG level before exercise (>250 mg/dL ± ketones) is the major determinant for developing exercise hyperglycemia.

Factors predisposing to hyperglycemia include:

- High glycemic trend,
- Delaying exercises from last insulin injection,

- Prolonged low intensity exercises promoting lipid utilization and ketosis and
- Inadequate hydration.

3. Chronic Complications

Though rare, physical activity may adversely affect diabetes-related complications (See **Table 1**).

TABLE 1. Adverse Effects Associated with Physical Activity and Exercise

Predisposing Factor	*Adverse Effects*
Rise of blood pressure during exercises	Increased risk of retinal and vitreal hemorrhage and retinal detachment
Physical exercises	Increased proteinuria
Diabetic neuropathy	Increased risk for foot ulcers, articular and tissue injury Decreased heart rate to physical activity Exaggerated orthostatic hypotension Induction of angina

MANAGEMENT STRATEGIES TO PREVENT EXERCISE-INDUCED COMPLICATIONS

Hypoglycemia can be prevented with insulin dose reduction and dietary modification when exercise is pre-planned. Extra calorie intake is the only option when exercise is unplanned and sporadic. Additional BG monitoring at bedtime and 3.00 AM are warranted, especially after unaccustomed physical activity.

1. Diet Management during Exercise in T1DM

- Diet should comprise of complex carbohydrates (70%) to increase muscle and liver glycogen stores. Increased fat intake should be avoided to prevent ketosis.
- 1.5 g/kg of extra carbohydrate for every hour of moderate to intense activity.
- *Prolonged exercising* may require calorie intake *before, during and after* the exercise. A carbohydrate beverage (1-2 g/kg) taken approximately 1 hour prior to a physical activity enhances glycogen stores and thus supplement energy stores and provide adequate fluids for hydration. A meal containing carbohydrates, fats, and protein should be consumed roughly 3-4 hours prior to competition to allow for digestion and to maximize endogenous energy stores. This is especially important for activities lasting a longer duration.
- Additional low glycemic index (GI) food at bedtime if BG ≥100 mg/dL.

2. Insulin Adjustments with Exercise in T1DM

Insulin levels are influenced by multiple factors and therefore dosing adjustments have to be done on an individual basis. Factors affecting insulin levels are the dose and type of insulin, timing of injections, site of injection, duration and intensity of physical exercise, emotional stress and fitness status.

Prevention of Hypoglycemia

- For pre-planned physical activity consider reducing pre-meal insulin by 30-50% or delaying activity to avoid exercising during peak levels of insulin action.
- With prolonged exercise, consider reducing evening intermediate or long acting insulin by 20-50% to prevent late onset hypoglycemia.
- If on insulin pump – for short periods of exercise, stop insulin infusion by discontinuing the device before and during exercise; and for pre-planned exercises, consider reducing by 50% of the basal infusion rate from 60 minutes prior to exercise.
- Also consider reducing the overnight infusion rate by 10-30% to prevent late onset hypoglycemia.

Exercise Hyperglycemia

If the BG levels are >250 mg/dL and ketones are *negative*, insulin supplementation is required before exercise. If the BG levels are >250 mg/dL and ketones are positive, 5-10% of extra insulin supplementation and delaying exercise till urinary ketones are negative is advised.

10

HYPOGLYCEMIA

Anju Virmani

SUMMARY OF RECOMMENDATIONS

- Hypoglycemia in a child with diabetes is defined at a blood glucose (BG) level <70 mg/dL. In an infant or toddler, BG should be maintained above 100 mg/dL.
- Treatment should aim for best possible glycemic control, without significant hypoglycemia.
- The child, family, school staff and other caregivers should be educated about suspecting, confirming and managing hypoglycemia.
- Ideally the child should have an I-card or wear some form of identification indicating that he/she has diabetes.
- Sugar or glucose (1-3 teaspoons), is useful to immediately raise BG, followed 10-15 minutes later by a small snack. Glucagon (0.3 to 0.5 mg subcutaneously (SC) for a young child, 1.0 mg for an older child) should be available at all times. Injection Glucagon is available in India, and all families should be encouraged to buy it for emergencies, and carry it during travel.
- Prevention of hypoglycemia includes attention to bedtime and midnight BG, delayed hypoglycemia after exercise, and hypoglycemia unawareness syndrome.
- Pathological causes include hypothyroidism, celiac disease, and renal failure.

INTRODUCTION

Hypoglycemia ("hypo") is the commonest acute complication of diabetes control in children. It is usually defined as a blood glucose (BG) <70 mg/dL, but in toddlers, action should perhaps be taken at levels <100 mg/dL. A severe hypo is defined as one where the person requires help to manage it. A hypo may be the cause of an injury or accident, and if severe, can end up in seizures or coma. Even mild hypoglycemia can interfere with academic performance, and in the very young child, repeated episodes can cause cognitive dysfunction. Hypos can be so frightening for caregivers that they may choose to maintain high sugars to avoid

such episodes, so it is crucial that soon after diagnosis, they must be taught how to prevent and to manage hypos.

CAUSES

Hypoglycemia is commonly due to:

- Excessive insulin action,
- Inadequate or delayed food intake, or
- Excessive or unplanned exercise.

Hypos can occur with several regimens. The older split-mix regimen, comprising two shots of regular and NPH insulin can lead to hypoglycemia on an almost daily basis unless a lot of care is taken to provide mid-meal and bedtime snacks are not taken. The current insistence on frequent self-monitoring of BG (SMBG) at home, and on multi-dose regimens which work on the basal-bolus concept, which matches insulin to each significant meal and snack, have made it possible to minimize the number of hypos. Newer continuous glucose monitoring systems (CGMS) and perhaps insulin analogs are also enabling patients to prevent hypos, especially at night. Conversely, attempts at very tight glycemic control can increase the number of episodes. Hypos can also be common in situations where food supply is erratic, e.g. in very poor families.

Hypos are particularly common in the honeymoon phase, when the initial glucotoxicity settles down, so that insulin requirements fall rapidly. If the child is admitted at the time of diagnosis, insulin dose may need to be reduced by 10% at the time of discharge to prevent hypos, which may occur with the increased activity at home. Ongoing frequent SMBG guides the caregivers on how much insulin to give before each meal, so the insulin doses can be drastically reduced during this phase, and increased once the BG levels start rising.

Hypos are common in toddlers and under-5 children, since eating can be erratic, and the thin layer of subcutaneous fat means that the insulin may often end up in the muscle and so get absorbed rapidly. For them, insulin analogs can be useful, since they can be administered immediately after a meal, the dose depending on the BG as well as the amount of food eaten. Also, the shortest needles should be insisted upon: currently 4 mm needles are the shortest available in India.

Later in life, if hypos suddenly and unexpectedly increase in frequency, one should think of hypothyroidism, celiac disease, renal compromise and/or failure, or rarely adrenal insufficiency. All these conditions are more common in T1DM. With ongoing, regular monitoring for these comorbidities, one is less likely to be caught by surprise. Hypos can also occur after consumption of alcohol, and can

be very risky, since coma may be mistaken for drunken stupor, and corrective action may not be taken. Adolescents and young adults should be warned of this.

In general, throughout the lifetime of a person with diabetes, constant vigil is needed, with timely intake of food, especially before and after exercise, frequent BG monitoring, proper rotation of injection sites, and judicious use of analogs and insulin pumps where they can be afforded, to reduce the frequency of hypos.

CONSEQUENCES

Hypoglycemia can result in abnormal behavior, drowsiness, convulsions, coma, or if prolonged, death. It can be so frightening that the diabetic child and his/her family may refuse to try for tight glycemic control for fear of hypoglycemia. Recurrent hypoglycemia can lead to hypoglycemia unawareness, increasing the risk of later episodes.

Severe hypoglycemia is more likely in:

- Toddlers and very young children,
- Adolescents, especially when they are rebelling, or have consumed alcohol,
- Those with longer duration of diabetes,
- Those who have renal failure, undiagnosed hypothyroidism and celiac disease, and
- Those with low HbA1c values.

SYMPTOMS AND SIGNS

Symptoms and signs of hypoglycemia may be:

- *Adrenergic:* uneasiness, shakiness, palpitations, and/or cold sweats.
- *Neuroglycopenic:* difficulty in vision, hearing, or concentrating, slurred speech, confusion, dizziness, abnormal gait, drowsiness, coma, seizures, and death ("dead in bed").
- Headaches, mood swings, poor school performance, nightmares, and depression, apart from the classical symptoms.
- Transient neurologic deficits: including hemiplegia and aphasia, which can occur with prolonged hypoglycemia.

Some Caveats

1. Symptoms and signs do not correlate well with BG levels, and may vary from person to person, and episode to episode.
2. Marked symptoms may occur if the BG drops sharply ("pseudohypoglycemia"), so it is important to test BG whenever possible to

confirm if the level is indeed low. Otherwise, patients often treat themselves for adrenergic symptoms merely because there is a drop in BG from high to normal values.

3. Conversely, a hypo maybe missed and BG appears to be normal or even high if rebound hyperglycemia occurs quickly, or testing is delayed.
4. The accuracy of capillary testing and CGMS is less in the low range. Testing BG at alternative sites (e.g. forearm) is encouraged as it causes much less pain. However, these sites are not reliable when BG is changing rapidly, and so should not be used for testing when hypos are suspected.
5. CGMS make it possible to detect trends, i.e. whether the BG is rising or falling, and this can be more helpful in preventing hypos. Thus if the BG is falling sharply, a small snack can be taken before the level actually goes low. It also helps pick up asymptomatic hypos, and thus reduces rebound hyperglycemia.

Though there is no specific cut-off value for defining hypoglycemia, most people would consider levels below 70 mg/dL as diagnostic, and aim to keep BG above 80-90 mg/dL. In very young children, higher levels are targeted, because symptoms may not be picked up easily. This can be avoided if CGMS are used, since the BG can be assessed very often, and symptoms need not be relied upon. Adrenergic symptoms and counter-regulatory responses are reduced in the following situations:

- During sleep,
- After an episode of severe hypoglycemia,
- In those with tight control, and
- In those with long duration of diabetes.

In these circumstances, greater vigilance is needed. In fact, if adrenergic symptoms are very mild or ignored, then neuroglucopenic symptoms may be the first indication of trouble ("**hypoglycemia unawareness**"). Hypoglycemia unawareness may occur in a child having repeated episodes of hypoglycemia. It is often reversible, with hypoglycemia awareness returning once there are less hypos with less strict control of blood sugars. It is therefore important to ensure ongoing frequent SMBG, to the extent the family can afford, before all meals, and especially before and after exercise, during illnesses, and periodically in the middle of the night. CGMS provide a wealth of information about glucose patterns in individual patients, especially night BG patterns, allowing greater prevention of problems, while reducing the number of needle pricks. As costs come down, CGMS may be practical in more and more patients (see Chapter 17). In children who do not test frequently for financial or other reasons, families should be asked to be extra vigilant, and make sure BG is tested when hypoglycemia is suspected.

Severity

1. *Mild hypoglycemia* is defined as when the patient can manage to treat him/herself. This may be
   A. *Symptomatic* ("documented symptomatic hypoglycemia"), or
   B. *Asymptomatic:* Asymptomatic episodes are important because they increase the risk of severe hypoglycemia and of hypoglycemia unawareness.
2. *Moderate hypoglycemia* is defined as when the patient needs help to treat the hypo. All hypos in very young children would be considered moderate, since they will need help.
3. *Severe hypoglycemia* is defined as when the patient has altered sensorium (confusion, coma or convulsions) and so needs glucagon or IV glucose for management. Glucagon or IV glucose may also be needed in case vomiting is severe and does not allow oral carbohydrates to be retained.

MANAGEMENT

The aim of treatment is to normalize BG levels to above 100 mg/dL, and ensure recovery from symptoms.

Mild to Moderate Hypoglycemia

If the BG is more than 60 mg/dL and the sensorium is normal, the child should be given:

1. 5-15 g of simple carbohydrate orally. This should preferably be in the form of free sugars, because the presence of fat delays the absorption of the sugar. Thus the child can be given glucose, sugar tablets, candy, sugar, juice, honey, or a regular sweetened beverage (not diet drink). Emphasize to caregivers that fat-containing sweets like chocolate or *mithai* must be avoided for initial management.
2. This is followed after 10-15 minutes by a retest of BG, and then
   A. If BG still low, repeat 10 g glucose as above.
   B. If BG > 70 mg/dL, give a snack e.g. glass of milk, fruit, sandwich, biscuits, chocolate, etc., to make sure that the BG does not dip again. If this is at a mealtime, the meal can be given.
3. Rest: No further strenuous physical activity should be allowed.

Severe Hypoglycemia

This needs urgent action. The management includes the following steps:

1. *Injection of glucagon,* if available, given intramuscularly (IM) or subcutaneously (SC) 10-30 µg/kg. Broadly, the dose is 0.5 mg for children younger than 10 years of age; and 1 mg for older children and adolescents. Once the sensorium improves, a snack should be given (as above); to make sure BG does not dip again. Glucagon can cause transient nausea or vomiting.
2. *If glucagon is not available:* the child should be put in a lateral position to prevent aspiration and immediately taken to the nearest medical facility. There, an IV push of 5 mL/kg of 10% dextrose or 2 mL/kg of 25% dextrose should be given, and a drip of maintenance fluids started till the sensorium stabilizes (or vomiting subsides) and the child can tolerate oral intake comfortably. At this time, a snack should be given, as above. Observation for 12-24 hours is desirable because vomiting or altered sensorium may recur. Anti-epileptic drugs should not be started, since the reason for the seizure is known.
3. *If for any reason the child cannot be taken to a medical facility, or en route:* if it is possible to quickly organize a thick paste of sugar (powdered sugar with a few drops of water), this can be smeared on to the dependent cheek pad, with the child of course in a lateral position. A powdery substance like glucose powder, or thin liquids like glucose solution or honey, should NOT be given forcibly to the semiconscious/unconscious child.

PREVENTION

Special attention must be paid to high-risk groups, which include:

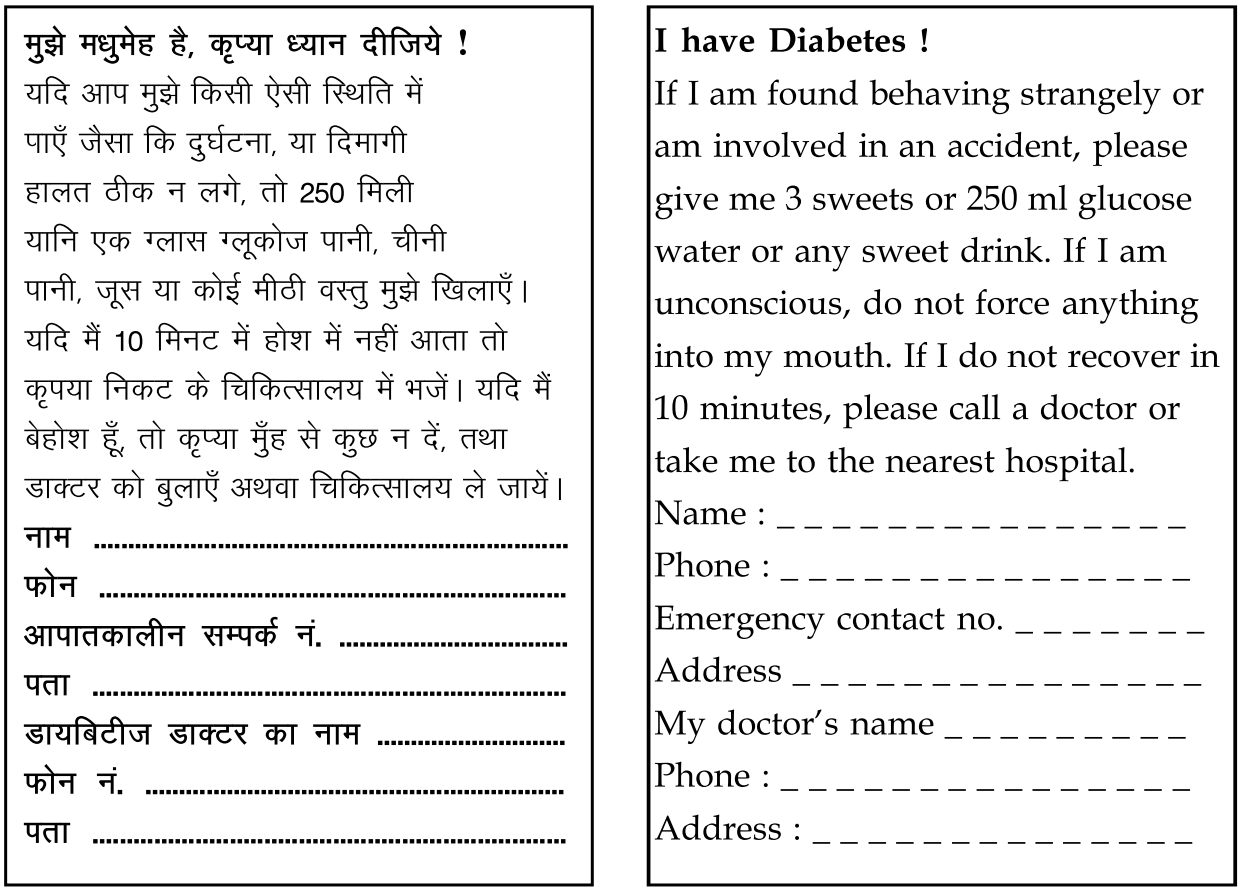
- Very young children and toddlers; or those not able to communicate normally for any reason.
- Children with low HbA1c.
- Children on low cost regimens (NPH absorption is very variable and can be associated with a significant risk of hypos. Twice daily regimens should no longer be advised. The risk of hypos is lower with insulin pumps, and with basal-bolus regimens using insulin analogs.)
- When treatment regimen or daily routine is changed (e.g. small child moves from play school to regular school; class teachers no longer supervise eating of tiffin; or during school trip, or preparation for a sports day or a cultural evening, etc.)
- During sick days, especially with vomiting. Usually BG levels are high during sick days, but hypos can also occur. Frequent BG monitoring is essential on such days.
- Athletes.

- When hypoglycemia has occurred recently.
- Children with significant autonomic neuropathy.
- Associated diseases: renal failure, possible hypothyroidism, celiac disease, or adrenal insufficiency.

SOME PRACTICAL HINTS

- BG should be checked frequently daily for all children, but more often in high-risk groups or times, e.g. during and after strenuous sport. It should also be checked at 2-3 AM periodically, and 10-12 hours after alcohol ingestion. Mid-meal snacks are important for those on NPH insulin.
- The close family members, as well as teachers, bus driver, sports teacher, coach should all be aware of the symptoms, and the action required to be taken. Extra carbohydrate is necessary for every 45 minutes of sports or play to prevent a hypo: the coach may have to remind the child to eat. Two or three sweets preferably in dull colored pillow packs and a packet of sweet biscuits must always be available, in the child's pocket AND school bag, in the school bus or van, in the sports teacher's locker, in the school medical room, in the teachers' bag during a class trip, etc.
- The child and family must be asked if they are carrying a diabetes identity card, a sample of which is appended below **(Fig 1)**.
- Families should be encouraged to keep Injection Glucagon at all times at home and also when traveling. This may be life-saving.
- Families should be encouraged to keep a thick sugar paste in a sealed box or a tube of sugar gel at home and when traveling.
- BG testing must be done often when traveling or during sports. The family and child must know that simple carbohydrate must be given (15 g, contained in 3 teaspoons of sugar or about 120 mL juice, raises sugar by about 20 mg/dL) and exercise should be stopped if BG dips.
- Patients should be encouraged to take milk or other slowly absorbed snack (e.g. few nuts) at bedtime, if bedtime BG is less than a level decided with the doctor. This is especially important if there has been strenuous sport in the evening, **since hypos can occur up to 12 hours after exercise**. A bedtime snack is not necessary for those on insulin pumps, since the night-time basal rate can be adjusted.
- During all routine visits, prevention and treatment strategies should be briefly asked for, presence of the diabetes I-card verified, doubts clarified and knowledge gaps filled. Families must be reminded that emergencies occur without warning.

FIG 1: Sample of a Diabetes Identity Card: front (Hindi) and back (English)



मुझे मधुमेह है, कृप्या ध्यान दीजिये !
यदि आप मुझे किसी ऐसी स्थिति में
पाएँ जैसा कि दुर्घटना, या दिमागी
हालत ठीक न लगे, तो 250 मिली
यानि एक ग्लास ग्लूकोज पानी, चीनी
पानी, जूस या कोई मीठी वस्तु मुझे खिलाएँ।
यदि मैं 10 मिनट में होश में नहीं आता तो
कृपया निकट के चिकित्सालय में भजें। यदि मैं
बेहोश हूँ, तो कृप्या मुँह से कुछ न दें, तथा
डाक्टर को बुलाएँ अथवा चिकित्सालय ले जायें।
नाम .....
फोन .....
आपातकालीन सम्पर्क नं. .....
पता .....
डायबिटीज डाक्टर का नाम .....
फोन नं. .....
पता .....

I have Diabetes !
If I am found behaving strangely or am involved in an accident, please give me 3 sweets or 250 ml glucose water or any sweet drink. If I am unconscious, do not force anything into my mouth. If I do not recover in 10 minutes, please call a doctor or take me to the nearest hospital.
Name : _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Phone : _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Emergency contact no. _ _ _ _ _ _ _
Address _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
My doctor's name _ _ _ _ _ _ _ _ _
Phone : _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Address : _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

- After each episode of hypoglycemia, the insulin-diet-exercise regimen should be reviewed to identify triggers so they can be avoided in the future.
- Prevention is important as repeated episodes can interfere with school performance and sports, cause long-term cognitive dysfunction, cause hypoglycemia unawareness, prevent the parents from trying for tight glycemic control due to anxiety, result in accidents, and even death (e.g. "dead in bed").

NOCTURNAL HYPOGLYCEMIA

This should be suspected if the child

- Has nightmares,
- Wakes up confused or with a headache,
- Has low or unexpectedly high fasting BG, or low bedtime sugars.

A bedtime glass of milk may be useful, especially after strenuous play in the evening. Insulin doses should be aggressively reduced to prevent nocturnal hypoglycemia. CGMS is particularly useful in detecting the timing and severity of night hypoglycemia.

11

DIABETIC KETOACIDOSIS

Anurag Bajpai

SUMMARY OF RECOMMENDATIONS

- Diabetic ketoacidosis (DKA) is a life-threatening condition requiring early diagnosis and appropriate treatment.
- DKA should ideally be managed in a center equipped to treat the disorder under the supervision of an experienced pediatrician. In resource-poor settings stabilization followed by early referral to a higher center is recommended.
- Laboratory tests should be interpreted with caution due to known fallacies.
- Children younger than 5 years and those with severe DKA should be managed in an ICU.
- Close clinical and laboratory monitoring is essential for successful management of DKA.
- Careful hydration is the mainstay of management of DKA. Rapid and excessive fluid administration should be avoided due to the risk of cerebral edema.
- Insulin should be withheld in the initial hydration phase and in the presence of hypokalemia.
- Continuous intravenous infusion of insulin is the standard of care for pediatric DKA. In resource-poor settings intermittent intramuscular or subcutaneous insulin may be used. Intravenous bolus of insulin should be avoided.
- Potassium replacement is required in children with DKA even if the initial potassium levels are normal. It should be started after the hydration phase, but considered in the initial phase if hypokalemia is present at diagnosis.
- Bicarbonate should be used only in children with pH less than 6.9 and hyperkalemia.
- Resolution of acidosis is the main criteria for reduction of insulin infusion rate.

- Mannitol and dextrose should be available at bedside of all patients with DKA for emergent treatment of cerebral edema and hypoglycemia.
- Cerebral edema should be considered in all patients with sudden deterioration of neurological and clinical status.
- Insulin infusion should be discontinued 30-60 minutes after the administration of subcutaneous insulin.
- Appropriate management during sick days and invasive procedures is essential for prevention of DKA.

ABOUT THE RECOMMENDATIONS

These recommendations aim at providing practical guidelines for treatment of children with DKA. Although the guidelines represent standard of care for pediatric DKA, we understand that the same may not be feasible in many setups of the country. The relevant adaptations for resource-poor settings have been italicized.

INTRODUCTION

Diabetic ketoacidosis (DKA) is the most severe acute complication of diabetes mellitus. Previously believed to be limited to subjects with type 1 diabetes mellitus (T1DM), DKA has been increasingly observed in children with type 2 diabetes mellitus (T2DM) and maturity onset diabetes of young (MODY). DKA is the most important cause of mortality and morbidity in T1DM. Every year thousands of children with DKA are missed across the globe with lethal consequences. Early identification and management is therefore essential.

EPIDEMIOLOGY

In western countries 25-40% freshly diagnosed children with T1DM present with DKA. This figure varies from 16-67% depending on geographical, racial and socioeconomic factors. *Although large epidemiological data from India is lacking, the figure is substantially higher than the developed countries.* Risk factors for DKA at diagnosis of T1DM include young age, lower socioeconomic status and lower prevalence of T1DM in the community. Missed diagnosis of DKA is fatal and may partly explain the supposed low prevalence of T1DM in Indian children. In children with established T1DM the risk of DKA is around 1-10% per year. This usually occurs due to omission of insulin or inadequate management during stress or infection. Children on insulin pumps are prone to develop DKA even after short duration of interruption of pump therapy, as they do not have basal insulin

on board. Recurrent DKA may be a pointer to psychosocial issues and attempts to escape hostile home environment.

PATHOPHYSIOLOGY

DKA is the end result of insulin deficiency and counter-regulatory hormone excess (glucagon, catecholamines, cortisol and growth hormone). The disorder is usually precipitated by infection, stress and trauma, conditions associated with increased insulin requirement and higher level of counter-regulatory hormones. Insulin deficiency is the main cause of ketogenesis, while both insulin deficiency and counter-regulatory hormone excess cause hyperglycemia. Accumulation of ketoacids causes acidosis, which in turn produces Kussmaul breathing (acidosis), abdominal pain (acidosis) and fruity odor (acetone). Hyperglycemia results in increased urinary water losses due to osmotic diuresis and dehydration. Osmotic diuresis is associated with increased urinary losses of sodium, potassium and phosphate leading to significant deficits of these electrolytes (**Table 1**). Potassium levels are of special concern as correction of metabolic acidosis following therapy and administration of insulin leads to intracellular migration predisposing the individual to severe hypokalemia. Severe hypophosphatemia is associated with shift of oxygen dissociation curve to the left due to reduced 2,3-DPG levels causing tissue hypoxia and rhabdomyolysis. Exogenous chloride load due to normal saline and potassium chloride results in the development of hyperchloremic metabolic acidosis masking resolution of DKA. Demonstration of low blood ketones in this setting points to hyperchloremic metabolic acidosis. The condition is self-limiting and does not require continuation of insulin treatment.

TABLE 1. Fluid and Electrolyte Deficits in Childhood DKA

Factor	*Deficit*	*Assessment*
Fluid	70 mL/kg	Over-estimated
Sodium	4-6 mmol/kg	Over-estimated
Potassium	5 mmol/kg	Under-estimated
Phosphorus	0.5-2 mmol/kg	Same
Chloride	4 mmol/kg	

DIAGNOSIS

There is a need for high index of suspicion for DKA. DKA should be excluded in all children diagnosed with T1DM irrespective of symptoms (**Table 2**).

Criteria for Diagnosis

The classical triad used for the diagnosis of DKA includes:

- *Hyperglycemia*–Blood glucose > 200 mg/dL (11.1 mmol/L)
- *Metabolic acidosis*–pH < 7.3, serum bicarbonate < 15 mmol/L

TABLE 2. Pointers to the Diagnosis of DKA

Pointer	*Differential diagnosis*	*Pointer to DKA*
Encephalopathy	CNS infection, malaria, poisoning	Acidotic breathing
Acute abdomen	Pancreatitis, appendicitis	No tenderness
Dehydration	Gastroenteritis	Normal urine output
Tachypnea	Bronchial asthma, pneumonia	No chest signs
Hyperglycemia and acidosis	Septicemia, renal failure	Ketosis
Ketoacidosis	Starvation, organic academia	Hyperglycemia

- *Ketosis*–Blood ketone ≥ 3 mmol/L *or* urine ketone > 2+

Table 3 details the classification of the severity of the DKA as mild, moderate and severe and guidelines for patient care.

TABLE 3. Classification of the Severity of DKA

Features	**Mild**	**Moderate**	**Severe**
Dehydration	<5%	5-10%	>10%
pH	7.2–7.3	7.1–7.2	< 7.1
Base excess	–5 to –10 mmol/L	–10 to –15 mmol/L	< –15 mmol/L
Treatment			
Insulin administration	Subcutaneous	Infusion	Infusion
Fluid correction	Over 6-10 hours	Over 48 hours	Over 72 hours
Patient care setting	Emergency room	Inpatient service	Intensive care unit (ICU)

Practical Issues with Diagnostic Tests

- Blood sugar may be normal at presentation in children with recurrent vomiting, reduced carbohydrate intake and those who have received treatment (euglycemic DKA). Euglycemic DKA has also been reported during pregnancy and with the use of sodium-glucose co-transporter-2 inhibitors.
- Venous blood gas is unreliable in children with hemodynamic compromise.
- Hyperglycemia causes shift of fluids from the cells causing dilutional hyponatremia. Measured sodium levels are lower by 2 mmol/L for every 100 mg/dL increase in blood sugar and should be corrected according to the formula below:

  $$\text{Corrected sodium} = \text{Measured sodium} + \frac{(\text{Glucose mg/dL} - 100)}{100} \times 2$$

- Serum amylase levels may be elevated in DKA and should not be considered a pointer to pancreatitis.
- Elevated total leukocyte count is common in DKA and is not a marker of infection in the absence of fever.
- Blood ketone strips measure β-hydroxybutyrate (BOHB), the major ketone in DKA. Normal blood ketone levels are 0.6 mmol/L and levels more than 3 mmol/L are indicative of DKA. Blood ketone levels by point-of-care testing (POCT, ie at the bedside) correlate well with laboratory measures up to ketone levels of 3 mmol/L, but correlation is poor beyond 5 mmol/L. The Abbott Optium FreeStyle (previously called Optium Xceed) glucose meter provides the opportunity to check POCT blood ketone levels.
- While interpreting the results of urine ketone strips, one needs to consider the following caveats:
  - They measure acetoacetate (AcAc) and not BOHB and may therefore miss the diagnosis of DKA in the initial phase.
  - BOHB is converted to AcAc during treatment of DKA resulting in persistently positive urinary ketones.
  - They get rapidly denatured if exposed to room air.

MANAGEMENT

Setting

DKA is a life-threatening condition and should be managed in a hospital equipped with facilities for intravenous infusion and measurement of blood gas and electrolytes. The child should be managed by a pediatrician experienced in the treatment of DKA. *Children younger than 5 years of age and those with severe DKA should be admitted to an ICU.* We realize that this is not feasible in many set-ups in India and have therefore also provided guidelines for resource-poor settings as well. All efforts should however be made to transfer the patient to appropriate centers after initial stabilization.

Clinical Evaluation

The important clinical aspects to be noted during evaluation include the following:

- ***Airway, breathing and circulation (ABC)***
  - Airway should be secured in children with altered sensorium.
  - Endotracheal intubation should be avoided if possible, as it may cause sudden increase in CO_2 levels triggering cerebral edema.

- Nasogastric tube should be inserted and nasogastric aspiration should be done in the presence of altered sensorium. Nasogastric drainage is desirable in children with recent intake of sugar containing liquids to avoid sudden increase in blood sugar levels after improved gastric emptying with treatment of DKA.

- ***Weight***–All calculations should be based on current weight and not on that from previous records.
- ***Height***–Height should be measured in older children to calculate body surface area.
- ***Level of dehydration***
  - The usual level of dehydration in DKA is 5-10% (often overestimated in DKA).
  - Key indicators for hydration status include sunken eyes, absence of tears and reduced skin turgor (5% dehydration).
  - Prolonged capillary refill time (> 3 seconds), cold periphery and hypotension suggest greater level of dehydration.
  - Clinical assessment of dehydration may be difficult and levels of blood urea, hematocrit and serum albumin may be used as surrogate markers of dehydration.
- ***Identification of precipitating factor***
  - *First presentation*–Infection.
  - *Known case*–Missed insulin dose, infection and insulin pump malfunction.
- ***Hemodynamic status***–Blood pressure, heart rate, and capillary refill time.
- ***Neurological status***
  - Glasgow coma status should be assessed.
  - Special care should be taken to identify pointers of cerebral edema (unequal or dilated and fixed pupils, cranial nerve palsy, papilledema and brisk deep tendon reflexes), which may rarely be present at diagnosis.

Investigations

- ***Serum sodium (Na)***
  - *Status*–Deficit (20% of total body sodium, 4-6 mmol/kg)
  - Sodium levels are falsely reduced in hyperglycemia (use corrected sodium)

- *Implication*–Rapid decline is a risk factor for cerebral edema. Aim should be to maintain corrected sodium in a stable range. Rapid increase in serum sodium with polyuria is a dangerous sign and may indicate the development of cerebral edema and cerebral herniation.

- ***Serum potassium (K)***
  - *Status*
    - *Intracellular*–Deficit (20% of total body potassium, 3-6 mmol/kg).
    - *Extracellular*–Elevated due to acidosis and insulin deficiency.
  - *Implication*–Treatment of DKA is associated with hypokalemia due to intracellular shift secondary to reversal of metabolic acidosis and correction of insulin deficiency.
- ***Blood ketones***
  - Blood ketones by a POCT meter should be measured at diagnosis and two hourly to provide information about the resolution of DKA.
- ***Anion Gap (Sodium – [Chloride + Bicarbonate], 10-12 mmol/L)***
  - Anion gap provides information about non-measurable anions (ketoacids in DKA).
  - High anion gap indicates severity of DKA and levels tend to fall with correction of ketoacidosis.
  - Persistent metabolic acidosis with normal anion gap following treatment of DKA is suggestive of hyperchloremic metabolic acidosis.
- ***Plasma osmolality***
  - *Status*–Elevated (300-350 mOsm/kg).
  - *Implication*–Aim is to have gradual fall in osmolality of 2 mOsm/kg/ hour. More rapid fall is a risk factor for cerebral edema.
- ***Blood lactate***
  - *Status*–Normal (0.4-1.8 mmol/L).
  - *Implication*–Lactic acidosis in DKA should prompt evaluation for cerebral edema, infection or hemodynamic compromise.
- ***Serum phosphate***
  - *Status*–Deficit (0.5-1 mmol/kg).
  - *Implications*–Hypophosphatemia may be associated with decreased

responsiveness to insulin and lactic acidosis. Severe hypophosphatemia is associated with rhabdomyolysis and renal failure.

- ***Infection screening***
  - *Blood counts*–Transient leukocytosis is common in DKA. Consider infection only in the presence of persistent leukocytosis and fever.
  - *Urine examination*
  - *Blood and urine cultures*
  - *Chest x-ray* in the presence of persistent tachypnea and chest signs.
- ***Renal function tests***–High urea level is indicative of severe DKA.
- ***Electrocardiography***–For evidence of hypo/hyperkalemia.

STEPS IN MANAGEMENT

Initial Stabilization

- ***ABC***–Assess the adequacy of airway, breathing and circulation
- ***Fluids***–10 mL/kg normal saline over 1 hour (repeat if required) in children with hemodynamic instability. No role of colloids at this stage. There is no need for initial bolus if the child has no dehydration, tachycardia or hypotension.
- ***Oxygen*** therapy in the presence of shock
- ***Respiratory support*** if required
- Nil by mouth; oral intake should be avoided till the child becomes conscious with *no* vomiting
- Central venous catheterization should be avoided in DKA due to increased risk of venous thrombosis. It should be placed only when mandatory and removed as soon as possible.

SPECIFIC MANAGEMENT

1. Fluid Therapy

Fluid therapy forms the mainstay of treatment for DKA. Significant improvement in clinical condition and blood glucose can be achieved by fluid resuscitation alone. Rapid and excessive fluid intake is however a risk factor for developing cerebral edema and should be avoided. The aim is to provide maintenance requirement and deficit **evenly over 48 hours**. Urine output replacement is not required. In most cases the fluid deficit is 5-10%. The fluid requirement is usually around 3-3.5 L/m^2/day (see **Table 4**). Care should be

taken to avoid fluid administration more than 3.5 L/m^2/day (or more than double maintenance) due to the risk for cerebral edema. The amount of fluid replacement given in other centers prior to referral should be considered while calculating fluid requirements. In children with severe DKA and very high plasma osmolality fluid correction should be planned over 72 hours.

TABLE 4. Guidelines for Fluid Infusion Rate (mL/Hour) in DKA

Weight	Level of Dehydration			Weight	Level of Dehydration		
	Mild/Nil	*Moderate*	*Severe*		*Mild/Nil*	*Moderate*	*Severe*
5 kg	24	27	31	**38 kg**	101	125	156
7 kg	33	38	43	**40 kg**	104	129	162
8 kg	38	43	50	**42 kg**	107	133	168
10 kg	48	54	62	**44 kg**	110	137	174
12 kg	53	60	70	**46 kg**	113	141	180
14 kg	58	67	79	**48 kg**	116	146	186
16 kg	64	74	87	**50 kg**	119	150	191
18 kg	70	80	95	**52 kg**	122	154	197
20 kg	75	87	104	**54 kg**	124	158	203
22 kg	78	91	110	**56 kg**	127	162	208
24 kg	80	95	115	**58 kg**	130	167	214
26 kg	83	100	121	**60 kg**	133	171	220
28 kg	86	104	127	**62 kg**	136	175	226
30 kg	89	108	133	**64 kg**	139	179	232
32 kg	92	112	139	**66 kg**	142	183	238
34 kg	95	116	145	**68 kg**	145	187	244
36 kg	98	120	151	**70 kg**	148	191	250

2. Insulin Administration

Insulin should be started only after 1-2 hours of hydration as blood glucose levels fall rapidly even without insulin. Early insulin treatment is associated with drastic fall in plasma osmolality, hypokalemia and increased risk of cerebral edema.

Route

- *Continuous intravenous infusion*–Preferred route. Initial insulin bolus should be avoided, as it is a risk factor for cerebral edema.
- *Preparation*–Insulin infusion should be given using a dedicated intravenous line. Insulin should not be given using central venous catheter, to avoid frequent interruption.

- The intravenous tubing should be flushed with insulin as insulin binds to the plastic tube.
- Regular insulin should be given using an infusion pump. Dissolve 50 units of insulin in 50 mL normal saline. Rapid acting insulin analogs have no advantage over regular insulin when used as an infusion.
- *Burette set may be used if infusion pump is not available with 50 units of regular insulin dissolved in 500 mL normal saline.*

Infusion rate

- *Initial:*
  - *Mild DKA, infant, severe hypokalemia*–0.05 unit/kg/hour
  - *Moderate, severe DKA*–0.1 unit/kg/hour
- *Subsequent modification:*
  - *Reduction*–The insulin infusion rate should be reduced only after resolution of acidosis. The infusion rate should then be decreased in a quantum of 0.02 unit/kg/hour.
  - *Increase*–The dose should be increased if fall in glucose is less than 50 mg/dL/hour. The dose should be increased in quantum of 0.02 IU/kg/hour. Wait for at least 30 minutes before modifying the dose again.

Options for Resource-Poor Settings

If the facility for intravenous insulin is not available, intramuscular or subcutaneous insulin can be used in children with normal perfusion. The first dose should be 0.3 unit/kg followed by 0.1 unit/kg hourly.

Rapid acting insulin analogs are preferable if available due to rapid onset and short duration of action.

Recurrent intravenous boluses of insulin should be avoided due to high risk of cerebral edema.

3. Electrolyte Management

Sodium

- Most patients have significant sodium deficits (4-6 mmol/kg). Slow rise in sodium levels in the setting of rapid fall in glucose is a risk factor for cerebral edema.
- The sodium content in fluid should be no less than 77 mmol/L (half normal saline). Normal saline (154 mmol/L) should be used in the first six hours of hydration. Thereafter the sodium content in the fluid should be between 77-154 mmol/L.

Potassium

- Significant total body potassium deficit occurs in DKA (3-6 mmol/kg).
- Extracellular potassium levels may however be high due to acidosis and insulin deficiency. Correction of metabolic acidosis and insulin administration causes intracellular shift of potassium predisposing to severe hypokalemia.
- *Management*
  - Potassium replacement should be started in the hydration phase (20 mmol/L) in the rare scenario of hypokalemia at presentation. Insulin therapy should not be started if potassium is less than 3.5 mmol/L.
  - In all other situations potassium replacement should be started after the initial hydration at the time of initiation of insulin infusion.
  - Potassium infusion should be started a dose of 40 mmol/L unless serum potassium is more than 6 mmol/L, the patient is anuric or ECG changes of hyperkalemia are present.
  - Insulin infusion rate should be reduced or stopped in children who develop hypokalemia during treatment of DKA despite increased potassium infusion.

Dextrose

- *Rationale*
  - Hyperglycemia resolves prior to correction of acidosis
  - Decreasing insulin infusion rate with lowering of blood glucose would prolong duration of acidosis
- *Management*
  - *Initial fluid*–Dextrose free
  - Add dextrose according to blood glucose.
    - < *17 mmol/L (300 mg/dL)*–5% dextrose; also add if fall of glucose is more than 90 mg/dL/hour
    - < *11.1 mmol/L (200 mg/dL)*–10% dextrose (10% dextrose solution with half normal saline sodium concentration can be prepared using combination of normal saline and 25% dextrose in a ratio of three to two).

4. Acid Base Management

- *Rationale*–Alkali treatment should be avoided as

- Acidosis resolves with hydration and insulin
- Rapid correction of acidosis associated with risk of
  - Hypokalemia (intracellular shift of potassium)
  - Lactic acidosis due to left-ward shift of oxygen dissociation curve and decreased tissue oxygen delivery

- *Alkali treatment*
  - *Indications*
    - pH less than 6.9 with refractory hyperkalemia
  - *Plan*
    - Sodium bicarbonate 1-2 mmol/kg as infusion over 1 hour
    - Should be diluted in half normal saline
- *Adverse effects*
  - Hypokalemia (intracellular shift of potassium)
  - Cerebral edema (osmotic effect)
  - Cerebral acidosis (low brain penetration of bicarbonate)

MONITORING (See Table 5)

- **Clinical**-Hourly
  - *Neurological status*–Level of consciousness, pupils
  - *Hemodynamic status*–Heart rate, blood pressure, respiratory rate
  - Fluid input and output
- **Laboratory**
  - Blood glucose hourly
  - *Venous blood gas*–pH, bicarbonate, lactate, base excess (4-6 hourly)
  - *Electrolytes*–Sodium, potassium (4-6 hourly)
  - Blood ketone (4 hourly)
- **Expected Response (See Table 6)**
  - **Blood glucose**
    - *Hydration phase*–Rapid decrease by 100-200 mg/dL over one hour
    - *Continuation phase*–Decrease by 50-100 mg/dL/hour
    - *Reasons for poor response*

TABLE 5. Monitoring Chart for Diabetic Ketoacidosis

Parameter	Time (in hours)									
	0 hr	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
Clinical										
Sensorium	√	√	√	√	√	√	√	√	√	√
Blood pressure	√	√	√	√	√	√	√	√	√	√
Hydration	√	√	√	√	√	√	√	√	√	√
Heart rate	√	√	√	√	√	√	√	√	√	√
Laboratory										
Blood glucose	√	√	√	√	√	√	√	√	√	√
pH	√	×	×	×	√	×	×	√	×	√
Bicarbonate	√	×	×	×	√	×	×	√	×	√
Blood ketone	√	×	×	×	√	×	×	√	×	
Corrected sodium	√	×	×	×	√	×	×	√	×	×
Potassium	√	×	×	×	√	×	×	√	×	√
Effective osmolality	√	×	×	×	√	×	×	√	×	√

- Dilute insulin
- Insulin sticking to intravenous tubing
- *Action*–Prepare new insulin infusion with new IV tubing

- **Metabolic acidosis**-Recovery over 12 hours
  - *Reasons for persistent acidosis*
    - Infection
    - Lactic acidosis
    - Cerebral edema resulting in hemodynamic instability
    - Hyperchloremic metabolic acidosis
  - *Actions*
    - Exclude infections, consider antibiotics
    - Evaluate for clinical features of cerebral edema
    - Consider changing to Ringer's Lactate if hyperchloremic acidosis

- **Serum potassium**
  - *Desired*-should not fall to hypokalemic range
  - *Actions:*Increase potassium in fluid to upto 60 mmol/L; reduce insulin infusion if persistent hypokalemia

- **Serum sodium**
  - *Desired*–Increase by 3 mmol/L per 100 mg/dL fall in glucose
  - Less increase is a risk factor for cerebral edema
- **Ketones**
  - Rapid decrease in blood ketones
  - Urine ketones may persist for up to 48 hours as urine ketosticks measure AcAc
    - BOHB is the main ketone in DKA
    - BOHB is converted to AcAc during treatment

TABLE 6. Laboratory Parameters and Response to Treatment in DKA

Parameter	*Expected response*	*Worry if*	*Suggested action*
Blood sugar	50-100 mg/dL/hour decline	Decline > 100 mg/dL/hour Decline < 50 mg/dL/hour	Add dextrose to IV hydration fluid Prepare fresh infusion, flush tubing with insulin
Blood pH	Resolution by 12 hours	Persistent at 12 hours	Exclude infection, shock, lactic acidosis
Serum Na	Increase	Increase < 2 mmol/L/hour	Increase sodium concentration in fluid
Serum K	Gradual decrease	Hypokalemia	Increase potassium concentration in fluid
Anion gap	Resolution by 12 hours	Elevated at 12 hours	Exclude lactic acidosis, consider infection
Plasma osmolality	Gradual fall	Decrease by > 2 mOsm/kg/hour	Increase sodium concentration, decrease fluid rate
Blood count	Decrease	Persistently elevated	Exclude infection
Blood urea	Decrease	Persistently elevated	Exclude renal failure

DISCONTINUATION OF ACUTE TREATMENT

- **Indications**–Normal hydration status, sensorium, oral acceptance and blood gas.
- **Protocol**
  - Insulin infusion should be continued till a major meal. If a child desires to have a snack in between dose of insulin infusion may be increased by 100% for 30 minutes to provide adequate coverage.

- Initiation of insulin regimen at transition provides faster glycemic control compared to sliding scale. Insulin requirement following DKA is usually 2-2.5 unit/kg/day.
- Subcutaneous insulin should be given 60 minutes before stopping insulin infusion for short acting insulin and 30 minutes for rapid acting analogs. Early discontinuation of insulin is associated with recurrence of hyperglycemia. Basal insulin should be given 12 hours prior to the planned transition.
- Monitor blood glucose after one hour and two hourly thereafter for six hours.

COMPLICATIONS

Table 7 lists the complications likely to occur following DKA.

TABLE 7. Complications Following DKA

Acute	*Chronic*
Cerebral edema Infection - Bacterial, fungal Hypoglycemia Hypokalemia Hypophosphatemia Renal failure Acute respiratory distress syndrome Venous thrombosis	Growth hormone deficiency Mental retardation Diabetes insipidus

Cerebral Edema

Cerebral edema is the most serious complication of DKA and the most common cause of death. The incidence of clinical cerebral edema in western countries is 0.5-1.0%. Radiological features are however present in most cases. The incidence of cerebral edema has been shown to be higher in limited Indian data about the condition. The etiology of cerebral edema in DKA is unclear, but is related to rapid shifts in plasma osmolality following treatment and direct effect of the disease in the form of cerebral hypoperfusion and hypocapnia.

- ***Risk factors***
  - *Patient related*
    - Age less than 5 years
    - *Severe disease*–Severe acidosis, high plasma osmolality, low CO_2 and high blood urea

- *Treatment related*
  - *Insulin*–Insulin bolus, multiple intravenous injections
  - *Fluid*–Excessive volume (> 4 L/m^2/day), hypo-osmolar fluid
  - *Alkali treatment*

- ***Onset***–Usually 4-12 hours of treatment (can occur at any time and may even be present at diagnosis specially with intravenous fluid treatment from another center)
- ***Indicators to diagnosis***
  - Persistent hemodynamic instability
  - Worsening in clinical condition after initial improvement
- ***Clinical features***
  - *Early*–Headache, vomiting, drowsiness, irritability, relative hypertension with bradycardia compared to earlier readings
  - *Late*–Unconsciousness, focal neurological deficits, papilledema, fixed dilated pupils, cranial nerve palsies
- ***Diagnosis***–Clinical, no need to confirm with imaging. Neuroimaging should however be considered after stabilization in patients with persistent neurological features to exclude intracranial hemorrhage, rhinocerebral mucormycosis and cortical venous thrombosis.
- ***Treatment***
  - *Mannitol*–0.25-1 g/kg intravenous push *or*
  - *Hypertonic saline*–10 ml/kg of 3% saline over 30 minutes
  - *Fluid restriction*–Reduce fluid rate by 33%
  - *Head end elevation*
  - *Ventilation*–Ventilation should be done for impending respiratory failure. Hyperventilation should however be avoided as CO_2 levels below 25 mm Hg are associated with cerebral hypoperfusion.
- ***Outcome***–Following clinically evident cerebral edema
  - Mortality–20-30%
  - Morbidity–30%
- ***Prevention***
  - Avoid insulin bolus

- Judicious fluid therapy
- Avoid repeated boluses
- Fluid replacement <3.5 L/m^2/day
- Gradual correction in children with high plasma osmolality
- Avoid sodium bicarbonate
- Continue normal saline in children with high plasma osmolality

Infections Associated with DKA

- ***Agents***–Bacteria, fungi (rhinocerebral mucormycosis, aspergillosis)
- ***Indicators***
  - Persistent fever and leukocytosis
  - Black nasal discharge (mucormycosis)
  - Hemoptysis (pulmonary aspergillosis)
- ***Diagnosis***–Blood culture, chest x-ray, and sputum culture. It is always better to send blood, urine, and other suspicious secretions for culture at the beginning of therapy.
- ***Treatment***
  - Bacterial infections–Antibiotics
  - Fungal infections–Itraconazole, amphotericin B

Renal Failure

Development of renal failure during management of DKA is an ominous sign as it predisposes to cerebral edema and acute respiratory distress syndrome. Decrease in urine output to less than 0.5 mL/kg/hour should point to the diagnosis of renal failure and mandate reduction in fluid infusion rate. Hypophosphatemia and rhabdomyolysis are precipitating factors for renal failure. Early consideration for hemodialysis is required in this setting due to the difficulties in fluid and electrolyte management.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidosis is usually observed around 8-12 hours of therapy when ketoacidosis has resolved. It is caused by excessive administration of chloride in the form of sodium and potassium chloride. The condition should be considered in the presence of persistent metabolic acidosis with normal blood ketones. Chloride load (Na – Cl = 32 mmol/L) is a reliable marker of hyperchloremic metabolic acidosis. The condition is self-limiting and should be managed with changing the fluid to Ringer's lactate with lower chloride content.

Hypophosphatemia

Hypophosphatemia is common during management, but is usually asymptomatic. Severe hypophosphatemia (levels less than 1 mg/dL) is associated with muscle pain, cramps, rhabdomyolysis and hemoglobinuria. Correction of hypophosphatemia is desirable in this setting.

PREVENTION OF DKA

Primary

- High index of suspicion for T1DM.
- Frequent sugar monitoring and careful management during sick days and invasive procedures in children and adolescents with T1DM.
- Close sugar monitoring and rapid correction of hyperglycemia of patients on insulin pumps. All children on insulin pump should have access to vials/ pens of rapid acting insulin.

Secondary

- Early diagnosis of ketoacidosis.
- Blood ketone level in all children at diagnosis
- Home blood ketone monitoring during sick day
- Careful fluid and insulin management.

Tertiary

- Early identification and treatment of cerebral edema.
- Appropriate treatment of infections.

12

THE FIRST MONTH AFTER THE ONSET OF TYPE 1 DIABETES MELLITUS

Ganesh S. Jevalikar

SUMMARY OF RECOMMENDATIONS

- The first month after the diagnosis of type 1 diabetes mellitus (T1DM) sets the foundations for long-term outcome of T1DM care.
- Patients and families should be evaluated by a team consisting of a pediatric endocrinologist, nurse educator, nutritionist, and psychologist. Meeting with other patients and families can be a big help.
- Clear and truthful messages given in a compassionate manner are necessary and false reassurances are best avoided.
- Emphasis should be given on a comprehensive diabetes care using a physiologic insulin regimen.
- Frequent contacts with diabetes care team are necessary in the first month including structured email and phone support.
- Higher insulin doses are required soon after diagnosis due to increased appetite and recovery of weight. Soon after, the dose requirement invariably comes down and honeymoon phase may set in. Frequent blood glucose (BG) monitoring and anticipatory guidelines for insulin dose adjustments, therefore are necessary.
- A healthy lifestyle including healthy meals, exercise and reduction of sedentary activities should be encouraged. A written plan of insulin and food adjustments for exercise should be given.
- Taking multiple opinions is common in the first month. Hence, uniform messages need to be given by all specialists to avoid confusion in the mind of patients and their caregivers.
- The child should be encouraged to resume school as early as possible. Written guidelines should be given to school authorities about diabetes and hypoglycemia management.
- Diagnosis of a child with T1DM evokes several psychological reactions and can disturb the entire family. However, with adequate support of diabetes care team and family, T1DM can be very well managed.

INTRODUCTION

The diagnosis of type 1 diabetes mellitus (T1DM) changes the life of the patient and family drastically. All of a sudden families are faced with a lifetime disorder needing multiple pricks for insulin administration and blood glucose (BG) testing with significant readjustments to their diet and lifestyle. The patient and family go through several emotions including denial, anger and frustration finally leading to acceptance of the eventuality and adjustment to the new life. This transition takes variable amount of time for each patient depending on his or her knowledge, education provided, psychological strength and family support. A good start with clear and truthful messages positively helps the patient in this transition. Therefore the first month after diabetes onset is a critical time period from the management point of view. In addition several medical issues related to insulin dose, appetite and insulin side effects are common at this time. This chapter outlines some of the problems observed in the first month after onset of diabetes. Specific aspects of insulin dose, regimen, hypoglycemia management and diabetes education are also discussed elsewhere in the *Diabetes Guidelines.*

BREAKING THE NEWS

Clinicians must show utmost care and compassion while revealing the diagnosis. At the same time giving false messages like "insulin dose is only for a few days" need to be avoided. The following points need to be discussed in detail:

1. What is T1DM and how does it happen?
2. Explaining and reassuring parents that T1DM may happen to any child; often does not have family history and is frequently sudden in onset. Parents should be reassured that it is not the result of any mistake on the part of the child and the family.
3. Need for insulin therapy and subcutaneous injections and reasons why oral antidiabetic medications are unhelpful.
4. Explain the urgent need for insulin initiation to prevent diabetic ketoacidosis (DKA).
5. Importance of the physiologic insulin regimen.
6. Importance of BG monitoring, diabetes logs and other components of diabetes management.
7. Reassurance that with good glycemic control normal growth and participation in regular academic, cultural and sports activities are possible.
8. Reassurance on flexible lifestyle and improved lifespan with modern diabetes treatment.

Often the families are extremely anxious to know if any curative treatment is available. Therefore counseling that although at present there is no medication (including alternate medications), procedure or transplant that can 'cure' T1DM, the same may be available in future helps to avoid a feeling of hopelessness and motivates patients.

Children and adolescents should be encouraged to be a part of the discussions. Clinicians must allow the family some time to accept the diagnosis and focus only on survival skills initially.

An initial meeting (and ongoing contact) with "senior" and well-adjusted patients is most essential and helps in acceptance of the diagnosis and acceptance of insulin therapy as the only available treatment.

HOME VERSUS IN-HOSPITAL INITIATION OF THERAPY

Traditionally most children with T1DM are admitted in hospital for initiation of insulin treatment. However, ambulatory management of stable patients is being increasingly done in centers with structured diabetes care teams and 24-hour email or telephonic support.

Advantages of hospital admission include the following:

- Opportunity for intensive education and concentrated learning
- Supervised administration of insulin
- It takes the burden off the family thereby giving them more time to get over the initial shock of diagnosis.

Disadvantages of hospital admission include:

- Increased cost of treatment
- Home and hospital settings are different and families may be less relaxed in a hospital
- Reliance on hospital staff for diabetes care.

Table 1 lists the checklist before discharge of any newly diagnosed diabetic child from the hospital. Although families are expected to learn essential skills and perform insulin injections and BG testing at home, with adequate support from diabetes care team this can be done with fair ease.

TABLE 1. Checklist Before Discharge of T1DM Patients from the Hospital

- Resolution of DKA, absence of vomiting
- Parents/caregivers have received education on basic survival skills
- Parents/caregivers are confident in giving insulin and testing blood glucose
- Availability of following supplies are ensured:
  - Insulin syringe/pen with extra needles
  - Lancets for blood glucose monitoring
  - Glucometer with test strips ± serum/urine ketone strips
  - Glucagon injection
  - Blood glucose diary
- Contact details of the person to be contacted in emergency

INITIAL EVALUATION

All patients with T1DM are evaluated for the possibility of DKA at diagnosis with clinical features, urine/serum ketone testing and a blood gas if clinically indicated.

Testing for autoimmune antibodies (anti-GAD-65, ZnT8, IA2, ICA and IAA) is not mandatory for all cases, but might be helpful where a differential diagnosis of type 2 diabetes mellitus (T2DM) and monogenic diabetes are being considered.

All patients with T1DM should be screened for celiac disease (serum anti-tissue transglutaminase IgA along with total IgA levels) and hypothyroidism (serum TSH). Thyroid function testing should be deferred in very sick children with DKA till recovery.

An initial ophthalmic examination to look for cataract, refractory errors or presence of optic atrophy (suggesting diagnosis of Wolfram syndrome instead of T1DM) should be part of evaluation.

COMPONENTS OF DIABETES MANAGEMENT

1. Insulin Dose, Regimen and Delivery Device

In the first few days after diagnosis, especially after recovery from DKA, dose requirement can be high due to glucotoxicity(1.5-2 unit/kg/day or higher). Higher or additional doses of prandial insulin may be necessary if there is excess appetite and higher frequency of snacking. With weight regain and return of the

appetite to normal, the dose requirement decreases gradually to 0.5-1 unit/kg for prepubertal children and 1-1.5 unit/kg/day for pubertal children.

The honeymoon phase (partial remission phase) may set in the first month of diagnosis itself and is usually heralded by normal or low BG readings needing dose reduction. Frequent contacts with the patient are essential to guide appropriate reduction of insulin dose. In some patients insulin doses may need to be skipped or stopped for a few days to weeks. In these patients BG monitoring is very important to pick up the end of the honeymoon phase.

The type of insulin delivery device used (syringe, pen or pump) depends on patient's preference, socioeconomic status and age of the child. It should be emphasized that equally good glycemic control can be achieved using any of these devices. If syringes are being used, matching of the type of syringe with the insulin vial (e.g. 40 IU syringe for insulin strength of 40 units/mL) must be emphasized. In the initial period after diagnosis disposable insulin pens maybe used to allow patient to get familiar with insulin type and delivery device for long-term use. Most centers do not routinely use insulin pumps at the time of diagnosis, as the families have to learn complexities of pump therapy while still coming to terms with the diagnosis and learning basic diabetes management skills.

Right from the onset emphasis should be given on physiologic insulin regimen (basal-bolus treatment). For those who cannot afford basal insulin analogs, NPH insulin given twice daily can provide similar glycemic control.

2. Blood Glucose (BG) Monitoring

Monitoring and recording of BG is as important as taking insulin. Testing frequency is higher in the initial period including BG before and 2 hours after meals and at midnight. This helps in insulin dose titration, identification of low sugars, responses to meals/exercises and identification of honeymoon phase needing anticipatory dose reduction.

BG level readings along with insulin doses should be recorded in a diabetes log. The same also should contain remarks explaining high or low glucose readings.

BG targets should be individualized. In the first few days, strict glycemic control is not a necessary goal, focus being learning basic techniques in diabetes management. Parents tend to get extremely worried about high or low readings; hence clear-cut instructions on how to manage these are required. A 24-hour helpline is ideal but not practical in most Indian centers.

Frequent communication with the diabetes team on email or phone is helpful in dose adjustments until parents learn the skill for preventive and corrective adjustments of insulin doses. This transfer of responsibility takes variable amount of time depending on understanding of the family and acceptance of the diagnosis.

3. Nutrition

Most questions of parents initially are related to diet. It should be emphasized from the start that the diet of a diabetic child is nothing but a healthy meal plan with balancing of food and insulin doses. Clinicians should not fall in the trap of *'can have'* and *'can't have'* categories of foods. Several myths related to a diabetic diet such as *'diabetics can't eat rice'* or *'diabetics need to eat every 2 hours'* need to be specifically discussed by a nutritionist with experience in management of childhood T1DM.

In the first few days following diagnosis, the child tends to eat more and with higher frequency. Insulin doses should correspondingly be increased and extra doses may be required for heavy snacking. For between-meal snacks, meal options containing no or low carbohydrates can be given (cucumber salad, butter milk, tea without sugar etc.). Adequate water intake should be encouraged. After regaining lost weight, appetite comes back to normal and insulin doses need to be reduced.

4. Exercise

Exercise should be encouraged as a part of healthy lifestyle and a written plan to prevent exercise-induced hypoglycemia should be given. Monitoring of BG before and after exercise maybe helpful to make individual plan. Prevention of hypoglycemia maybe done by reduction of insulin dose preceding exercise and/ or extra carbohydrate containing snack.

5. Hypoglycemia – Recognition and Management

Special care should be taken to avoid hypoglycemia in the first few days, as it can be a very unpleasant experience causing important barrier in long-term glycemic control. All families must receive education on recognition, prevention and treatment of hypoglycemia including administration of glucagon injection.

6. Identification

Persons with diabetes should be encouraged to use identification cards, bracelets, bands or pendants, which help to identify them as a patient with T1DM. These should contain instruction for glucose administration for unconsciousness, emergency contact number and number of treating diabetes team.

7. Diabetes Education

Comprehensive diabetes education by certified diabetes educators is the key to long-term diabetes control. In the first month, it is important to focus the education on essential survival skills, which include the following:

- Insulin administration

- BG monitoring
- Writing BG readings in a log
- Management of hypoglycemia
- Ketone testing and sick day management
- Basics principles of healthy eating.

The pace of education should be individualized for each family. Different tools including handouts, pictures and videos should be used. Families should be encouraged to write down a list of questions before each visit. Families tend to ask several questions at the same time and may need to be repeatedly requested to first learn the essential skills. In addition, sources of further reading including patient education books and verified website names should be given.

It is important to identify the correct caregiver to be given education as it is not uncommon for several family members to accompany a child at the diagnosis, however, over a period of time the management is done by the child alone or one of the parents.

Return Visits within the First Month

Frequent contact with diabetes team is essential in the first month. In the initial few days, daily contact on telephone helpline and/or email may be required. Frequency of clinic visits are individualized depending on the travel distance and other expenses involved, but at least 3-4 visits are necessary for learning basic diabetes management skills.

COMMON PROBLEMS IN FIRST MONTH

Multiple Opinions

As a rule most of the families with T1DM seek multiple opinions from allopathic as well as alternative therapies in the hope for cure or treatments other than insulin (e.g. oral medications, alternative treatments, stem cell transplants etc.). Clinicians should give uniform messages and emphasize the importance of insulin therapy. Open discussion with families should be encouraged.

Several relatives and 'advisors' tend to give unsolicited advice and may cloud thinking of the family. Patient and the family should be advised to accept advice only if it is based on sound scientific knowledge.

Alternative Therapies

Till date no therapies are available that can cure or halt the progression of T1DM. Many families try alternative therapies including herbal remedies and natural home remedies. It is helpful to have discussion on this during initial visits

and emphasize the need for continuation of insulin. Many of the therapies might coincide with the honeymoon phase thereby giving an impression of their effectiveness; however, ultimately leading to disappointment. Experiences of other families can be shared with the new patients to help them make an informed choice.

Hair fall

Following treatment of diabetes, several patients report significant hair fall causing distress to the family. This commonly results from telogen effluvium related to stress of illness. Patients should be reassured about temporary nature of hairfall and may be given multivitamins containing biotin for 1-2 months.

Abdominal Distension

Significant abdominal distension and upper abdominal discomfort can be seen due to abdominal wall weakness, hypokalemia, excess eating and gaseous distension. Treatment is symptomatic. This usually improves after initial month.

Replenishment of Potassium Stores

All patients with ketoacidosis should receive potassium supplements; initially intravenous and subsequently oral (1-2 mEq/kg/day) till discharge from hospital.

Insulin Edema

Insulin edema is a rare complication of insulin therapy and is commonly reported within few days of initiating insulin therapy or intensification of therapy in a poorly controlled diabetic. It tends to be more common in underweight subjects and severity may vary from mild pedal edema to frank anasarca with pleural effusion and cardiac failure. In mild cases it may subside without any treatment over a few days to weeks; however, severe cases may need salt and fluid restriction with diuretic therapy.

Eye Changes

Frequent changes in lens curvature (resulting in change of refraction) are seen in first few days after diabetes diagnosis. During this time, a change of glasses is best avoided. Cataracts can be seen during recovery from DKA. These are mostly reversible but rarely may persist and require surgical extraction.

Resuming School

Children should be encouraged to resume school as early as possible. A medical certificate explaining the reason for absence from school needs to be issued. The school authorities need to be given written information about T1DM, recognition and treatment of hypoglycemia and individual instructions regarding dosing and food regimen of the child. In general, care should be taken not to keep meal

timings drastically different from peers, as it might lead to psychological problems in the child.

If necessary class teacher and principal of the school need to be informed that diabetes is not contagious and a diabetic child can participate in usual sports, cultural and academic activities.

Intercurrent Illnesses

In general, treatment of intercurrent illnesses is similar as in any non-diabetic child. However whenever possible use of unnecessary medications like cough syrups should be avoided and dispersible tablets should be preferred in place of syrups if available.

Sick day guidelines need to be readily available to all the families including instructions on when to take child to hospital.

PSYHCHOLOGICAL ASPECTS

Children and families with T1DM have significant risks for psychological problems, which can affect glycemic control and the long-term outcome. These problems are often strongly affected by family distress. Adjustment difficulties are common and may persist leading to poor glycemic control.

All children and their families should be screened for psychological problems at the time of diagnosis by a psychologist experienced in childhood diabetes. It is extremely beneficial to meet other families who have been managing diabetes well. The diabetes care team should maintain a database of families willing to support and help in counseling of newly diagnosed patients.

Healthy family functioning is very important to successful diabetes management. Family discord or dysfunction is an important risk factor for poor glycemic control and recurrent DKA. It should be emphasized that diabetes care is teamwork and no single person can handle its burden. A clear-cut sharing of responsibilities between the child, and caregivers (mother, father and other relatives) is necessary. In a joint family, head of the family should be taken into confidence to enable successful diabetes management.

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SICK DAY MANAGEMENT

Aspi J. Irani

"SICK DAY" RULES

- Never *omit* insulin when sick. Insulin dose can be *reduced* only if child is anorexic or vomiting with blood glucose (BG) below 80 mg/dL.
- Follow BG and urine or blood ketones. These should be checked every 2-4 hours. Never go by the appetite alone.
- Give additional supplements of rapid acting analog or regular insulin when ketones are raised with BG above 180 mg/dL.
- If child cannot eat his/her usual diet, give plenty of liquids orally in frequent small sips. Offer sweetened liquids when BG is less than 180 mg/dL and salty liquids when BG is above 180 mg/dL.
- If BG is less than 60-80 mg/dL with raised ketones and the child cannot accept or retain oral liquids, consider "mini dose glucagon". If this is not practical, hospitalization for intravenous dextrose is required.
- Hospitalize urgently for impending diabetic ketoacidosis (DKA) if the child has more than 3 vomits, significant abdominal pain, drowsiness or breathlessness.
- It is the responsibility of the medical team to ensure that every patient is fully conversant with these "sick day" guidelines. Clear written instructions should be given to the family and the school authorities.

INTRODUCTION

Children with diabetes are not more susceptible to infections than those without diabetes, provided the diabetes is in good control. If diabetes is poorly controlled, infections tend to be more severe and unusual infections can develop.

The line of treatment of any illness in a child with diabetes does not differ from that in a child without diabetes. Whenever possible, tablets or sugar-free syrups can be used; however, if this is not possible then one should not hesitate to use sugar containing syrups as the influence on blood glucose (BG) would be marginal.

When children with diabetes develop an infection or other severe illness there are two factors that can adversely affect diabetes control:

1. ***The release of stress hormones and cytokines in response to the illness:*** These raise BG *despite poor oral intake* and can lead to ketoacidosis (DKA). This is often seen during illnesses, which are associated with fever.
2. ***Anorexia, nausea, vomiting or diarrhea:*** When these dominate the clinical picture, without a febrile response, hypoglycemia commonly develops. It is important to note that vomiting without diarrhea, if associated with raised BG, is often due to insulin deficiency *per se*.

The net effect of the two opposing factors, which can be present together in a given illness, is difficult to predict and hence a safe rule is to *follow the BG and ketones (in urine or preferably in blood) rather than the appetite in planning insulin therapy on sick days.* For this, BG and ketones should be checked frequently, once in every 2-4 hours.

DKA is by far the commonest diabetes-related cause of death in children and adolescents with type 1 diabetes mellitus (T1DM). The commonest cause of DKA in a known diabetic (other than insulin omission) is lack of knowledge of sick day management.

It is important to educate the patient and family members about handling sick days to prevent DKA, dehydration, and hypoglycemia. Guidelines for this should be given to the patient in writing; they should be clear and should be reinforced periodically, during each clinic visit.

MANAGEMENT OF DIABETES DURING A SICKNESS

1. Monitoring on Sick Days

Blood glucose and ketones must be checked every 2-4 hours. There is only one meter available in India that checks blood ketones and the cost of each ketone strip is very high (Rs. 150/- approximately). In practice therefore,a majority of the patients depend on the less reliable urine ketone tests. If a patient does not have a BG meter, they may test urine glucose using ketodiastix strips though this is far from the ideal.

Blood testing reflects the glucose or ketone level at the time of testing and gives a precise measurement whereas urine tests reflect the average level since the time urine was last passed. Unlike urine, blood has the added advantage that it can be drawn whenever needed.

Blood ketone test measures β-hydroxybutyrate (BOHB) which is the predominant ketone body in DKA. The urine test measures acetoacetate (AcAc). In normalcy, the ratio of BOHB to AcAc is 1:1 while in DKA it can be as high as

10:1. Hence, urine tests underestimate the degree of ketosis. During recovery from ketosis, as BHOB gets converted to AcAc; urine tests may show (false) persistence of ketosis for up to 24 hours with risk of overtreatment with insulin and late hypoglycemia.

A BG level above 180 mg/dL signifies insulin deficiency and the need for additional insulin. Presence of ketones in urine or blood would mean either carbohydrate deficiency due to poor intake (in which case the simultaneous BG would be less than 100 mg/dL) or insulin deficiency (when associated with BG over 180 mg/dL).

2. Insulin on Sick Days

The aim of insulin therapy on sick days is to keep BG between 80-180 mg/dL and ketones at trace or absent in urine and <0.6 mmol/L in blood.

Insulin should never be completely omitted even if the child refuses to eat.

Insulin dose can be reduced only when BG is below 80-100 mg/dL and the child cannot eat. In this case, the short or rapid acting insulin is *withheld* while the intermediate or long acting insulin is continued as usual. If however, the urine ketones are also positive (more than trace), the dose of the intermediate or long acting insulin (as the case may be) should be reduced by 20-30%. **Table 1** summarizes the suggested reductions in routine insulin dose to prevent hypoglycemia.

TABLE 1. Reduction in Usual Insulin Dose to Prevent Hypoglycemia on "Sick Days"

Blood glucose	*Ketones*	*Action*
<80 mg/dL	Absent / trace (<0.6 mmol/L)	Omit regular insulin or rapid acting analog if oral intake is poor. Continue NPH or long acting basal analog
<80 mg/dL	> Trace (>0.6 mmol/L)	*Also* decrease NPH or long acting basal analog by 20-30%

When BG is over 180 mg/dL, the patient needs a supplement of short or rapid acting insulin to be given immediately, either subcutaneously or intramuscularly. The supplement is calculated as a percentage of the total daily dose (TDD). TDD refers to the sum of all insulins taken in 24 hours on routine days. The supplement may range from 5-20% of TDD depending on BG and ketone levels. It is always given as regular insulin or rapid acting analog.

As a rough guide, when BG is over 180 mg/dL with absent or trace urinary ketones, a supplement of 5-10% of TDD may be taken; the supplement should be 10-20% if ketones are small or moderate and 20% if ketones are large. Insulin

supplements (5% of TDD) would also be needed if BG is between 100-180 mg/dL with moderate or large ketones. **Table 2** gives at a glance the calculation of insulin supplements.

Retesting is done at 2-4 hours intervals with supplements taken whenever indicated.

When taking serial supplements it must be remembered that some of the previous dose may not have been absorbed or may not have acted as yet. With rapid acting analogs the rate of absorption is 30% per hour, hence at the end of 2 hours 60% would have been absorbed while 40% is yet to commence working and this amount should be subtracted from the calculated amount of the next supplement.

TABLE 2. Insulin Supplements (Expressed as a Percentage of TDD) to Prevent DKA on "Sick Days"

Blood glucose	*Urine ketones*	*Blood ketones*	*Extra insulin* (% of TDD**)*
100-180 mg/dL	Moderate / large	>1.5-3 mmol/L	5%
>180 mg/dL	Absent / trace	<0.6 mmol/L	5-10%
180-400 mg/dL	Small / moderate	0.6-1.5 mmol/L	10-15%
>400 mg/dL	Small / moderate	0.6-1.5 mmol/L	15-20%
180-400 mg/dL	Large	>3 mmol/ L	20%
>400 mg/dL	Large	>3 mmol/L	20%

*Supplements are given as regular insulin or preferably as a rapid acting analog.

**TDD or total daily dose of insulin refers to the sum of all insulins taken on a routine day.

Insulin requirement may go up during the incubation period of an illness. Increased requirement may last for as much as a week after recovery from the illness. In patients who are in the remission phase of diabetes, insulin requirement may shoot up rapidly during an illness.

3. Diet on Sick Days

The patient who cannot eat his/her regular meals should be offered plenty of salty liquids (such as rice *kanji,* vegetable soup, *dhal* soup, buttermilk, milk without sugar, or chicken soup) if BG is above 180 mg/dL. Sweet liquids (non-diet soft drinks without fizz, fruit juices, milk with sugar, WHO-ORS or melted ice-cream) should be consumed if BG is below 180 mg/dL.

These liquids must be taken in small and frequent sips to minimize chances of vomiting. It should be kept in mind that an anorexic child is more likely to accept items of his/her choice. Cool liquids are preferred as they are less likely to induce nausea or vomiting.

4. Mini Dose Glucagon Rescue

If the BG is below 60 mg/dL with more than trace ketones in urine (blood ketones >0.6 mmol/L) and patient cannot accept or retain any oral liquids, glucagon (if available) can be injected in a dose of 10 µg per year of age (minimum dose: 20 µg and maximum: 150 µg). For this, glucagon powder must be dissolved in the diluent provided (1 ml = 1000 µg) and injected intramuscularly using a 100 IU insulin syringe. One unit (1 IU) would provide 10 µg; hence 2-15 units would be needed depending on age. This mini dose raises BG by 60-90 mg/dL for a period of 60 minutes *without aggravating nausea*. Glucagon can be repeated in double the dose if BG does not rise sufficiently after 20-30 minutes.

Many patients in our country may not afford glucagon and unfortunately it is also not freely available at all times. In case the patient does not have glucagon, then the child would need to be hospitalized for intravenous dextrose in case of impending hypoglycemia.

5. Do not Delay Hospitalization when there are Signs of Impending DKA or Impending Severe Hypoglycemia

Hospitalization may be required either for impending severe hypoglycemia (as discussed above) or impending DKA.

If the child vomits more than 3 times, is drowsy or exhausted, has significant abdominal pain or is breathless, immediate hospitalization for intravenous fluids and insulin infusion is a must. Earlier hospitalization should be considered if the child is below the age of 5 years or the caretakers are incapable of managing at home. It must be remembered that the single most important factor that correlates with mortality in DKA is the duration of the process.

6. Sick Day Management in Patients on Insulin Pump

The principles of sick day management in pump users are the same; the finer differences are discussed in the chapter on pumps.

Every patient must be familiar with the sick day guidelines for managing diabetes during an illness. They must know what to check; how frequently to check; how much of extra insulin to take; when to reduce insulin; what oral intake is appropriate; and when to rush to hospital.

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PSYCHOLOGICAL ASPECTS

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SUMMARY OF RECOMMENDATIONS

- The treating team should be able to identify various psychological problems affecting the child or adolescent and his/her family members and to manage these issues effectively.
- Childhood diabetes is a family disease. Teamwork involving all close family members is essential for the successful management.
- Learning and cognitive defects are common in these children especially if they have poor glycemic control.
- The main psychologic problems include anxiety disorders, eating disorders and depression.
- The spectrum of eating disorders varies from severe malnutrition to obesity.
- Maintaining a good quality of life helps to achieve good diabetic control.
- A good peer group support is essential for a better outcome.
- Many children find it difficult to manage blood glucose testing or take insulin injections during the school hours. They may omit some doses and try to manipulate SMBG results. Hence the presence of a knowledgeable person at school is a must for effective treatment outcome.
- Periodic reinforcement of effective family participation should be ensured by doing regular family-based programs.
- Multisystemic therapy is more effective than discussing the issues with the child alone.
- Regular interventions to reduce anxiety and improve the management of stress should be a part of the treatment program.
- It is ideal to have a mental health specialist in the management team looking after young people with diabetes.
- Subtle parental supervision should continue throughout adolescence.

INTRODUCTION

Children with diabetes and their family members may experience various psychological problems in their life, often leading to depression and loss of self-esteem. These problems affect the treatment results adversely, leading to a vicious cycle of events. The treating team should be able to anticipate, detect and deal with these issues and manage them at appropriate times. This will decrease the incidence of both short-term and long-term complications and help to achieve a better quality of life (QOL).

DIABETES, THE FAMILY DISEASE

Childhood diabetes is a "family disease". The impact of the disease affects not only the child, but also also the entire family. For managing effectively, each member of the family should play his/her role perfectly. Effective family communication, sharing responsibilities, and solving problems collectively, will go a long way in the successful management of the disease. On the contrary, if the child is being blamed and crucified for his/her "sugars not getting controlled properly", and if the family members also join the team of "accusers", the self-esteem of the child will be so low that he/she may develop severe psychological problems such as depression and denial. Hence the whole family should be there with the child during the "ups and downs", not only for the sugars, but also for all their achievements as well as setbacks. Children (and adolescents) need family support for all their activities, including glucose monitoring, choosing appropriate diet and getting enough time for play and sports. Hence the healthcare providers (HCP) should aim for achieving and maintaining a good parents-child-siblings teamwork for the effective management of the disease.

EFFECT ON INTELLIGENCE AND LEARNING CAPACITY

Learning and cognitive defects are common in children with diabetes, especially during times of marked hyper- or hypoglycemia. Various studies have documented increased incidence of cognitive and learning difficulties, decreased intelligence, snags in attention and processing speed, defective long-term memory and imperfect executive skills in affected children. Some abilities such as attention capacity, processing speed and executive skills are more commonly affected in children with early onset diabetes, while other features such as verbal and intelligence scores are related to severe hypoglycemia. Many studies have also pointed out the influence of frequent swings in the blood glucose levels (hypo- and hyperglycemia) on the prevalence of learning disabilities. All children with diabetes should be monitored for school performance and learning difficulties. If found abnormal, they should be assessed for thyroid function, and also referred for detailed evaluation and treatment.

PSYCHOLOGICAL PROBLEMS

The child with diabetes has to face several painful and stressful situations on a daily basis. The pain of daily multiple injections and glucometer readings, periodic lab investigations, frequent hospital visits and occasionally admissions, cross consultations and diet and activity restrictions all result in a state of chronic stress in the child. The realization that the disease "will be there with him/her till the end of his/her life" often causes resentment, denial, and depression. Since diabetes management is like walking on a tightrope, with frequent falls into hypo- and hyperglycemia, they get a feeling of insecurity, which may come in the way of their ambitions. Restraints imposed by family members and school authorities regarding activities, sports, and (sometimes unnecessary) diet restrictions may make them avoid socializing and become reclusive. Often their classmates, teachers, and family members tend to overprotect them or try to isolate them from the mainstream, increasing the feelings of severe loneliness. The child may have to handle the feelings of being a burden on the family, and resentment of siblings and parents. All these factors can cause or worsen depression. The same problems may occur in one or more family members.

Children or family members who experience a state of depression and other severe psychological stress have inadequate coping skills and may not be able to muster effective family or peer group support. Main psychologic problems are anxiety disorders, eating disorders and depression. Various studies show that at least 10% of children develop depressive disorders and 30% experience anxiety disorders in the first 10 years after diagnosis. Girls outnumber boys in developing these psychological problems. There is a direct link between psychological issues and glycemic control even though many with good glycemic control have depressive symptoms. Most children will not articulate their problems unless specifically asked for, but a few will demonstrate emotional outbursts and anger.

Eating Disorders

A diagnosis of diabetes results in "strict" diet control imposed by doctors, parents, relatives and/or teachers. Many of these overdone restrictions are due to wrong beliefs and local customs prevailing in that area or those appropriate for type 2 diabetes. The tendency to equate childhood diabetes with adult-onset diabetes is common and makes matters worse. The young child with diabetes often presents with marked weight loss and may experience further loss of weight and even become malnourished due to strict diet restriction. In the long run, the affected child develops a variety of eating disorders, with girls (30%) outnumbering boys (5%). The abnormal glycemic control is the key problem and the whole group of eating disorders revolves around this condition. If the episodes of hypoglycemia are frequent, the fear of low sugars makes the child to eat snacks and sweets at

odd times, completely upsetting glycemic control. Adolescents, who take care of injections and glucose monitoring by themselves, tend to manipulate self-monitoring of blood glucose (SMBG) readings, omit insulin injection, do too little or more exercise, and adopt abnormal dietary practices. Increase in body mass index (BMI) during adolescence leads to obesity in adult life. Various complications including diabetic ketoacidosis (DKA), microvascular complications such as retinopathy, nephropathy and neuropathy are more common in these children. Eating disorders are often associated with other psychiatric disorders as well.

Depression, Anxiety and Fear

When we disclose the diagnosis, children and parents often go into a state of depression. Parent's expectations are blown apart when they realize that their child, who was completely normal till recently, now has a serious illness requiring lifelong injections, rigorous monitoring and that he/she is likely to develop many acute and chronic complications. In this era of internet, many will do frantic "Google search" and find conflicting information aggravating their mental agony. In this stage, they tend to do "doctor shopping" or seek the help of alternate medicine if not properly counseled (denial). Younger children have negative experiences of hospitalization, injections and diet restrictions. Overprotective attitude and the grief of parents often transmit to the child. Affected children do have fear about insulin injection, frequent blood tests and possibility of "tiredness" (hypoglycemia) at school. As they get older, they will have anxiety about chronic complications, lifespan, marriage issues, studies and professional carrier.

Clinically significant depression is noted in 30% of parents and at least 25% of them develop post-traumatic stress disorder.

QUALITY OF LIFE

Maintaining good quality of life positively influences the ability of the child to cope with the diabetes, and its complications and have a better relationship with parents and peers. Many parents treat their child with pity, but often many children cope and lead a normal life despite these limitations. Use of positive skills is critical in this issue. These skills include good problem-solving ability, communication and effective techniques for stress management and relaxation. Teaching these skills to the child and family members are important in diabetes management.

PEER RELATIONSHIPS

Peer relationship affects the mindset of children especially adolescents. In children with diabetes, peer influence affects psychological wellbeing and treatment adherence, and thus glycemic control. Adolescents often spend more time with their friends, rather than with their family members and are often influenced by

them. They seek peer support for their behavior and for achieving their future dreams. Good peer support and emotional backing will definitely give them more courage to face life in a better way as many parents continue to be overprotective even during this most important transitional phase of one's life and deny the desired personal freedom. In fact friends do give them good emotional support, often more than a family member. Peer pressure, at times can lead to the adolescent going astray and indulging in smoking or drugs or other bad habits.A good peer group, especially those with diabetes, where they can exchange their worries, anxieties and suggestions for more improvements with others facing the same problem, is a key element for optimal management. In a recent study, a good peer group support was found to have a positive impact in reducing the HbA1c level.

PROBLEMS AT SCHOOL

Most children with diabetes are well adapted to school life with good school attendance, fairly good academic achievements, and participation in extracurricular activities like painting, singing and other cultural activities. However, many studies have pointed out their reluctance to participate in sports activities. This may be due to an inherent fear (low sugar phobia) resulting from restrictions imposed by the family members and health care team alike. Some children experience severe school attendance problems. The major reasons for school phobia are lack of support from school employees and mocking and teasing by their classmates. In our country, most schools do not recognize the need for the presence of a trained nursing staff who has the knowledge of identifying and managing hypoglycemia, and who knows the technique of administration of insulin (at least to a young child) and the concept of a "sick room" is virtually nonexistent. Any child with a disease becomes a "curiosity" in school; every act of diabetes self-care, including glucometer-based random blood sugar (GRBS) monitoring and administering the insulin injection becomes "news" among his/her classmates. The poor child may be forced to go to a place like toilet to test and for injection. This may lead to omitting the insulin injections during school hours, thus totally toppling the concept of basal bolus regime. This results in chaos in sugar control, and the child manipulates the SMBG results to avoid criticism and rude remarks from his/her treating personnel and parents alike.

Working hours in majority of schools in our country are from 10.00 AM to 4.00 PM; in major metros the children may have to leave for school as early as 7.15 AM and return at about 2.30 PM and some schools function in a separate shift from 12 noon to 6.00 PM. These awkward time schedules create more problems for the child regarding insulin administration, SMBG monitoring and consuming a diet suggested by the treating physician based on a "strict" carbohydrate counting.

INTERVENTIONS

Treatment Adherence

Very few children or adolescents adhere to the treatment protocol strictly and some demonstrate severe non-adherence despite effective counseling by the treating team. Regular and effective follow-up of the children and their parents is a must for a good outcome. SMBG recording should be monitored patiently and suggestions for modifying the diet and insulin based on the results should be discussed with the child and family members in a simple, non-accusatory and easy-to-understand manner. Positive reinforcement consisting of "praise and point rewarding system" will really boost confidence resulting in a better glycemic control and reduction in short-term and long-term complications.

Ensuring Effective Family Participation

Like the child, the whole family undergoes the phases of depression, anxiety and stress while coping with the different phases of the illness. In some situations there may even be complete loss of control. Often in these circumstances, the child or adolescent is blamed. Any psychiatric illness of a key caregiver, e.g. one of the parents, may result in poor control and even recurrent episodes of DKA. Hence periodic reinforcement of effective family participation should be ensured by conducting regular family based programs with specific emphasis on effective family communication and problem-solving skills.

Multisystemic Therapy

Many researchers have found that "multisystemic therapy" is more effective (including reduction of HbA1c levels) than discussing the issues with the child or adolescent alone. Multisystemic therapy means that the treating team should focus on all individuals who directly or indirectly influence the care of diabetes and disease progress i.e. peers, schoolteachers, and employers in addition to the immediate family members. In our country, where many schools lack a trained nurse, the team should train a responsible teacher or an attendant for monitoring and supervising the diet, exercise, SMBG, and insulin administration. Contact details of persons to be called in case of an emergency and emergency supply for tackling hypoglycemia, includinga packet of glucose, some biscuits, and if possible a glucometer should be available in the staff room/sick room, which will be very helpful in tackling a situation of hypoglycemia. Many researchers have found that multisystemic therapy definitely reduces the HbA1c levels in diabetic children in the long run.

Coping and Social Skills

Coping and social skills of the affected child and key caregivers are of paramount importance in managing this disease effectively. Interventions to

improve theses skills should be a regular event in the diabetes management programs. These programs should aim to increase the competence and mastery in diabetes care and decrease the negative coping styles with constructive behavioral adaptations. Training to impart coping skills with special training to deal with peer teasing and social isolation is important to improve the quality of life. Training peers and family members similarly, can help them to support diabetes care, which is of great advantage for the glycemic control and the general wellbeing of the young diabetic children.

Anxiety and Stress Management

Psychological stress can interfere with metabolic control and treatment adherence. Hence regular interventions to reduce anxiety and improve the management of stress should be a part of the treatment program. In Indian context, yoga and other relaxation techniques should be tried as methods of effective stress management.

Psychological Interventions

It is necessary to have a mental health expert in the team managing diabetic children and adolescents, along with other specialists, e.g. ophthalmologist and nephrologist. Many children and their parents are hesitant to seek the help of a "psychiatrist"; so a counselor with childhood diabetes can significantly improve the quality of diabetes management. Gently probing some of the following issues may help prioritize a psychologist referral in areas where such help is not readily available: regularity in school attendance, playing at school and home and interacting with friends and siblings, crying without apparent reason, deliberately harming self or others, suicidal ideation, difficulties with sleep, or anxiety regarding simple tasks.

CONCLUSIONS

It is important to consider diabetes as a family issue rather than an individual problem. Most children and their family members are eventually able to accept the illness and adjust with its often-unpredictable course. Yet several psychological issues can arise, both in children and their caregivers resulting in a decreased QOL and increased risk for complications. Subtle parental supervision should continue throughout adolescence. Families definitely benefit from psychological interventions. Hence regular monitoring of psychological issues in the child, adolescent, and his/her parents and siblings and effective interventions will have long-term benefits in the proper management of this chronic illness. *Subtle parental supervision* should continue throughout adolescence.

15

PROCEDURES AND SURGERY

M. Vijayakumar

SUMMARY OF RECOMMENDATIONS

- Surgical procedures in diabetic children and adolescents should be undertaken only in hospitals where a dedicated team and facilities for their care are available.
- There should be a written protocol or guidelines regarding the management of these children.
- They should be admitted the day prior to a major surgery, for optimizing the immediate glycemic status; target blood glucose (BG) is 90–180 mg/dL.
- Hourly monitoring of capillary glucose should be started in the pre-operative period itself.
- 5% dextrose (with 0.45% normal saline) is the ideal fluid to be started. 10% dextrose is needed if hypoglycemia is anticipated. 0.9 % saline should be considered if there is a fall in serum sodium.
- After the surgery, potassium should be added at a rate of 20 mmol in each liter of maintenance fluid.
- Maintenance IV insulin infusion should be started at least 2 hours prior to surgery, through a separate line and should be continued post-operatively until the child is on regular oral feeds.
- Minor surgical procedures are managed by subcutaneous insulin.
- If the child is receiving oral drugs such as metformin, drug administration should be stopped 24 hours before the procedure and restarted at least 48 hours after surgery. Meanwhile, glycemic control is achieved by parenteral insulin preparations.

INTRODUCTION

Glycemic status of a child requiring surgery is controlled by various factors. Stress hormones associated with the underlying illness and the surgical procedures cause insulin resistance leading to hyperglycemia. Hyperglycemia predisposes to infections, increases fluid losses and may lead to diabetic ketoacidosis (DKA).

Surgery and its preparations impose caloric restrictions predisposing to hypoglycemia. Hence net glycemic status is unpredictable, pointing towards the need for frequent monitoring of blood glucose (BG) and insulin dose adjustments to achieve normal BG levels and to avoid DKA. Moreover, clinical manifestations of both hypo- and hyperglycemia may not be clinically identified in a child under anesthesia.

The ideal BG level during a surgical procedure is between 90–180 mg/dL. The ideal HbA1c before an elective surgical procedure is around 7.5%.

Surgical interventions should be undertaken only at centers where well-trained staff and facilities for diabetes care are available. There should be a written protocol or guidelines for management of a child with diabetes.

CLASSIFICATION OF SURGICAL PROCEDURES

For the purpose of management, surgical procedures are divided into minor and major procedures.

Minor Surgical Procedures

Minor surgical procedures are done under local anesthesia or brief general anesthesia of 1–2 hours duration. These procedures do not produce major alteration in the glycemic status of the child. Examples of commonly done surgical procedures include abscess drainage, insertion of intercostal drainage tube, adenotonsillectomy and endoscopy. Patients usually get discharged on the same day of the procedure.

Major Surgical Procedures

These procedures require prolonged general anesthesia of more than 2 hours, and duration of post-operative diet restriction is also more. The child may need to remain in the hospital for a few days. All these factors predispose to metabolic decompensation. Examples include major urological procedures, cardiac surgery and abdominal explorations.

PLANNED SURGICAL PROCEDURES

In planned surgical procedures, glycemic status of the child should be estimated several days before the procedure. If good glycemic control is not achieved, the child should be hospitalized and monitored. The surgical procedure may be delayed till good glycemic control (HbA1c ~7.5%) is ensured by intensive insulin management, if need be with admission to a hospital.

Major Surgery

The child should be admitted on the previous day, for fine-tuning the glycemic status. The surgical procedure should be scheduled as the first case of the day.

For major procedures, solid food should be avoided for 4–6 hours before surgery. Hourly capillary BG monitoring should be initiated in the preoperative period itself.

The usual doses of insulin and bedtime snacks are given the previous night. Blood/urine ketone levels are measured (if BG levels are above 250 mg/dL). Additional doses of short-acting insulin may be needed if the patient has hyperglycemia. If the child develops hypoglycemia, IV infusion with 5–10% dextrose is started.

The usual morning subcutaneous insulin injections should be omitted.

Insulin Infusion

IV line is secured and insulin infusion is started at least 2 hours before surgery (dilute 50 units of regular insulin in 50 mL of normal saline, which gives 1 unit of insulin in 1 mL of fluid). **Table 1** provides the guidelines for IV insulin infusion doses during surgery for children, depending on the BG levels.

TABLE 1. Guidelines for IV insulin during surgery (ISPAD Guidelines 2014)

• Add soluble (regular insulin 50 units to 50 mL normal saline (0.9% NaCl), making a solution of 1 unit of insulin/mL and attach to syringe pump with appropriate label. • ***Insulin infusion rate:***		
Blood Glucose in mmol/L	***Blood Glucose in mg/dL***	***Insulin Infusion Rate***
<6–7	<~110–140	0.025 mL/kg/hr (0.025 unit/kg/hr)
8–12	~140–220	0.05 mL/kg/hr (0.05 unit/kg/hr)
12–15	~220–270	0.075 mL/kg/hr (0.075 unit/kg/hr)
>15	>~270	0.1 mL/kg/hr (0.1unit/kg/hr)
• Blood glucose (BG) should be measured hourly when the child is on IV insulin. • Aim to maintain BG between 5–10 mmol/L (90–180 mg/dL) by adjusting insulin infusion hourly. • Do not stop insulin infusion if BG is <5–6 mmol/L (90 mg/dL), as this will cause rebound hyperglycemia. Reduce the rate of infusion. • Insulin infusion can be stopped temporarily if BG is <4 mmol/L (55 mg/dL), but not for >10–15 minutes.		

If the child has hyperglycemia, an initial bolus of insulin, at a dose 5–10% of the total daily insulin dose, should be administered at the start of infusion, followed by continuous infusion at a dose shown in **Table 1**. Capillary BG levels should be checked every hour and glucose infusion rate adjusted accordingly. The aim is to keep the BG level between 90–180 mg/dL. Reduce the rate of insulin infusion if BG levels fall below 90 mg/dL (do not stop infusion because it will produce

rebound hyperglycemia). Monitoring of BG should be done as long as the child is on insulin infusion. Blood or urine ketone levels should be estimated if BG levels are above 250 mg/dL.

If the child is on continuous subcutaneous insulin infusion (CSII or insulin pump), it is continued, or replaced by IV insulin infusion if the pump is not working properly or if the surgical team is not confident about its use. If using pump, insulin is given at a basal rate with correction doses administered (as required) before and after the surgical procedure.

After surgery, insulin infusion should be continued until the child is able to take oral feeds satisfactorily. Thereafter the usual previous treatment regime is re-started (the child may require a slightly higher dose of insulin for the first few post-operative days).

Maintenance Fluid

IV fluids should be started 2 hours prior to the procedure to minimize the risk of hypoglycemia due to fasting. IV maintenance fluid is connected via a separate line. The IV fluid should contain 5% dextrose in 0.45% saline. 10% dextrose should be used if hypoglycemia is anticipated (e.g. initial BG < 90 mg/dL). If BG levels are high (>250 mg/dL), 0.45% normal saline without dextrose is used initially but 5% dextrose is added when BG levels fall below 250 mg/dL.

Hourly monitoring of electrolytes (Na and K) should be done and the fluid should be changed to 0.9% saline if the serum sodium levels start falling. After the surgery, potassium chloride should be added (20 mmol to each liter of the maintenance fluid). If the child develops hypotension or shock, Ringer's lactate or normal saline (without added potassium) should be infused rapidly. IV fluid should be continued till a satisfactory oral intake is documented.

Table 2 provides the details of the calculation of the amount of maintenance fluid to be administered, using the Holiday and Segar formula.

TABLE 2. Holiday and Segar Formula for Calculation of the Amount of Maintenance Fluid

Body weight	*Fluid requirement for 24 hours*
Up to 10 kg	100 mL/kg
11–20 kg	1000 + 50 mL/kg for every 1 kg more than 10 kg
> 20 kg	1500 + 20 mL/kg for every 1 kg more than 20 kg
Note: Maximum amount should be 2000–2500 mL. Alternate method of calculation: 1500 mL/m^2/day	

Minor Surgery

Insulin titration can be attempted using subcutaneous insulin itself. If surgery is planned in the morning, 50% of the usual dose of basal insulin (NPH/ Detemir) is given. Basal insulin need not be reduced if the child is on long acting insulin analogs like Glargine or Degludec. Short acting insulin should be omitted unless the morning glucose level is very high. Breakfast should be delayed until the procedure is completed. Check BG hourly both pre-operatively and during the procedure. Small doses of rapid acting insulin are given if BG levels are high. If the procedure is likely to be prolonged, IV maintenance infusion of 5% dextrose with 0.45% saline and IV insulin infusion should be started separately (as for a major surgical procedure). After surgery, check BG and give the remaining dose of insulin and food to the child.

EMERGENCY SURGICAL PROCEDURES

In surgical emergencies, good pre-surgical titrations of BG levels are not possible. Always check BG and blood or urine ketones, electrolytes and blood gases (ABG, if BG levels are high). If the child has DKA, surgery is delayed (if possible) until the DKA has resolved completely (see the chapter 11 on DKA for management details). Thereafter follow the protocol for managing an elective surgery.

CHILDREN ON ORAL ANTIDIABETIC DRUGS

Metformin (or any other antidiabetic drug) is stopped 24 hours before surgical procedures. The child should be put on insulin infusion as mentioned above. These oral drugs should be withheld for at least for 48 hours after surgery.

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CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII)

Anurag Bajpai

SUMMARY OF RECOMMENDATIONS

- Continuous subcutaneous insulin infusion (CSII, insulin pump) provides better glycemic control with lower frequency of hypoglycemia and better quality of life compared to multiple daily injections.
- Careful patient selection and intensive education is essential for successful insulin pump treatment.
- Children on insulin pump should check blood glucose (BG) levels at least four times a day.
- Emergent correction of hyperglycemia is mandatory for prevention of DKA in children on insulin pump.
- Insulin injection by a pen should be used to correct hyperglycemia in children on insulin pump in the presence of ketosis.
- Closed loop systems with glucose detection directed insulin release would pave the way for physiological glycemic control.

INTRODUCTION

The ultimate aim of management of type 1 diabetes mellitus (T1DM) is to deliver insulin according to real time glucose levels. This requires a three-level functionality with continuous insulin delivery, real time glucose measurement and dose modification as per the readings. Currently available insulin regimens are unable to replicate physiological insulin secretion. Under physiological circumstances, insulin is secreted at a basal rate to suppress hepatic glucose production with extra insulin released in the portal circulation in response to meals. While none of the currently available systems allows portal delivery of insulin, continuous subcutaneous infusion of insulin (CSII) using an insulin pump comes closest to physiological insulin replacement.

HOW DOES IT WORK?

Insulin pumps are electronic devices that inject insulin using a subcutaneously inserted catheter (**Fig 1**). The pump is connected to the catheter with a tubing and can be detached during contact sports, bathing or swimming. The pump has

a reservoir to store insulin and delivers it at a preset rate (basal rate) and can be programmed to give insulin boluses along with meals (meal bolus) and in the presence of hyperglycemia (correction bolus) (**Fig 2**). Rapid acting insulin analogs are used in insulin pumps due to their rapid onset and short duration of action.

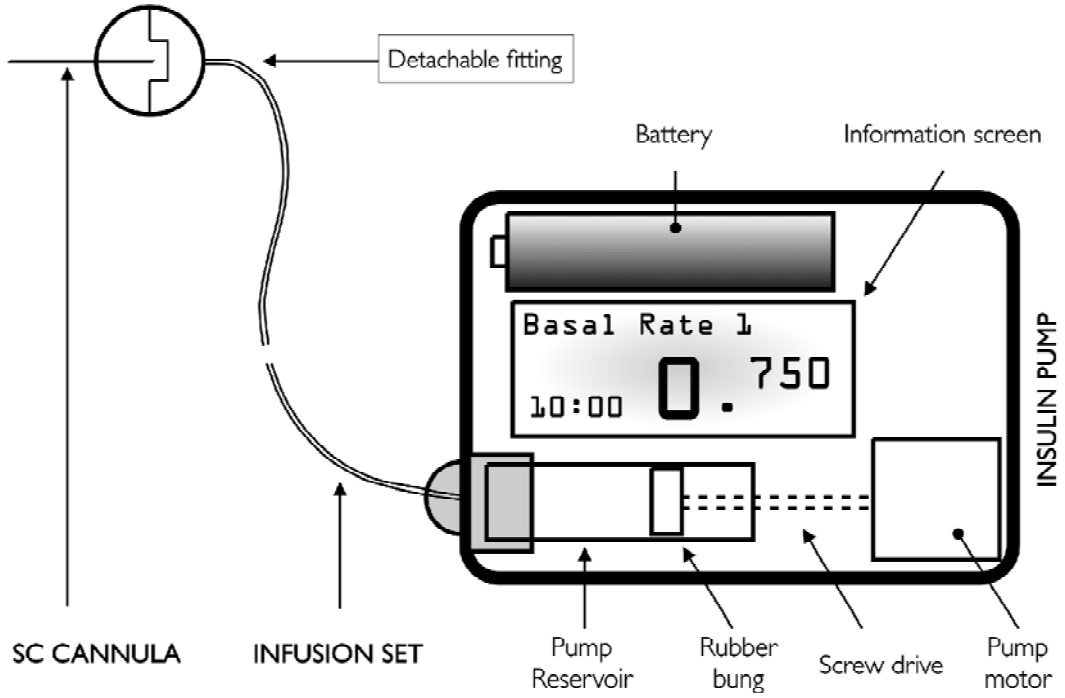

Fig 1. Diagrammatic representation of insulin pump

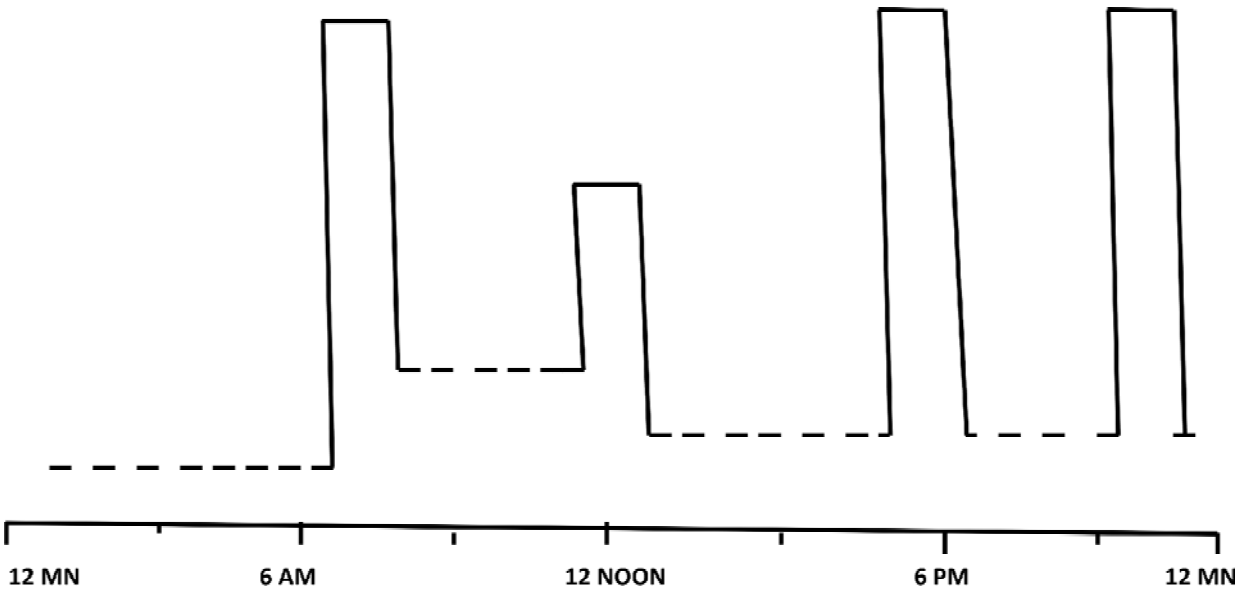

Fig 2. Insulin infusion pattern in insulin pumps with variable basal rates for different times of the day and meal time boluses. *A low basal rate has been set for 1 AM to 7 AM, a high one for 9 AM to 12 noon, and an intermediate rate for 2 PM to 1 AM. Similarly, meal boluses are higher for breakfast, evening snack at 5 PM and dinner at 10 PM, with a smaller bolus for lunch at 12 noon.*

WHY SHOULD WE USE INSULIN PUMPS?

Insulin pumps provide a mechanism of near physiological insulin delivery while avoiding multiple injections. The advantages of insulin pumps over multiple daily injections include ability to make minute dose adjustments (0.025 to 0.05 units), potential of varying basal rates for different times of the day, different patterns of meal boluses and suspension of insulin during hypoglycemia. This is expected to result in improvement in glycemic control, reduction in glycemic variability and lower hypoglycemia. These observations have been confirmed in pediatric studies that show a modest reduction in HbA1c, reduced rate of hypoglycemia, lower insulin requirement and greater time spent in target range. Contrary to previous observations a recent large study of exchange registry of children with T1DM has observed lower diabetic ketoacidosis (DKA) rates with insulin pump compared to multiple daily injections. The major advantage of insulin pump is in improving quality of life with flexibility to manage diabetes. Sensor-augmented pump therapy is associated with further reduction in rates of hypoglycemia provided the sensors are worn for over 70% of the time.

WHO SHOULD USE INSULIN PUMPS?

Every child with T1DM is a potential candidate for insulin pump. In particular, age of the child and duration of diabetes should not be considered while deciding the need for pump therapy. Insulin pumps are particularly indicated in children with inadequate glycemic control despite multiple daily injections. Careful patient selection is however mandatory for successful CSII therapy. Parents should be counseled that insulin pumps are not quick fix solutions for diabetes and the commitment required for pumps is much more than that for multiple daily injections. Thus, a family finding it difficult to manage split-mix regimen is extremely unlikely to succeed with insulin pumps. Another major limitation of pump therapy is the cost (Rs 150,000 or more at initiation and Rs 5,000 per month subsequently). They are particularly helpful under following circumstances:

1. Infants and toddlers with erratic eating habits
2. Recurrent unpredictable hypoglycemia
3. Active lifestyle with inconsistent meal times and levels of physical activity
4. Professional athletes
5. Excessive glycemic excursions
6. During pregnancy

Pre-Requisites for Initiating Insulin Pump Treatment

Before starting insulin pump therapy, it is important to ensure the following:

1. Motivation on the part of the child and family.
2. Willingness to perform a minimum of four blood glucose (BG) measurements daily.
3. A good knowledge of carbohydrate counting and glycemic index.
4. An understanding of sick day and hyperglycemia management.

Inappropriate patient selection may result in worsening of glycemic control and need for reverting to basal-bolus treatment by multiple injections.

WHO SHOULD PRESCRIBE AN INSULIN PUMP?

Initiation and maintenance of the insulin pump requires considerable understanding on the part of health care providers. Thus it should be initiated only in a center equipped with following facilities:

1. Physicians with considerable experience in insulin pump therapy.
2. Dieticians well versed with carbohydrate counting and dietary modifications.
3. Diabetes educators with practical knowledge about insulin pumps.
4. Structured protocol for initiation of insulin pump, education program and troubleshooting for pump therapy.
5. Helpline facilities for patients.

WHICH PUMP SHOUD BE USED?

Insulin pumps have been available for over four decades, but have come of age recently with tremendous advancements in technology. Initially insulin pumps were mere mechanical devices that delivered insulin. Subsequent insulin pumps were able to calculate insulin boluses according to manually entered carbohydrate count and BG readings. Seamless transfer of readings of the glucometer provided smarter ways of managing diabetes. The development of continuous glucose monitoring system (CGMS) has revolutionized insulin pump treatment with the development of pumps that stop insulin infusion after development of hypoglycemia (Low glycemic suspend) and stop insulin infusion with a fall in BG levels indicating the risk of impending hypoglycemia (Smart guard mechanism). Comparison of currently available pumps in India is presented in **Table 1**.

TABLE 1. Comparison of Insulin Pumps Available in India

Model	*Multiple basal doses*	*Multiple bolus types*	*CGMS integration*	*Hypoglycemia response*
MMT 715	Yes	Yes	No	None
MMT 722	Yes	Yes	Yes	Alarm
MiniMed 754 Veo	Yes	Yes	Yes	Low glycemic suspend
MiniMed 640 G	Yes	Yes	Yes	Smart guard

Major criteria for selection of insulin pumps include the cost of pump, patient commitment to glucose monitoring and technological prowess. Thus while sensor-augmented pump with smart guard mechanism provides state of the art insulin treatment, its use is limited by prohibitive cost of the pump and sensors. The ideal candidate for such a pump is a technologically savvy family with commitment to use CGMS. Similarly, basic pump would be a better option for families with limited technological understanding.

HOW TO INITIATE PUMP THERAPY?

Initiation of insulin pump therapy requires intense education of the child and family spread over multiple sessions. Close review of BG logs by health professionals during the first couple of weeks is highly recommended. Continuous glucose monitoring (CGM) could be very helpful during this period.

Patient Orientation

A comprehensive review of patient and family's knowledge about diabetes should be undertaken. Following issues specific for insulin pumps need to be stressed:

- Pump functions – Different modes, setting of basal rates, retrieval of data
- Technique of catheter insertion
- Carbohydrate counting
- Calculation factors
- Blood sugar monitoring and modification of insulin dose
- Management during sick day and exercise
- Management of hyperglycemia.

Initiation of Insulin Treatment

Comprehensive pump initiation planning is pivotal for success of pump therapy. The family should be counselled about the possibility of glycemic excursions during the initial phase on insulin pump as this could be a cause of concern.

Insulin Dose

The total daily dose of insulin should be reduced by 20% while starting on insulin pump. The dose should be reduced further in children with hypoglycemia while less reduction is required in children with high HbA1c levels. The calculation of basal dose, insulin to carbohydrate ratio and correction factor is based on the total daily dose as highlighted below.

Basal dose – Basal dose is calculated as 50% of total daily dose (TDD). This should initially be evenly distributed throughout the day. Subsequently different basal rates may be required for different periods of the day.

Lower basal rates are usually needed in the late evening/midnight (between 8 PM and 2 AM) and during the day (between 10 AM and 4 PM). Higher basal rates are often needed in the early evening (from 4 PM to 8 PM) and morning hours (from 2 AM to 10 AM) usually during puberty commensurate with the dawn phenomenon. Many prepubertal children need a higher basal rate late in the evening (9 PM to 12 midnight) representing a reverse dawn phenomenon. Basal rates should be tailored to the levels of physical activity and dietary intake. Setting different basal rates for days with normal, increased (sports day) and reduced activity (holiday) is desirable.

Temporary basal rate - Temporary basal rate is used during short term periods of variable insulin requirement like vigorous physical activity, fever, vomiting or hyperglycemia. This should be used only for a short time and not as a short cut to basal rate modifications.

Bolus dose – The dose of meal bolus is determined by the estimated carbohydrate content of the meal and pre-meal BG level. The meal bolus can be given as a standard dose (all insulin released immediately), square wave (insulin released over a time period of 30 minutes to 8 hours) or a combination of both (dual bolus, **Fig 3**). Dual wave bolus is recommended with meals with high fat content while linear dose is indicated if the glycemic index of the meal is high. Meal bolus should be used for all carbohydrate containing meals or snacks in a child on insulin pump as compared to only for major meals for children on multiple daily injections. Thus the bolus dose represents a substantially higher proportion of the TDD in children on insulin pumps (60-70%) compared to those on multiple daily injections.

Insulin to carbohydrate ratio (ICR) represents the amount of carbohydrate (in grams) covered by 1 unit of insulin. This is estimated by dividing 500 by the total daily dose of insulin. Higher ICR is recommended for young children while lower levels may be required for adolescents.

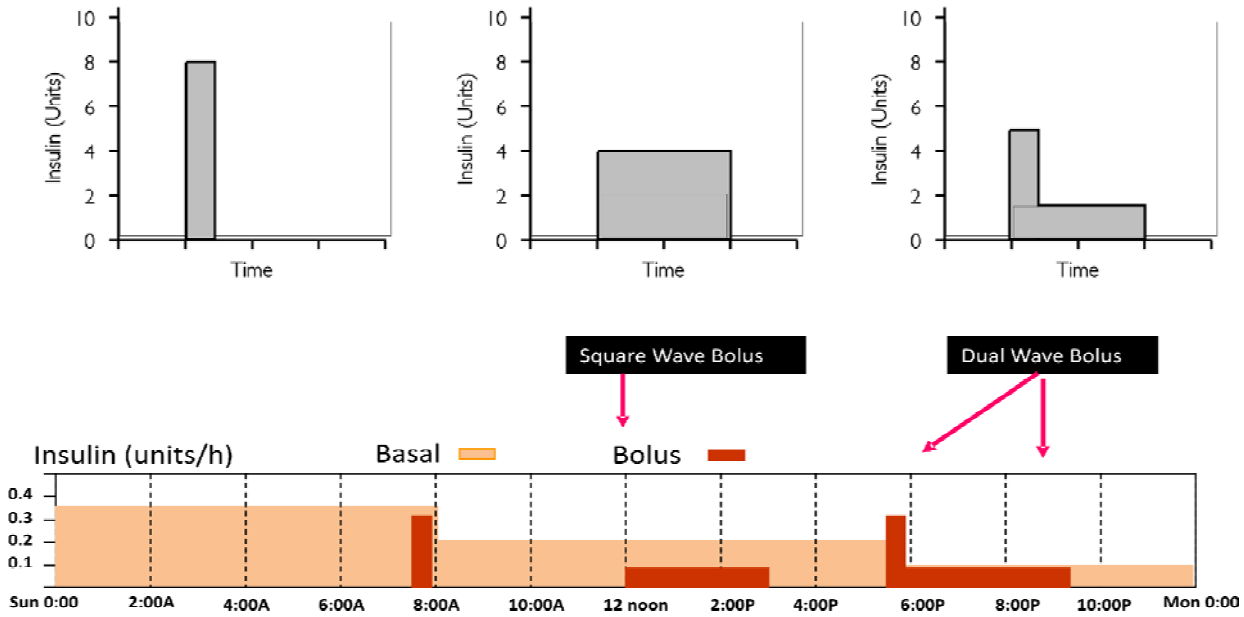

Fig 3. Variations of meal time bolus as standard, square and dual wave bolus. *Note the 3 different basal rate blocks also, in this child's regimen.*

Insulin to carbohydrate ratio (ICR) = 500 ÷ Total daily dose of insulin g/unit

Correction bolus is determined based on *insulin sensitivity (correction factor)*. This provides information about the amount of BG (in mg/dL) lowered by 1 unit of insulin.

Correction factor = 1800 ÷ Total daily dose of insulin mg/dL/unit

Insulin sensitivity varies with time of the day. Lower insulin sensitivity is observed in adolescents during early morning hours and toddlers during evening resulting in the need for increased insulin requirements during these periods.

The dose of *meal bolus* is calculated as shown below:

$$\text{Meal bolus} = \frac{\text{Anticipated carbohydrate intake (g)}}{\text{Insulin to carbohydrate ratio}} + \frac{\text{Blood glucose} - 180}{\text{Correction factor}}$$

Correction factor can also be used to estimate a negative correction in the presence of hypoglycemia (in a patient on 50 units of insulin a day, giving 1 unit less at meal times should allow the BG to rise by 36 mg/dL). Correction bolus should also consider the amount of *residual insulin* which represents the amount of remaining insulin of the previous bolus. This is determined by the assumption that 30% of insulin bolus is used up every hour. These calculations are loaded at the time of pump initiation. The patient only needs to feed the carbohydrate count and BG level and the calculation is performed by the insulin pump.

Bolus dose can also be calculated from total daily dose in patients unwilling to do carbohydrate counting. Initial dose is calculated by the formula below.

$$\text{Meal bolus} = 24 \times \text{basal rate} / 3 \text{ units}$$

This calculation however assumes similar carbohydrate contents of the meals and should be discouraged.

WHAT SHOULD WE LOOK FOR ON FOLLOW-UP VISITS?

Follow-up of children on insulin pump treatment should include close monitoring of insulin pump site and skin for any evidence of infection or lipohypertrophy. BG records should be reviewed and the dose of insulin adjusted. Total daily dose, basal dose, bolus dose and number and amount of correctional boluses should be reviewed. While changing the total daily dose the correction factors and ICR should be appropriately adjusted. Patients should be informed about the need for careful monitoring and dose adjustments.

HOW TO MODIFY INSULIN DOSES?

Glucose monitoring should be done at least four times a day (pre-meals and bed time). More frequent monitoring may be required in children with poor control. CGM would be of great help during this period.

Basal Rate Adjustment

The basal rate is adjusted according to pre meal BG levels. The dose should be modified in quantums of 10% if the levels are not under control.

Meal Bolus Adjustment

The meal bolus adjustments are made based on the changes in BG levels after meals. Increase in two-hour post meal BG levels up to 60 mg/dL is considered acceptable. The doses should be adjusted if the changes are outside the range.

Correction Bolus Adjustment

The accuracy of correction bolus is assessed by the BG levels one hour after the correction bolus. The dose is appropriate if the levels are within 30 mg/dL of the target range.

TROUBLESHOOTING

Careful management during periods of pump dysfunction, intercurrent illness and procedures is required to prevent complications. The overriding principle of pump trouble shooting is *"Pull out when in doubt"* as most situations can be efficiently handled with subcutaneous or intravenous insulin while the issues are resolved.

Hyperglycemia

Careful management of hyperglycemia is mandatory to prevent the development of DKA in children on insulin pumps. This is important as insulin pumps deliver rapid acting insulin only with no cover of long acting insulin. Thus even small interruptions in insulin pump infusion can lead to the development of DKA. All children on insulin pump should therefore stock pens of rapid acting insulin. Correctional insulin boluses are required if BG is more than 180 mg/dL. Ketones (urine or blood) should be checked in children with BG more than 270 mg/dL. The pump should not be used to correct hyperglycemia when ketones level is more than 0.6 mmol/L and insulin should be given via pen. In the absence of ketones, a single correctional bolus could be given by the pump as illustrated below.

$$\text{Dose} = \frac{\text{Blood glucose mg/dL} - 180}{\text{Correction factor}} - \text{Residual insulin}$$

Individuals with persistent hyperglycemia 1 hour after the bolus should receive rapid acting insulin using a pen (total daily dose/6 units). This should be followed by initiation of basal bolus regimen till the pump failure has been corrected. The pump should be carefully examined for battery status, the amount of insulin in the reservoir and site and patency of the catheter. The catheter should be removed and new tubing should be inserted if these measures are unsuccessful.

Hypoglycemia

Hypoglycemia should be managed as per standard guidelines followed by initiation of a temporary basal rate 20% lower than the current rate. This should be followed by evaluation and rectification of the possible cause of hypoglycemia.

Sick day

Sick day management should include revision of basal rate according to BG levels and modification of bolus as per carbohydrate intake. A high index of suspicion for DKA should be kept, with appropriate monitoring of blood ketones.

Hospitalization

In most settings, the insulin pump can be continued during hospitalization for minor illnesses, procedures or surgery. It should be discontinued in sick children with ketosis.

Worsening of Glycemic Control

Insulin pumps are an excellent way of giving insulin and managing diabetes mellitus. Their use may occasionally result in worsening of glycemic control. The important considerations in this setting are summarized below (**Table 2**).

TABLE 2. Important Considerations for Worsening of Glycemic Control while on Insulin Pump

Factor	*Pointer*	*Suggested action*
Missed meal bolus	Intermittent high values	Bolus reminders
Missed correction bolus	Persistently high values	Suggest bolus if BG is > 180 mg/dL
Inadequate basal dose	Recurrent correction bolus	Increase basal rate
Poor patient selection	Infrequent BG readings Frequently missed boluses	Re-education Pump withdrawal

WHEN SHOULD WE WITHDRAW PUMP THERAPY?

Insulin pump therapy withdrawal should be considered in the rare situation of worsening of glycemic control. Pointers to pump failure include non-compliance with glucose monitoring and bolus dose, frequent episodes of hypo- or hyperglycemia and recurrent DKA. The families should undergo reeducation about all aspects of pump therapy with special focus on problem areas. Pump therapy should be withdrawn in recalcitrant cases.

LIMITATIONS OF INSULIN PUMP THERAPY

High cost is an important limitation in the use of insulin pump. The minimum cost of an insulin pump is Rs 150,000 at initiation with approximately Rs 5,000 monthly expenses on consumables and insulin. There is also a need for close monitoring of BG to avoid hypoglycemia and hyperglycemia. The risk of development of DKA with pump dysfunction should also be considered.

FUTURE OF INSULIN PUMPS

Insulin pumps have evolved tremendously from wieldy devices that needed to be worn as a briefcase to small mobile devices giving electronic gadgets a run for their money. On the core however these changes have been incremental and not path-breaking. The insulin pump of the future is expected act as an artificial pancreas. To achieve this the pump needs to do the following.

1. Rapid sensing of BG.
2. Regulation of insulin secretion in response to changing glucose levels.
3. Meal specific glycemic response.
4. Secretion of glucagon in a glucose appropriate fashion to prevent hypoglycemia.

Most attempts for closing the loop have been restricted to reducing hypoglycemia by stopping insulin secretion on development of hypoglycemia (Low

glycemic suspend) or following rapid fall in BG (Smart guard). The exciting news as this *Diabetes Guidelines* goes to the press is that FDA has approved Medtronic's closed loop insulin pump *MiniMed 670 G* for patients with T1DM above 14 years of age. Another interesting advance in the area of insulin pumps is the use of dual chamber pumps that deliver glucagon or amylin in addition to insulin to ensure near physiological glycemic control.

Insulin pump therapy has revolutionized the management of a child with T1DM. Rapid improvements in technology have raised hopes of the availability of affordable artificial pancreas in the near future. For the present, however, these encouraging developments should be tempered by the real world issues facing the use of insulin pumps. It should always be remembered that insulin pumps are just another way of giving insulin and the smartest part of the pump remains the user. Careful selection and training of pump users results in dramatic improvement in quality of life of pump users.

ILLUSTRATIVE CALCULATIONS

Insulin plan for a child on split-mix regimen on 50 units insulin per day.

- **Initial calculations**
  - Total daily dose on subcutaneous insulin = 50 units
  - Total daily dose on insulin pump (reduce dose by 20%)= 50 – 10 = 40 units
  - Total daily basal dose (50% of daily dose) = 20 units
  - Initial hourly basal insulin rate = 20 ÷ 24 = 0.8 unit/hour
  - Insulin to carbohydrate ratio = 500 ÷ 40 = 12.5 g/unit
  - Correction factor = 1800 ÷ 40 = 45 mg/dL/unit
- **Meal bolus**
  - ***Parameters***
    - Pre-meal blood glucose = 270 mg/dL
    - Anticipated carbohydrate intake = 75 g
  - ***Calculation***
    - Insulin required to correct hyperglycemia = (270 – 180) ÷ 36 = 2.5 units
    - Insulin required for carbohydrate intake = 75 ÷ 12.5 = 6 units
    - Bolus = Correction factor + Correction = 6 + 2.5 = 8.5 units

- **Correction bolus**
  - ***Parameters***
    - Blood glucose two hour post-meal = 315 mg/dL
    - Pre-meal insulin 5 units
  - ***Calculation***
    - *Residual insulin* – 30% used per hour (2 units remaining at two hours)
    - *Correction dose* = (315 – 180) ÷ 45 = 3 units
    - *Correction required* = (3 – 2) = 1 unit

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CONTINUOUS GLUCOSE MONITORING (CGM)

Anurag Bajpai

SUMMARY OF RECOMMENDATIONS

- Continuous glucose monitoring systems are especially valuable in children with uncontrolled diabetes, significant glycemic excursions, hypoglycemia unawareness and recurrent severe hypoglycemia.
- Real time glucose monitoring with an insulin pump is associated with reduced rates of hypoglycemia and better glycemic control.

INTRODUCTION

Regular assessment of glycemic status is pivotal for successful management of children with type 1 diabetes mellitus (T1DM). Intermittent glucose monitoring by glucometers provides only a limited glimpse of the blood glucose (BG) profile and frequently misses asymptomatic hypoglycemia and glycemic excursions. Fear of hypoglycemia is the major obstacle to physiological glycemic control. These limitations led to the development of continuous glucose monitoring systems (CGMS).

HOW DOES IT WORK?

CGMS measures interstitial glucose at periodic intervals, providing semi-continuous information about the glycemic profile of the subject. It comprises of a glucose sensor, glucose monitor and a display device. The sensor is inserted subcutaneously and does not interfere with routine activities. Glycemic data from the CGM device can be downloaded and assessed later (retrospective CGM) or continually assessed using a monitoring device (real time CGM). The transfer of real time (RT) glucose data to an insulin pump provides opportunities to develop closed loop insulin pumps that infuse insulin according to BG levels.

WHEN SHOULD A CHILD WITH DIABETES USE CGM?

Current evidence does not favor universal use of CGM systems. Special circumstances where CGM would be of use include the following:

1. Divergent HbA1c and BG level.
2. Hypoglycemia unawareness, recurrent severe hypoglycemia or nocturnal hypoglycemia.

3. Initiation and adjustment of insulin pump therapy.
4. Marked unexplained glycemic excursions.

WHICH IS THE BEST CGM DEVICE TO USE IN CHILDREN?

Currently three CGM systems are available in India for use in children (**Table 1**).

Medtronic iPro2

The Medtronic iPro2 system has a sensor that is placed subcutaneously for up to 6 days,and measures interstitial glucose every 5 minutes. The system needs to be calibrated with glucometer readings twice a day. The data can be retrospectively downloaded and analyzed, or transferred to a compatible insulin pump with RT display. There are alarms for hypoglycemia and hyperglycemia above a preset limit. At the time of writing, the sensor costs about Rs 3,000 and the manufacturer provides technical support for uploading the data and getting the analysis to the family.

Abbott FreeStyle Libre Pro

Abbott FreeStyle Libre Pro has a sensor that is inserted subcutaneously in the back of the upper arm and measures interstitial glucose every 15 minutes (range 40-500 mg/dL). The glucose levels can be read with a lag of 15 minutes, using a reader, or downloaded to a computer for detailed information. The system does not require calibration with a glucometer, and can be used for 14 days. If the family is provided with the reader along with sensor being installed, they can make self-adjustment decisions on a real time basis. If the reader is available only at the clinic, the glycemic data can be reviewed mid-way after a week, and the response to treatment modifications assessed in the subsequent week's data.

The device has not yet been approved by FDA for use in children below 18 years. Limited data however shows that it can be used successfully in children and adolescents. Only the professional version of the device is available in India, to be procured by the health care provider only. Reports of the use of the system by patients with the reader at home have shown encouraging results in prediction of nocturnal and daytime hypoglycemia. At the time of writing, the cost of this sensor is around Rs 2,000, and the reader is Rs 5,000 (though technically not available directly to a patient's family but to their doctor).

Dexcom G4 Platinum/G5 Mobile System

The Dexcom G4 platinum/ G5 mobile system is approved for use in children above two years of age. The system consists of a small sensor that measures interstitial glucose every 5 minutes, a transmitter and a reading device. The G5 mobile system has the advantage of transferring and displaying RT data on a

compatible smart phone device. The system has inbuilt alarms for low and high blood glucose readings.

TABLE 1. Comparison of CGM Systems Available in India

Feature	*Medtronic iPro2*	*Abbott Libre Pro*	*Dexcom G4/5*
Measurement frequency	5 minutes	15 minutes	5 minutes
Sensor placement	Subcutaneous	Subcutaneous, on the back of upper arm	Subcutaneous
Sensor life	Up to 6 days	Up to 2 weeks	Up to 1 week
Calibration	Required	Not required	Not required
Real time information	When linked to pump	With monitor	Yes
Approved for use in children	Yes	Not yet	Above 2 years
Cost			
• Reader	Rs 50,000	Rs 5,000	Rs 100,000
• Sensor	Rs 3,000	Rs 2,000	Rs 5,000
• Transmitter	-	-	Rs 20,000

WHAT ARE THE ADVANTAGES OF CGMS?

CGMS provide semi-continuous information about BG profiles, allowing in-depth analysis of glycemic status. This is expected to result in better modulation of insulin doses, with lower risk of hypoglycemia. There is, however, paucity of randomized controlled studies about the use of CGM in children and adolescents. Most studies have been conducted in subjects with low rates of severe hypoglycemia or diabetic ketoacidosis (DKA), the key indications for CGM use. It is thus not surprising that most have not shown substantial reductions in the rates of hypoglycemia or DKA. Marginal benefits in HbA1c and time spent in the euglycemic range have been identified. The current evidence therefore does not favor universal use of CGM. RT-CGMS with hypoglycemia alarms are especially useful in children with recurrent unexplained hypoglycemia or hypoglycemia unawareness. RT-CGM devices should, however, be used for at least 70% of time to provide significant benefit.

WHAT ARE THE LIMITATIONS OF CGMS?

Widespread use of CGMS is limited by their cost and availability. Moreover, correlation of CGMS with laboratory or glucometer readings is modest. The Mean Absolute Relative Difference (MARD, an index of accuracy in comparison with blood glucose readings, the lower the MARD the greater the accuracy) ranges from 9% and 14%. Another important issue to be considered before widespread use of CGMS is the lag time between plasma and interstitial glucose.

CGMS represent significant advances in the management of children with DM. Further innovations and improved precision of these systems can give much tighter glycemic control without the risk of hypoglycemia. In the closed loop system, or artificial pancreas, BG measurements by RT-CGM are fed directly to the insulin pump, and a mathematical algorithm instructs the pump how much insulin is to be delivered.

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TRAVEL AND HOLIDAYS

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- Before planning a long journey a medical check-up and reinforcement of diabetes management education is essential.
- Information about types of foods and availability of medications, diabetes supplies and emergency medical services at the destination should be found out prior to travel.
- Extra diabetes supplies, emergency drugs and snacks must be taken and appropriately packaged.
- Additional activity and variable food intake while on vacation would necessitate frequent monitoring and adjustments in insulin doses.
- For travel by air, patients must take an official letter from the treating doctor for the customs and security personnel.
- Patients going abroad must be given written individualized instructions for insulin dose adjustments when crossing time zones.

INTRODUCTION

There is no restriction on travel for children with type 1 diabetes mellitus (T1DM); however, several precautions need to be taken before and during a long journey. Careful planning is essential to make travel safe and trouble-free.

PREPARATION BEFORE DEPARTURE

Planning should begin well in advance. The child with diabetes must undergo a detailed health check-up to detect and treat any problems that may need medical attention. The medical team should ensure that diabetes is adequately controlled and education in self-management of diabetes must be reinforced. Necessary vaccines for travel to a particular country must be administered as early as possible.

The patient should be provided with:

- Clear, detailed, written guidelines on management of hypoglycemia and sick days.

- Contact numbers of members of the medical team for telephonic advice in case of any emergency.
- Contact details of a doctor specialized in childhood diabetes, in the area or country that is being visited.
- A letter explaining the medical condition and treatment needs (specifying generic names and doses of the insulins that are used) for the reference of any physician who may be consulted during the trip.
- A prescription for insulin in case the patient runs out of stock during the trip.
- A letter for the airport security agencies stating that the child has T1DM and listing in detail the diabetes-related items that the child would be carrying with him/her in the hand baggage.

Patients must purchase an extra stock of all diabetes-related supplies and these should be distributed in two separate bags. The supplies should be packed in a sturdy case that can then be placed in the bags in such a way that there is no risk of damage.

If traveling by air, these supplies should be carried in hand, preferably distributed in two plastic bags, separate from the hand baggage. A bag for medical supplies and equipments would not be counted as carry-on luggage. The doctor's formal prescription and the chemist's original bill (both tallying with the medical supplies being carried) must also be available for hassle free security check at airports.

Insulin may be carried in insulated containers or cool packs or in a thermos that has been pre-cooled; but one must ensure that the insulin does not freeze.

Even patients who are on the insulin pump must carry vials of short and long acting insulin and insulin syringes in case of pump malfunction. They must also have the addresses of the pump company in the country they are visiting for assistance in case there is a pump malfunction.

The patient should also take along:

- A pair of comfortable shoes and foot care products including creams and bandages.
- Emergency drugs for non-specific ailments (diarrhea, vomiting and fever).
- A diabetes identification card translated in the local language, if visiting a different state in India or a foreign land.
- A few plastic pouches containing 3-4 teaspoonful of powdered sugar.

- *Snacks* – as it may not always be possible to get safe food or palatable food, and as the bus/train/flight may sometimes be late. These snacks should not need a cooler for storage.

The patient must learn some important phrases in the local language of the city or country being visited, to make it possible to convey messages for getting medical help and for ordering meals (e.g. "I have diabetes", "I am experiencing a hypo", "I need sugar", and "I need insulin" and so on).

An adolescent desirous of taking part in activities at high altitudes should be carefully assessed to rule out diabetes-related complications. Practical guidance on tackling the impact of altitude on diabetes control and on the various aspects of diabetes therapy must be provided. Measures to prevent altitude-related complications must be discussed at length. For details on this subject please refer to an excellent review by Pieter de Mol *et al* in "Diabetes Care", August 2014.

SECURITY CHECKS AT AIRPORTS

The security personnel at the airport should be informed at the outset that the child has diabetes.

It is necessary to furnish a detailed medical prescription stating that the child has T1DM and needs to carry life-saving supplies including insulin, injection devices; blood glucose meter and test strips; finger pricking devices; glucagon kit; urine ketone strips; alcohol swabs; sharps disposable containers; eatables that do not need refrigeration and in selected cases, an insulin pump and a continuous glucose monitoring system (CGMS) device.

One must ensure that the original pharmaceutical labels are retained on the insulin vials and the manufacturers' labels are intact on all the other equipments and materials. The glucagon kit should also be carried in the original box.

After completing the security check, the diabetes supplies can be distributed in two boxes and one box can then be kept with the accompanying person (if any).

The insulin pump and the CGMS device can be worn while passing through common airport security systems such as a metal detector, as these will not trigger an alarm nor damage the device. They should not be passed through the X-ray equipment. If going through airport body scanner, the pump and the CGMS device would need to be disconnected hence the patient can request an alternative pat-down screening process. Ideally, the patient should not be asked to disconnect the pump during security check; a letter from the doctor should clearly state this.

CAUTIONS DURING A FLIGHT

Insulin should never be kept in check-in luggage as temperature in the luggage hold is not regulated and hence there is risk of freezing or overheating.

In the aircraft an aisle seat would be preferred as it gives easy access to the toilets as also to insulin and to snacks stored in carry-on case.

The flight attendant or at least one other person on the flight and seated nearby should be informed that the patient has diabetes.

On a long journey, the patient should get up and move about every hour or so to prevent deep vein thrombosis. The patient should drink plenty of liquids to remain well hydrated.Alcoholic drinks and drinks that contain caffeine should be avoided.

Blood glucose (BG) should be checked every 4-6 hours during the journey.

When in flight there is no need to inject air or one may need to inject only half the amount of air in the insulin vial. Air bubbles may develop in the insulin cartridges during a flight because of pressure changes in the cabin. These must be carefully expelled so that insulin dose can be accurately measured. The pen needle should be immediately disconnected after each injection.

CAUTIONS AT DESTINATION

BG levels are likely to be lower on vacations due to reduced stress, more activity and unfamiliar foods. For this reason, frequent BG tests and knowledge of dose adjustments is important.

All the diabetes supplies must be carried in a backpack when on a day's sightseeing trip or outing. One should also carry enough drinking water. Insulin should not be kept in the boot of the car or bus as the temperature may be unacceptably high or low. If environment temperature is higher than 25-30^{0}C, insulin should be kept in a cool pack; if using a thermos one must ensure that insulin is not kept in contact with ice.

A diabetes identification card must be kept in the child's pocket at all times along with a plastic pouch containing powdered sugar. The card should be translated in the local language if visiting a different state in India or a foreign land.

If at all insulin needs to be purchased in a foreign country, it should be noted that in many countries insulin might be available only in 100 units/mL strength.

Patients on the pump must remember to reset the pump clock to the time at the destination.

INSULIN DOSE ADJUSTMENTS WHEN CROSSING TIME ZONES

The detailed itinerary with the timings of departure and arrival at various destinations, duration of each journey and differences in time between the places to be visited should be available.

Adjusting insulin dose and timings becomes necessary when crossing time zones during eastward or westward travel. With eastward travel the day becomes shorter and with westward travel it becomes longer.

During long journeys patients must keep their wristwatch unadjusted to display the time at the place of departure till the beginning of the first full day at the destination. This will help them understand better when insulin and meals are due.

Adjusting insulin dose and timings is easier if the patient is on a basal-bolus regimen with the long acting insulin analog, Glargine (or on the insulin pump) rather than on human insulin (regular plus NPH).

In a patient on a basal-bolus regimen with Glargine: During and after a long journey eastward or westward across multiple time zones, the basal insulin can be continued at intervals of 24 hours, at the corresponding time at the place of arrival. If this timing at the destination is unsuitable for taking insulin then it can be delayed or brought forward 1-2 hours each day to a preferred time. The bolus doses should be taken as usual before each main meal in an amount calculated from the carbohydrate content of the meal.

In a patient on NPH as the basal insulin: When traveling westward, the day becomes longer. It is advisable to keep the watch displaying the time at the place of departure and take insulin doses and eat accordingly. On reaching the destination, to cover meals during the extra hours gained (after the action of the last insulin dose wears off), supplements of rapid or short acting insulin can to be taken once in 4-6 hours. The patient can switch back to the normal routine on the first full morning/night (local time) after arrival.

In a patient on NPH as the basal insulin: When traveling eastward, the day is shortened. Before or soon after departure the patient can take the usual morning or evening dose (as the case may be). After 10-12 hours, he/she can take supplements of rapid or short acting insulin once in 4-6 hours to cover meals. From the first full morning or night after arrival, the patient can now start taking the routine insulin doses at the local time. Till this time, the patient must keep his watch unadjusted to display the time of the departure point.

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DIABETES CAMPS

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- Residential camps wherein children and adolescents with diabetes, their parents, and the medical team stay together for 3-4 days, should be an essential part of the diabetes management protocol.
- The aim of the camps is to bring together the patients and the medical team in a relaxed atmosphere, for group education in diabetes self-management and solution of psychosocial problems.
- Children and adolescents with diabetes and their parents must attend the camp.
- In selected cases, it is important to invite siblings and grandparents to attend the camp.
- The camp site should be a holiday resort, which provides a relaxed atmosphere, easily accessible, with a playground and halls for educational and recreational activities.
- The medical team should include pediatric diabetologist, psychiatrist, nutritionists, clinical psychologists, diabetes educators and play therapists and volunteers.
- Camp activities should include education in self-management of diabetes through lectures, demonstrations, educational games, informal psychotherapy and problem-solving sessions, besides games and entertainment programs.

INTRODUCTION

Residential camps wherein children and adolescents with diabetes, their parents, and the medical team stay together for 3-4 days, should be an essential and regular part of the diabetes management protocol.

The chief aim of the camps conducted in India so far, has been to bring together the patients and the medical team in a relaxed atmosphere, for group education in diabetes self-management and to discuss and solve their psychosocial problems.

There are differences in priorities between the camps conducted in the western countries and those conducted in India. The primary stress abroad is on providing children with diabetes a safe environment to participate in challenging physical activities under guidance and supervision.

The first residential camp ever for children with diabetes mellitus was conducted by Dr. Leonard F. C. Wendt near Detroit in the USA in 1925. In India, the first camp was held in the year 1983 at Khandala, a hill station near Mumbai, by the Juvenile Diabetes Foundation, Maharashtra Chapter.

The residential camps should be supplemented with "Day Camps" and "Adventure Camps".

THE NEED FOR CAMPS

Type 1 diabetes mellitus (T1DM) is the only chronic childhood disease in which the patients (and their family members) have to play the key role in day-to-day management. Patients must learn to inject insulin and test blood glucose (BG) and urine/blood ketones. They should have a sound knowledge of meal planning and activity planning to prevent swings in BG levels. They need to be well versed with the prevention, early recognition and first aid management of diabetic ketoacidosis and hypoglycemia. Finally, they must know how to integrate this information into their daily lifestyle *and* they should be in the right frame of mind to do so.

Children with diabetes and their families are invariably under tremendous emotional stress. At the outset, there is shock, resentment, anger, guilt and the "why only us?" feeling. Then there are false hopes, anxieties about the future, a feeling of hopelessness and of course, financial worries. When a large number of children and parents come together and discuss their problems in the presence of a psychiatrist or clinical psychologist who acts as a catalyst, it can work wonders.

This elaborate and practical education and psychosocial counseling cannot be imparted in a busy clinic: it requires plenty of time and a team effort. It is best imparted when the educators and the patients stay together for a few days in a relaxed atmosphere.

Siblings of patients too may suffer because of the restrictions imposed on the family's eating habits and lifestyle, the added stresses in the house and the extra attention received by the child with diabetes. Grandparents tend to have their own outdated views on what is good for the child and what is not. In joint families, this can lead to conflicts and may pose major hurdles. In selected cases, it is important to invite siblings and grandparents to attend the camp.

SELECTION OF THE CAMP SITE

The camp site should be a holiday resort so as to provide a relaxed atmosphere. The entire premises should be booked so that campers can be spared from prying eyes and awkward questions. It should be easily accessible by road. It should be comfortable with sufficient number of bathrooms and adequate water supply so that proceedings can begin on time each day. A large playground is a must so that children can have fun. There should be a minimum of three to four halls to conduct concurrent educational sessions for different categories of patients. There should be facilities for cooking food suitable for the campers. All these requirements should be available at a reasonable cost. The same place should preferably be available every year so that time is not lost in adjusting to a new setting.

SUMMER CAMPS OR WINTER CAMPS?

In our country, winter camps are preferred as the weather is pleasant and there is usually no water shortage at the holiday resorts. Further, families often prefer to visit their native place or go on long vacations during the long summer holidays.

WHO SHOULD ATTEND THE CAMPS?

Children and adolescents with diabetes and their parents must attend the camp. Adolescents with previous camp experience may attend alone to enable them to develop a sense of independence. It is a good idea to take along siblings and grandparents in selected cases.

A few married adults with onset of diabetes dating back to childhood must be a part of the camp. Those who are doing very well will serve as role models and a source of inspiration; those who are not doing so well and regret their initial casual approach to diabetes management will serve as a subtle warning.

The medical team should include the doctors (pediatric diabetologist and psychiatrist), nutritionists, clinical psychologists, diabetes educators, play therapists (to keep the little children busy with educational games) and volunteers.

CAMP ACTIVITIES

Camp activities should include education in self-management of diabetes by means of lectures, demonstrations, educational games and competitions; informal psychotherapy and "problem solving" sessions, besides games and entertainment programs.

To perfect injection and testing techniques. Children should take their insulin injections and check urine ketones and BG in a common hall under supervision. This helps them to perfect their techniques, learn from mistakes of others and also gives the newer patients the self confidence to inject themselves and prick themselves for checking BG.

Interactive lecture sessions. Sessions on record keeping, pattern adjustment algorithms, insulin supplements, hypoglycemia and sick day management should be age-appropriate. For these sessions patients can be divided in 3 groups: one each for parents, adolescents, and young adults. These should be interactive sessions rather than monologues. Besides imparting knowledge, stress must be laid on methods of bridging the gap between knowledge and its application; thus a psychologist must be part of these educational sessions.

Meal planning education. It must be emphasized that dietary advice on "what to eat" is for the entire family and not merely for the child with diabetes as "diabetes diet" is nothing but "healthy eating" for one and all. Sessions on "healthy eating" must be accompanied by sessions on "meal planning" or how to match food intake, insulin action and physical activity in children with diabetes. Those on the split-mix regimen must be taught the use of "carbohydrate exchanges" whereas sessions on "carbohydrate counting" should be conducted for those on basal-bolus regimens and insulin pumps. The role of snacks before (and after) unaccustomed exercise and insulin dose adjustments for exercise must be discussed. Diet options on "sick days" to prevent dehydration or hypoglycemia must be explained. A discussion on "barriers to implementation and how they can be overcome" is of utmost importance. Meal planning sessions must be conducted jointly by the nutritionist, the psychologist and the diabetologist.

Camp exhibition. All medications, equipments and gadgets used in management of T1DM along with relevant information pertaining to them can be displayed. There should also be exhibits showing carbohydrate exchanges and the food preferences for prevention of exercise-induced hypoglycemia and nocturnal hypoglycemia; and for treatment of hypoglycemia and for sick days.

Educational games and competitions. Children can be asked to enact plays in which all practical aspects of diabetes management are woven into a story. Quiz contests between parents and children or between groups of children can be very entertaining and educational.

"Tackling the disturbed mind". The issues to be discussed include:

- What is the cause of diabetes?
- Does diabetes impact the educational capabilities of the child?
- What should be told to the school authorities?
- How does one reveal the diabetes state to peers?
- What sort of jobs would be most suitable?
- How difficult would it be to obtain or maintain a job?

- What are the chances of finding a life partner and how should one reveal the diabetes state before finalizing marriage?
- What problems can arise during pregnancy and what are the risks to offsprings?
- What is the importance of good control?
- What are the long-term complications and can these be prevented or arrested if detected early?
- What is the expected lifespan?
- Will diabetes ever be curable?
- How can the childhood diabetes group work towards bringing down the cost of diabetes management?

These sessions may be conducted separately for the adolescents and for the parents with a combined session before the termination of the camp.

Interaction with siblings and grandparents. They should be taught how to inject insulin and glucagon, how to measure BG and the early recognition and first aid management of hypoglycemia. The grandparents need to be convinced about the various scientific aspects of diabetes management and an attempt should be made to enlist their cooperation. Siblings should receive a patient hearing and counselling with regard to the problems and difficulties they face because of the atmosphere in the house on account of the child with diabetes.

Entertainment programs. The post-dinner period at the camp can be used for entertainment programs, wherein the children can display their talent and skills in singing, dancing and so on.

POST-CAMP BENEFITS

At the conclusion of the camp, the participants should have accepted that:

- T1DM cannot be cured but can and should be controlled with insulin injections, meal planning, regular planned activity and regular monitoring.
- No other system of medicine has any effective treatment to offer.
- There is no basis for guilt for pricking the child often or imposing restrictions on the child's eating habits, as these are essential for the child's survival and long-term good health.
- The child can lead a full life and have a reasonably bright future if diabetes is kept in control.

Post-camp it is expected that:

- Patients would have acquired a better understanding of the disease and a thorough practical knowledge of its day-to-day management, so that they feel less confused and helpless.
- Having met so many others with the same problem, the feeling "why us" would be replaced with the assurance that "I am not alone".
- Patients would have established enduring friendships, which can be of mutual benefit in the long run.
- They would work together as a group to improve the lot of children with diabetes.
- They would be better placed to handle psychosocial pressures.
- Having met and interacted with seniors who are married and well settled in life, their anxieties about their own future would have been toned down to a large extent.
- They would no longer feel inferior.

ADVENTURE HIKES AND COMPETITIVE SPORTS

Strenuous planned physical activities may not be possible during the 3-4 days of residential camps. However, adventure hikes and sports days should be separately organized to supplement these camps. This would serve the dual purpose of teaching children how to manage diabetes in such situations and at the same time give them the confidence that no physical activity is beyond them.

DAY CAMPS

Day camps are less time consuming, more economical, and easier to plan and conduct. These should become a routine in centers, which do not have facilities to organize residential camps.

CAMP RESEARCH

The camp gives an ideal opportunity to conduct research as a large number of children and their families are accessible at one time.

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INFORMING THE SCHOOL AUTHORITIES

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- Children with type 1 diabetes mellitus (T1DM) spend a major share of their day in school. Hence staff members and a few close schoolmates should be familiar with the special needs of the child with diabetes mellitus.
- A social worker belonging to the medical team should meet the school authorities in person and also hand over written guidelines for care of the child or adolescent with T1DM.
- Messages related to various aspects of day-to-day care of a child or adolescent with diabetes while at school should be provided to school authorities by the concerned health care professional.
- The child with diabetes does need some special care and attention, which must be provided in an unobtrusive manner.
- Diabetes would not affect the academic performance and extracurricular activities of the child; provided it is well controlled and proper precautions are observed.
- Ideally the school should have a nurse who can administer and/or supervise the administration of a dose of insulin (if indicated), check blood glucose (when needed) and administer a shot of glucagon (during severe hypoglycemia).
- If a trained nurse is unavailable, 2 or 3 members of the teaching or administrative staff should be trained to do these procedures.
- The staff at school must have the telephone numbers of the child's parents and medical team members in case of any emergency.
- Glucose fluctuations (both hyper- and hypoglycemia) in the classroom have short-term effects on attention and on information processing skills.

INTRODUCTION

Children spend a large part of their day in school. Staff members and some close schoolmates of the child with type 1 diabetes mellitus (T1DM) should be familiar with the special needs of the child.

It is recommended that a social worker belonging to the medical team should meet the school authorities in person and also hand over written guidelines for care of the child or adolescent with T1DM.

MESSAGES TO BE CONVEYED TO SCHOOL AUTHORITIES

Each of the following messages needs to be conveyed in writing to the school authorities:

- T1DM is not a contagious disease. It is not caused by overeating or lack of physical activity or any other act of omission or commission on the part of the child or the family members.
- The child with diabetes needs to take insulin injections and check blood glucose (BG) 2-4 times each day. He/she must consume healthy food at fixed timings and take certain precautions prior to physical exercise. In all other respects the child is no different from other children and should be treated accordingly.
- A child with well-controlled diabetes can lead a near normal life.
- Diabetes would not affect the academic performance, provided it is well controlled.
- Diabetes will not affect the extracurricular activities of the child, provided certain pre- and post-activity precautions are observed.
- The child with diabetes *does need some special care and attention, but this must be provided in an unobtrusive manner.*
- Teachers and close friends should be familiar with the symptoms of high BG, in particular, polyuria and polydipsia. If the child frequently asks for permission to drink water or visit the rest room he/she should be granted permission; but the parents should be alerted, as these are indicators of poor diabetes control.
- Teachers and close friends should be conversant with the early symptoms and signs and the first aid management of hypoglycemia. If the child complains of hypoglycemia or is found to be drowsy, confused or behaving in an erratic manner, he/she should be promptly given 3 teaspoons of glucose powder or powdered sugar (which the child must carry in a plastic pouch in his/her pocket at all times). This should be followed after 15 minutes with a snack in the form of a fruit, sandwich or biscuits (which also the child should carry in his/her school bag at all times).
- Teachers must be aware that the child needs to eat on time; meals should never be skipped or delayed, even if, for some reason, the child needs to be detained in the school beyond routine timings.

- The child must be allowed to consume an extra snack before, and at times even during and after, unaccustomed physical activity.
- Child should be granted permission to take a shot of insulin and/or check BG, if he/she has been advised by the doctor to do so during school hours.
- Ideally the school should have a nurse who can administer and/or supervise the administration of a morning or afternoon dose of insulin (if indicated), check BG (when needed) and administer a shot of glucagon (in case of severe hypoglycemia). Frequent communication between the school nurse and the medical team can lead to improvement in control of diabetes.
- If the school does not have a trained nurse then 2 or 3 members of the teaching or administrative staff can be taught the procedures mentioned above. They should be assured immunity from liability under the "Good Samaritan" category.
- The staff at school must have the telephone numbers of the child's parents and medical team members in case of any emergency.

SCHOOL PERFORMANCE OF CHILDREN WITH DIABETES

Glucose fluctuations (both hyperglycemia and hypoglycemia) in the classroom have been shown to have short-term effects on attention and on information processing skills. This underlines the importance of trying to achieve a good control during school timings.

A recent study that compared academic performance and school absenteeism in children with T1DM and in their non-diabetic siblings, found that the child with diabetes had a poorer score than the sibling on both these parameters. In particular, those with diabetes did not fare as well as the siblings in writing skills and in mathematics. Those children on intensive treatment and those with lower HbA1c fared better than those on conventional treatment and those with higher HbA1c.

A meta-analysis has shown that children with earlier onset of diabetes and those with a history of hypoglycemic events or diabetes-related seizures tend to have somewhat more problems with cognition than those with later onset of diabetes and those without major hypoglycemia. The latter, in turn, were found to fare almost as well as peers without diabetes.

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DIABETES SELF-MANAGEMENT PATIENT EDUCATION

Anurag Bajpai

SUMMARY OF RECOMMENDATIONS

- Diabetes education is the cornerstone of successful management of children with type 1 diabetes mellitus (T1DM).
- Centers caring for children with T1DM should have a written and structured program for 'Diabetes Self-Management Patient Education'.
- The diabetes self-management patient education program should be individualized according to the age of the patient, stage of diabetes, socioeconomic and educational status and cultural values of the patients and their families.
- The diabetes education team should ideally comprise of a physician, a dietician, a psychologist with expertise in T1DM, and a diabetes educator.
- No child with T1DM should be discharged from the hospital without the understanding of survival skills of insulin injection, blood glucose testing and hypoglycemia, by the patient and the family.
- Diabetes self-management patient educational material written in lay terms in local language should be provided to the family.
- Families should be encouraged to join patient support groups for T1DM, at the time of enrolment.
- Patients and their families should have ongoing access to the education program with reinforcement during appropriate settings such as recurrent hypoglycemia and diabetic ketoacidosis.

INTRODUCTION

'Diabetes Self-Management Patient Education Program' is the cornerstone for success in the management of children with type 1 diabetes mellitus (T1DM). The lack of ongoing assistance from diabetes support staff in resource-poor settings as in India mandates greater empowerment of families with T1DM in self-

management. The education program should encompass all aspects of the disease, and needs to be individualized according to the age, stage of diabetes and educational status of the patient as well as the socioeconomic status and cultural background of the patients and their families. These guidelines aim to provide an overview of a diabetes self-management education program for Indian children. They should be individualized as per the needs and resources of centers caring for children with diabetes.

AIMS

Diabetes self-management education program aims to empower the child and the family in independent management of diabetes. The patient and the family should be trained to monitor blood glucose (BG) regularly and accordingly make ongoing adjustments in insulin dose, food and activity; handle special circumstances; identify and correct acute complications, especially hypoglycemia and diabetic ketoacidosis (DKA); and be aware of when to come to hospital for emergency care. They should also understand the predisposing factors and measures to prevent short and long-term complications of the disease.

GUIDING PRINCIPLES

Diabetes self-management education program is as much an art as science, and requires immense patience and knowledge on the part of the educating team. The program should include the child with diabetes and the parents or caregivers. Education of the school staff is also important.

Burdening of the family with too much information at a single point of time significantly limits patient retention. This should be avoided by giving education in a *structured and phased* manner.

The availability of a written structured education program individualized to the center's needs ensures uniformity of the education program. Educational handouts and/or leaflets written in local language are preferred. Use of online resources including websites, videos and mobile applications should be encouraged to provide ongoing education. The program should be interactive, and not didactic, to ensure ongoing feedback.

Meeting with families of children with diabetes diagnosed at a similar age is very helpful in imparting practical knowledge about the condition, and instilling confidence.

The first few days following discharge are crucial, given the significant changes in insulin requirement, nutrition and levels of physical activity. The families should therefore have ongoing access to a *patient helpline* to resolve these issues. The children and families should be encouraged to contact the helpline or the resource person of the self-education team, not only in emergencies, but also for clarifying

management problems through phone, mobile devices and applications such as "WhatsApp". Ongoing review of techniques (handling insulin, BG monitoring, self-adjustments, safe disposal of sharps) and reinforcement of information and key messages is needed.

Children diagnosed at a young age should be re-educated at a later age to ensure adequate understanding of the disease.

FEATURES OF A STRUCTURED PROGRAM

Structured diabetes self-education program should have the following features:

1. Structured and written format
2. Implemented by trained educator
3. Quality controlled
4. Audited

PERSONNEL AND DURATION

Diabetes education requires a multidisciplinary team involving the primary treating doctor (pediatrician or pediatric endocrinologist), diabetes educator, dietician, psychologist and social worker. The diabetes educator forms the core of the team and provides a forum for interaction with other members of the team. The team maybe modified according to the availability of resources and special needs of the children, but at the least should include a diabetes educator and a dietician.

The initial education program should be spread over 3-4 days to provide ample time for understanding all the aspects of the disease.

FORMAT

The diagnosis of diabetes usually comes as a big shock to the family. Most people think of diabetes as an adult disease and are not aware about diabetes in children and its long-term effects. The prospect of life-long daily multiple blood tests and insulin injections, coupled with guilt about the cause of the disease, is quite disconcerting for the family. There is usually a strong urge to seek 'permanent cure' using alternate therapies. The initial contact with the family should be used to allay the fears and guilt of the parents and to emphasize that insulin is the only form of treatment for T1DM.

The diabetes self-management educational program should be prioritized in to primary (essential survival skills; *'must know'*), secondary (*'should know'*) and tertiary *('might know'*) levels. Enrollment in a patient support group and meeting with other families with a child with diabetes is particularly helpful at this time point.

Table 1 provides a summary of the different levels of diabetes self-management education program. **Table 2** provides an overview of the structured day-wise format for a diabetes self-management patient education program spanned over three to five days.

Primary Education ("Must Know")

This covers the most important, essential aspects for care of children with T1DM. *No child should be discharged from a medical facility without imparting these skills. If the child was not admitted at diagnosis, these should be taught in the first 2 days.*

1. Disease

- Emphasize that diabetes is a life-long disease with numerous short and long-term complications.
- Normal outcome is possible with good control. Examples of role models from different fields of society go a long way in this regard.
- Parent's sense of guilt on the causation of the disease if any should be allayed by reassuring them that the disease was not caused by any act of commission or omission by the family.
- Basic information about the role of glucose and insulin in body systems and normal blood glucose (BG) levels.
- The cause of disease (insulin deficiency) and symptoms of diabetes.

2. Treatment

- Insulin is the only form of treatment.
- Daily multiple injections are required throughout life.
- No role of alternative medicines like oral antidiabetic drugs, homeopathy, ayurvedic or unani medicines.

3. Practical skills

- Overview of different insulin concentrations in vials, syringes (40 and 100 units) and pens, different lengths of syringe/pen needles.
- Injection technique
    i. Drawing up and mixing of insulin
    ii. Injection sites, angle and depth of insertion
    iii. Rotation of sites
    iv. Disposal of needles and sharps

v. Insulin pens – Storage, air shot to remove air bubbles.

- Insulin storage and transport
  i. Up to 3 months in refrigerator and 1 month at ambient temperatures up to 25°C.
  ii. During summer months, carry insulin in thermos/insulated carry case.
  iii. Never expose insulin to sunlight, or leave in a vehicle.
  iv. Never freeze insulin vials, or pack into baggage.
  v. If refrigerator is not available or there are frequent power cuts, store in air-cooled matka (see chapter on insulin use).
- Self-monitoring of blood glucose (SMBG)

4. Nutrition

- Healthy feeding pattern; no special "diabetic" diet
- Meal plan – According to insulin regimen
- Avoid simple sugars; importance of mid-meal snacks

5. Follow-up

- Diabetes diaries and log
- Honeymoon phase and the need for reducing insulin dose during this period
- *Hypoglycemia* – Causes, prevention, clinical features and treatment; 'hypo' emergency kit and diabetes patient ID card
- *Sick day guidelines* – Never skip insulin during illness
- Features of diabetic ketoacidosis (DKA)
- Complications and their screening

Secondary Education ("Should Know")

These aspects should be taught to all the children with diabetes and their families.

1. Disease

- Role of insulin and a brief overview of glucose homeostasis
- Difference between type 1 and type 2 diabetes mellitus
- Pathophysiology – Cause of T1DM
- Short and long-term complications of diabetes (nephropathy, neuropathy and cardiac disease)

TABLE 1. Levels of Diabetes Self-Management Education

Category	*Primary*	*Secondary*	*Tertiary*
Disease	Diabetes is a life-long disease Normal outcome possible Allay guilt and reassure	Role of insulin in glucose homeostasis T1DM vs. T2DM Pathophysiology Complications	Effects of insulin deficiency Classification of diabetes Role of autoimmunity Disease associations
Treatment	Insulin is the only form of treatment Need for daily multiple injections No role for alternative medicines	Insulin preparations Time course of action of various insulins Injection devices	Insulin regimens Insulin pumps Newer insulins Hope for the future
Practical skills	Injection technique Insulin storage and transport SMBG	Glycemic targets Insulin dose modifications Time sheet	Physical activity Ketone monitoring Glucagon injection
Nutrition	Healthy eating Avoid simple sugars Mid-meal snacks	RDA of nutrients for age Food exchanges High fiber intake	Carbohydrate counting Insulin to carb ratio Glycemic index Eating out
Follow-up	Diabetes diary and log Honey-moon phase Hypoglycemia Sick day guidelines	SMBG: Glucometers and logs Role of HbA1c 'Hypo' prevention Physical activity Annual complication screen	DKA prevention Continuous glucose monitoring (CGM)

2. ***Treatment***

- Forms and source of insulin
- Time course of action of different insulins
- Insulin injection devices

3. ***Practical skills***

- Insulin dose modifications
- Insulin guidelines for sick day management
- Anticipatory management of physical activity
- Glucagon injection for hypoglycemia

4. Nutrition

- Recommended dietary allowance (RDA) for macronutrients and calories
- Food exchanges
- High fiber diet
- Culturally acceptable foods

5. Follow-up

- Self-monitoring of BG (SMBG)
    i. Glucometer and log books
    ii. Glycemic goals
    iii. Ketone monitoring
- Role of HbA1c in monitoring of sugar control
- Prevention of hypoglycemia
- Physical activity program
- School planning and time sheet
- Planning for travel, examinations and camps

Tertiary Level ("Might Know")

This covers finer aspects of diabetes management and should be targeted to educated and highly motivated families and children.

1. Disease

- Effects of insulin deficiency
- No need for excessive restriction
- Classification of diabetes
- Autoimmunity and its role in T1DM
- Disease associations of T1DM (hypothyroidism and celiac disease)

2. Treatment

- *Insulin regimens*
- Overview of insulin pens and pumps
- Newer insulins – Oral and inhaled insulins
- Hope for the future– Islet cell transplant, stem cell transplant

3. *Practical skills*

- Proactive management of ketosis
- Indications for hospitalization

4. *Nutrition*

   a. Carbohydrate counting and calorie content of common products

   b. Glycemic index

   c. Insulin to carbohydrate ratio

   d. Adjustments for eating out

5. *Follow-up*

   a. Annual complication screening

   b. Continuous glucose monitoring systems (CGMS)

TABLE 2. Structured Day-wise Format for Diabetes Self-Management Patient Education

Day	*Disease*	*Treatment*	*Nutrition*	*Practical skills*
1	Role of insulin Life-long disease Allay guilt	Insulin is the only treatment No role for oral drugs	Healthy eating Frequent meals	Insulin storage Injection sites
2	Classification Complications Cause	Insulin regimens Site and rotation Injection devices	Age specific RDA Diet chart	Insulin mixing Insulin injection Time sheet
3	Hypoglycemia Sick day	Glycemic goals Dose adjustment	Food exchanges Glycemic index	Glucose testing Urine ketones
4	Feed back Education quiz	Honeymoon phase Practical guidelines	Carbohydrate count Insulin to carb ratio	DKA prevention Glucagon Diabetes log

AGE-SPECIFIC GUIDELINES

Diabetes self-management education should address age-specific requirements.

Pre-school Children

- Need for repeated counseling of parents to allay their anxiety and concerns.
- Need for frequent BG monitoring and insulin adjustment for unpredictable eating pattern.
- High index of suspicion for hypoglycemia
- Need for higher glucose cut-off

- Care in preschool setting to include school staff

School-age Children

- Increase self-reliance in glucose monitoring and management
- Emphasis on early detection of hypoglycemia in school
- Key adaptation for school programs including sports and physical activity
- Care during school trips, annual function and sports day

Adolescents

- Comprehensive re-education of children diagnosed at an early age
- Focus on peer pressure and social group effects
- Handling variations in eating and exercise (often tuitions or extra-academic burden)
- Weight control and healthy eating
- Caution against risk-taking behaviors like smoking, alcohol consumption and recreational drugs, discussion of sexuality
- Information about safe measures related to eating out, parties and sexuality

Diabetes education is the most important, though often neglected part of diabetes management of children. Formulation of standardized diabetes self-management patient education modules individually targeted to the center's needs is important to achieve this goal.

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DIABETES IN TODDLERS

Aspi J. Irani

SUMMARY OF RECOMMENDATIONS

- Toddlers present with more acute and severe symptoms of insulinopenia compared to older children.
- Their eating and their activities are unpredictable; hence hypoglycemia is a greater possibility.
- The most preferred regimen in toddlers is a "modified" basal-bolus regimen, in which rapid acting insulin analog is given *after* the meal in a dose based on the amount of carbohydrate consumed.
- Insulin pens that deliver half unit increments are to be preferred in toddlers.
- Repeated hypoglycemia can affect the developing brain and hence must be avoided at all costs. Therefore the goals of therapy are relaxed for this age group, if so needed.
- The availability of glucagon at home is of great importance in this age group.

INTRODUCTION

The term "toddler" refers to a child in the age group of 1 to 3 years, who is just learning to walk and talk. In recent years there has been a spurt in incidence of type 1 diabetes mellitus (T1DM) in this age group. This section outlines some of the important aspects of diagnosis and management of diabetes in toddlers.

DIAGNOSIS

The diagnosis of T1DM is often missed till late in this age group. Awareness and a high index of suspicion are important for early diagnosis. Diabetes must be suspected in any toddler presenting with:

- Excessive thirst and irritability
- Polyuria with polydipsia and polyphagia (the "classical triad")
- Weight loss despite a good appetite

- Candida dermatitis in diaper area that is recurrent or resistant to treatment
- History of ants collecting around the urine
- Dehydration with polyuria
- Breathlessness with increased air entry
- In the differential diagnosis of: "first episode of asthma", acute abdomen or drowsiness.

INITIAL MANAGEMENT

At diagnosis, it is advisable to hospitalize the toddler (even if non-ketotic) for 2-3 days to provide basic education in diabetes self-management. During the hospital stay the parents must be taught insulin injection technique and site rotation, technique of home blood glucose (BG) measurement and how to record the results, practical meal planning and early recognition and first aid management of hypoglycemia. Parents should be encouraged to prick themselves with an insulin syringe and with a bloodletting lancet so that they realize that these procedures are fairly painless.

One should arrange for the new family to be visited in the hospital or soon after discharge by the parents of one or two patients from the same locality to provide much needed emotional support and guidance in the early weeks after diagnosis. The latter ("mentor parents") should not only be well versed in diabetes self-management but also emotionally well adjusted.

The parents of the toddler must be convinced about three points at the outset:

1. There is no alternative to insulin treatment (which is essential for survival of the child).
2. All is not lost – the child can lead a full and near normal life provided diabetes is well controlled.
3. A cure for diabetes is not as yet available but may be available in future; till then keeping the child in good health (with the tools available at present) is important.

Intense counseling on these three aspects ensures that insulin will not be discontinued, that parents will not waste time looking for alternative therapies or a cure and that they will not lose hopes about the child's future.

INSULIN THERAPY

A split-mix regimen using a mixture of regular insulin and NPH insulin twice a day may be used in a toddler who has a predictable meal intake. However, toddlers being unpredictable and picky eaters, the split-mix regimen is generally associated with wild fluctuations in BG levels.

The most preferred regimen in toddlers is a "modified" basal-bolus regimen, in which rapid acting insulin analog is given *after* the meal in a dose based on the amount of carbohydrate consumed. This would be less stressful for the parents. Lispro insulin given after a meal has been shown to be as effective as when given before the meal and more effective than pre-meal regular insulin. For the basal insulin, glargine given once a day has been shown to be superior to NPH insulin given twice a day. This regimen of post-meal rapid acting analog with 1 injection of Glargine should be the regimen of choice for toddlers.

Insulin pens which deliver half unit increments are to be preferred to those providing 1 unit increments for finer tuning of insulin dose. In toddlers needing small doses, even a half unit adjustment would amount to a very high percentage change in dose. For instance, a change from 2 units to 2.5 units is a 25% increase, but a change from 2 units to 3 units would be a 33.3% change! Insulin diluted to strength of U-20 with appropriate diluents has been shown to remain stable and uncontaminated for 30 days; this would allow for finer tuning of the dose. Diluted insulin could be very helpful in treating toddlers with small insulin needs. Unfortunately, insulin cartridges are marketed in U-100 strength only and diluents for the same are not available in India at present. For short-term use, insulin could be diluted with normal saline.

Many centers have reported good results with use of the insulin pump or continuous subcutaneous insulin infusion (CSII) in the toddler age group, with a significant drop in HbA1c, several fold reduction in episodes of hypoglycemia, greater flexibility in lifestyle and greater confidence and independence in parents. When parents are intelligent and motivated and when finance is not an issue this would be a good option though it has not been consistently shown to give better outcomes than the basal-bolus regimen described above.

MEALS

Toddlers are fastidious eaters, and have a highly variable appetite from day to day. Rigid meal plans never work and have no role in a toddler with diabetes. Toddlers normally consume small and frequent meals. Portions offered should be small so as not to overwhelm the toddler. A variety of foods can be offered at meal time, so that the toddler is more likely to select an item. Food should be decorated well and attractive plates and cups should be used as eating is largely psychological. Forced feeding and expressions of anxiety about child's appetite should be strictly avoided as this will only lead to food refusal. Parents must ensure that meal times are pleasant. Toddlers prefer self feeding. Parents should set limits on time allowed for a meal. "Out of bounds" dietary items (junk foods of all categories) should not be kept in the house to avoid temptation. Food should never be used as a reward.

PREVENTION OF HYPOGLYCEMIA AND SETTING MANAGEMENT GOALS

Severe and frequent hypoglycemia, below the age of 3 years, can lead to permanent cognitive, intellectual and learning defects. MRI scans of such children have shown a significant incidence of mesial temporal sclerosis (MTS), a defect that is never observed in normal children.

The toddler cannot report hypoglycemia. Recognition of hypoglycemia can be difficult in this age group. The toddler may become pale, cranky, irritable, and lethargic. He may start to sweat or tremble, let out a particular cry, become clumsy, or develop a bluish tinge of lips or fingers. A temper tantrum may be the chief symptom of hypoglycemia. It is very important that patients have glucagon available at home and that they are trained to prepare and inject the same confidently during severe hypoglycemia.

Prevention of hypoglycemia is a very important aim of management in this age group. A delicate balance needs to be struck between what is desirable (good level of BG) and what is safe and practical. The American Diabetic Association recommends a goal of HbA1c <7.5% with fasting blood glucose (FBG) of 90-130 and postprandial BG (PPBG) of 90-150 mg/dL *across the pediatric age group*. This would be ideal if it can be achieved without significant hypoglycemia. Higher target BG level of 110-220 mg/dL with target HbA1c of 8 to 8.5%would seem more appropriate in most toddlers. In addition, it is important that the child should be leading a normal, happy childhood, and growing and developing normally.

It was earlier believed that the years before puberty did not contribute much to the development of microvascular complications; subsequent studies challenged this observation. A recent study with 20 year follow-up concluded that toddlers diagnosed with diabetes below the age of 3 years are more protected against microvascular complications than are those diagnosed in the pubertal years but the same study also found that if long-term glycemic control remained poor then this protection was erased over time.

Toddlers are very likely to get recurrent respiratory infections as they join a playgroup and come in contact with many other children. Frequent "sick days" can make diabetes management very difficult. All vaccinations (including the so called "optional vaccines") should be given as per the immunization schedule of the Indian Academy of Pediatrics. Good dental care should be stressed.

GUIDELINES FOR INJECTIONS AND HOME MONITORING OF BLOOD GLUCOSE

Parents must adopt "matter of fact" approach when performing the unpleasant tasks of injecting insulin and checking BG levels. They should be firm

but gentle and never display anxiety. Delaying tactics on part of the child and attempts to bargain must be quietly ignored. Parents must ensure that insulin, glucometer, strips etc. are ready before going to the child. The shortest and thinnest needle should be used as it would cause less pain and have lower risk of IM injection. A BG meter that requires the least volume of blood should be preferred. The child should know when he/she is about to be injected so that he/she is not scared every time the parents approach. Injections should not be given to the child when in bed. Distractions such as television, songs or special toys can be used. Child should be allowed to participate in some routines such as choosing the BG strip or the finger to prick. Parents should make it a point to display love for the child after giving the injection or a prick. All grown-up persons in the house should take turns to inject so that the child does not feel that one parent is causing all the pain; also the child can be managed in the absence of one or both parents.

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DIABETES IN ADOLESCENTS

Anju Virmani

SUMMARY OF RECOMMENDATIONS

- Many aspects of adolescence impact diabetes management, often adversely, and vice versa (diabetes makes adolescence more difficult).
- Growth and pubertal development must be monitored, and efforts made to ensure normalcy. Higher doses of insulin are needed to cope with the physiological insulin resistance of puberty.
- Monitoring for chronic complications should be done annually.
- Other special issues include emotional changes, academic and career issues, privacy, confidentiality and freedom, and transition to adult care.

INTRODUCTION

Adolescence is the period of transition from childhood to adulthood. There are numerous aspects of adolescence which impact diabetes management, often adversely. Likewise, the presence of a chronic condition like diabetes places great demands on the psychology of the youngster who is already going through a difficult period of his or her life. Recognition of these issues, and paying attention to them as the child with diabetes grows into an adult, will allow for a smoother transition through these difficult years. Some of these aspects are discussed below.

SPECIAL ISSUES OF ADOLESCENTS WITH DIABETES

Physical Changes

The adolescent growth spurt provides a significant proportion of the adult height of an individual, and linear growth and onset and/or progression of puberty may be adversely affected by poor glycemic control during this period. Body image issues are important during adolescence; short height or attenuated puberty then adds to the adolescent's stress, as he/she looks different. Some adolescents, especially girls, realizing that poor control helps them lose weight, intentionally miss insulin doses.

Insulin Resistance, Doses and Administration

There is significant insulin resistance during adolescence. Thus higher insulin

doses, to the tune of 1.5 to 2 units/kg/day, may be needed for about 2-3 years. Parents and the adolescent may hesitate to increase doses adequately, thus worsening control. The often-erratic lifestyle (e.g. long classes, tuitions, more eating out) means a need for more frequent injections, which the adolescent may refuse. Some adolescents on insulin pump demand to go back to multiple daily injections (MDI) as they "do not want a reminder of diabetes all the time" or it interferes with choice of clothes. Adolescents tend to have higher HbA1c levels in general, more frequent episodes of ketoacidosis as well as hypoglycemia. The aim of the diabetes care team should be to provide care such that physical, emotional and academic development is normal, complications are reduced, and discrimination is avoided. The best possible glycemic control should be aimed at.

Glycemic Control and Complications

All other risk factors, including diabetes duration being the same, puberty increases the risk of microvascular complications. Thus, for children whose diabetes onset is during the adolescent period, complications screening is recommended after diabetes duration of just 2 years rather than 5 years. From adolescence onwards, screening for hypertension, retinal examination, microalbuminuria, and serum lipids should be done annually. In case of poor growth or pubertal development, hypothyroidism, celiac disease and other autoimmune conditions should be looked for, and treated adequately. Sometimes, in spite of the team's best efforts, glycemic control may remain poor and cause delayed puberty. If puberty has not started by the age of 13 in a girl or 14 in a boy, low dose estrogen or testosterone should be given. Allowing puberty to be delayed beyond this age may adversely impact bone accrual as well as body image.

Mental and Emotional Changes

Risk taking and mood swings are an integral part of growing up. They reduce compliance with diabetes self-care and worsen control. The desire of the parents to control contrasts with the adolescent's need for freedom, creating conflict. The adolescent's need for peer approval and to move away from the family also interferes with communication within the family, and add to the stress of this period. Eating disorders may begin to manifest.

Social and Cognitive Development

This new maturity may mean that the young patient with diabetes realizes the full impact of diabetes upon the rest of his/her life, which is like being newly diagnosed. This may cause depression, denial, or other mental health problems. Social independence and development of self-esteem may be restricted by diabetes. The adolescent may need privacy (especially from parents) during examination and also history taking or discussion.

Academic and Career Issues

These are worries for the adolescent, and are impacted, often negatively, by diabetes. Parents may refuse to allow the adolescent to apply for courses which involve moving out of the house.

Financial Independence

This is delayed and reduced by diabetes. Many of them feel resentful of the financial burden diabetes imposes.

Experimentation

The adolescent may try smoking, alcohol, other drugs, or sexual exposure, with a negative impact on general health as well as glycemic control. It may be difficult to elicit this history from the adolescent if caregivers are present in the room, and there is no provision for privacy. Caregivers sometimes angrily question the need for privacy, and may get even angrier if they realize that advice about contraception or de-addiction has been given. On the other hand, the adolescent may misunderstand any questions about such sensitive issues and accuse the health care personnel (HCP) of voyeurism or sexual harassment. Whether the HCP should inform caregivers about risky behavior raises difficult ethical concerns.

TRANSITION OF CARE

The diabetic adolescent/young adult is likely to be referred to an adult clinic. He/she may resent being seen in the pediatric endocrinologist's clinic along with little children, and yet also may have a difficult time adjusting to the new caregivers and the more impersonal atmosphere of adult clinics.

Ideally, transition programs should be made to help the adolescent move from the pediatric to the adult clinic. The age at which this transition should be made should depend on the maturity and wishes of the patient and of the family. In actual practice, the unfortunate lack of enough trained pediatric endocrinologists has meant that many concerns are unmet, and patients move randomly to whatever service is available and most convenient, rather than ideal.

BASIC NEEDS OF THE ADOLESCENT

As far as possible, the adolescent should be offered:

1. Where available, a clinic attended by pediatric endocrinologist, adult endocrinologist, and counselor familiar with type 1 diabetes and comfortable with adolescents. The counselor may form the bridge between the patient, family members and doctors, and also help detect when psychiatric treatment is needed.
2. Physical privacy during history or examination, with adequate chaperons if

relevant. Consultations in large outpatient clinics can be very embarrassing for the young person.

3. Personal privacy – some time for direct talking to the doctor/team member without parents/ caregivers in the room.
4. Nutrition-related advice relevant to changing needs, e.g. adequate protein, iron, calcium and vitamin D intake.
5. Monitoring of growth and puberty to ensure they are progressing at a normal pace, and advice about handling pubertal changes.
6. Explanation that higher insulin doses may be needed to compensate for the insulin resistance of puberty. Some girls may do well with small doses of metformin, especially if they develop obesity and/or polycystic ovarian syndrome (PCOS).
7. Encouragement to take more frequent injections or, if the financial situation permits and other factors are conducive, change over to the insulin pump, to increase flexibility in lifestyle, which is very important at this age.
8. Information about tackling and preventing acute and chronic complications.
9. Monitoring of blood pressure, eye changes, lipids, microalbuminuria, at regular intervals to enable early detection of microvascular complications.
10. Sensitivity to the possibility of eating disorders, and risk-taking behavior, and ongoing counseling for preventing and/or solving these problems.
11. Explicit age- and maturity-appropriate discussion on how to cope with peer pressure to experiment with smoking, alcohol, other drugs, or sexual exposure, and advice on contraception if they are (or likely to be) sexually active. They should be discouraged from an early age from smoking, binge drinking, or taking drugs.
12. Confidentiality when giving advice on contraception: Indian families are often unwilling to bring up the topic of sexuality or contraception, so extreme care and sensitivity are needed. Giving contraceptive and other such advice without parental involvement is legally a grey area for adolescents below the age of 18 years, but may be crucial.
13. Encouragement to the family members to give adolescents the greater freedom they need, while keeping the channels of communication open, no matter how difficult the adolescent gets. Breakdown of communication could mean even worse compliance and even total loss to follow-up.
14. Opportunities to meet older persons with type 1 diabetes, so they can realize that careers, marriage, parenthood, etc. are all possible with diabetes.

15. Career counseling so they can maximize their potential, and allow them to achieve financial independence as well as self-esteem. Some career options are not open to persons with diabetes. Unfortunately, at present diabetes debars one from many government jobs in India.
16. Frank discussion of what the issues bothering the patient are—e.g. looks, sexuality, etc. and understanding these from the patient's perspective.
17. Empathy along with firmness as regards compromises in care—e.g. if the adolescent is not willing to test often, or if the intake of junk food goes up.
18. Involvement of the adult physicians, counselors, gynecologists, and other medical personnel they may need to see, so that transition is easier and smoother.
19. Discussion involving the family about driving. Many parents allow underage driving, and must be discouraged from doing so. When driving is learnt and permitted, all must fully understand the importance of being able to handle hypoglycemia (suspecting, testing, treating, and preventing), as even mild hypos can disrupt driving. They must be aware of the very high risk of drinking and driving, more so with hypoglycemia, for accidents, including fatal accidents.
20. Clear instructions on which emergency service the adolescent should contact in case of need.
21. Encouragement to carry an identity card stating, "I have diabetes. If I am found behaving strangely or unconscious, please give me the candy in my pocket, and contact the following numbers…" (See Chapter 10).
22. Formal assessment of the psychological state of the adolescent: Ideally, all children with diabetes, particularly the adolescent patient, should have a psychology evaluation. Examples of the tools used include the Center for Epidemiological Studies Depression Scale for Children (CES-DC), Mind Youth Questionnaire (MY-Q), DAWN Youth Quality of Life tool and DASS 21 (Depression, Anxiety Stress Scale-21) for assessment of quality of life and mSCOFF questionnaire for eating disorders. However, there is a great paucity of trained personnel in India. Therefore, the pediatrician or diabetes specialist may make an initial evaluation and prioritize the decision for referral. Chapter 14 gives some useful aspects to probe with the family and patient, to make this preliminary evaluation.

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TYPE 2 DIABETES IN CHILDHOOD AND ADOLESCENCE

Ganesh S. Jevalikar

SUMMARY OF RECOMMENDATIONS

- Type 2 diabetes mellitus (T2DM) in children and adolescents is increasingly being seen in India.
- The Asian Indian phenotype is considered at high-risk for development of T2DM.
- The age of onset of T2DM in declining in India.
- T2DM should be suspected in pubertal children who are overweight, and have signs of insulin resistance, positive family history of diabetes and an incidental or asymptomatic presentation.
- If clinical differentiation from type 1 diabetes mellitus (T1DM) is not possible, fasting C-peptide, T1DM-associated autoantibodies and clinical course might be useful guides for diagnosis.
- Detailed evaluation of lifestyle risk factors and family habits is of paramount importance in developing an individualized treatment plan.
- Screening for comorbid conditions and components of the metabolic syndrome is necessary at diagnosis and periodically thereafter.
- Screening for diabetes complications should begin at the onset and be done annually (more frequently if clinically indicated).
- Although lifestyle management is the cornerstone of treatment, pharmacologic treatment should begin at the time of diagnosis.
- Metformin and insulin are the only medications currently approved. The choice of treatment is guided by the clinical presentation and level of glycemia.
- Lifestyle management consists of individualized diet plan, lifestyle modification and family-centered behavioral modification.
- Poor adherence to therapy is common.
- Complications rates are higher than in those in T1DM with similar glycemic control.

BACKGROUND AND EPIDEMIOLOGY

Childhood type 2 diabetes mellitus (T2DM) is a relatively new disease for pediatricians, being described as late as in the 1990s. Although, worldwide, type 1 diabetes mellitus (T1DM) is the most common type of childhood diabetes, childhood onset T2DM has already become the most common type in certain ethnic groups (native Americans, African Americans and Pacific Islanders) and some countries (Japan and Taiwan).

A decline in the age atonset of T2DM has been documented in the INDIAB study by the Indian Council for Medical Research (ICMR). Population-based studies on the exact prevalence of T2DM are lacking amongst Indian children. Clinic-based studies have documented the proportion of T2DM amongst children and youth to range from 6-8% of cases in some centers to as high as 48% from a South Indian center. Reasons for this apparently high incidence from South India are not known, but reasons such as genetic and environmental factors (e.g. white rice consumption) or a referral bias have been speculated. Large epidemiologic studies are needed to clarify these issues in the future.

PATHOPHYSIOLOGY

T2DM results from relative insulin deficiency against a background of insulin resistance. Most children with T2DM have one or both parents affected with T2DM indicating strong genetic susceptibility. Obesity is seen in most but not all cases and is the most common environmental risk factor. A diet high in simple carbohydrates coupled with lack of physical activities and sedentary lifestyle plays an important role in the causation of T2DM. Most cases are seen during or after puberty indicating a role of the physiological insulin resistance of puberty. Truncal fat and visceral adiposity are directly related to risk of diabetes. Intrahepatic fat and adipokines also play an important role in impaired insulin sensitivity. *In utero* nutrition and low birth weight with rapid postnatal catch-up is linked with increased risk of T2DM in later life.

As in adults, adolescents with T2DM have significant impairment of insulin secretion and insulin-mediated glucose disposal. This has been shown in longitudinal studies of children and adolescents who progressed from impaired glucose tolerance (IGT) to diabetes. Early onset of disease, faster progression from prediabetes to diabetes and frequent failure of oral antidiabetic drugs supports aggressive nature of the beta cell dysfunction.

DIAGNOSIS

The biochemical criteria for the diagnosis of childhood onset T2DM are not different from that of T1DM or adult T2DM. However since an incidental presentation is more common, the diagnosis may need repeat testing for

confirmation. Glycosylated hemoglobin (HbA1c) should not be used as a standalone criterion to diagnose diabetes in children at present due to lack of standardization across laboratories in India and the lack of data in children.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) represent prediabetes stages with impairment of carbohydrate metabolism in the fasting state and post-carbohydrate load respectively. These may be transient states, with reversal to normal glucose tolerance in as many as 60% individuals. However, persistent weight gain with lifestyle risk factors increases the risk of progression to overt T2DM.

Differentiation from Other Types of Diabetes

Clinical clues to the diagnosis of T2DM are:

- Onset during or after puberty
- Overweight or obesity
- Incidental or atypical presentation (repeated skin infections, candidiasis and poor wound healing)
- Family history of T2DM in one or both parents or first degree relatives
- Markers of insulin resistance (IR)
    - Acanthosis nigricans or skin tags
    - Polycystic ovarian syndrome (PCOS)
- Other components of metabolic syndrome such as increased waist circumference, hypertension and dyslipidemia

In most children, the diagnosis of T1DM versus T2DM can be made on clinical basis. The occurrence of acute or subacute symptoms, ketoacidosis and lack of family history in a non-obese child points to T1DM, whereas presentation in an obese adolescent with asymptomatic or incidentally detected diabetes with signs of insulin resistance and family history of T2DM points to T2DM. In an increasing number of cases the distinction is not clear-cut and there maybe an overlap in clinical features. Due to the rising incidence of obesity and T2DM, features such as overweight, acanthosis and family history may be present in T1DM. A small percentage of children with T2DM (5-15%) may have ketoacidosis. In these circumstances further laboratory testing may be helpful.

In such patients fasting C-peptide and testing for diabetes autoantibodies should be performed. Fasting serum C-peptide is best done after initial hyperglycemia has been controlled to rule out the effect of glucotoxicity. Anti-GAD-65 antibody is the most common antibody test done in India. Expanded screening including zinc transporter antibody (Anti-ZnT8), tyrosine phosphorylase

antibody (IA2A) and insulin autoantibody (IAA) is now available as a panel and may be done if economically feasible.

If for any reason these tests cannot be done, the decision regarding initial management is based on severity of symptoms and hyperglycemia. If diagnosis is not clear, it is safer to start the patient on insulin. Subsequent clinical course over 1-2 years is helpful as patients with T1DM usually have absolute insulin dependency by this time whereas glycemic control with addition of metformin and successful weaning of patients to no or very minimal (0.2 to 0.3 units /kg) insulin doses suggests T2DM.

Monogenic diabetes should be considered in the presence of family history of youth-onset diabetes (usually not requiring insulin). Dependence on the classical clinical criteria of three generations with diabetes may result in missed diagnosis in several cases of maturity-onset diabetes of the young (MODY), therefore a high index of suspicion is necessary. Genetic testing for MODY is now available in India and should be offered if the diagnosis is suspected.

EVALUATION

The following points are important in the evaluation of a child with T2DM:

- Detailed history of diet and lifestyle including exercise habits, screen time (including television, computer, I-Pad, mobile phone, video game etc.) and sleep habits is necessary.
- Behavioral and psychological history to look for depression, eating disorders and body image disorders.
- The focus of lifestyle history should be the entire family and not just the child.
- In addition to the family, the school environment, peer pressures, bullying etc. needs to be assessed.
- Complications of diabetes maybe present even at the onset meriting clinical and laboratory evaluation (e.g. fundus examination, examination for peripheral neuropathy and lab evaluation for nephropathy). Presence of comorbid conditions such as obstructive sleep apnea, depression, polycystic ovarian syndrome and components of metabolic syndrome (**Table 1**) needs specific attention.
- The presence of underlying predisposing conditions such asTurner syndrome and Klinefelter syndrome should be considered.

TABLE 1. Screening For Comorbid Conditions Associated with Type 2 Diabetes Mellitus

Comorbidity	Screening	Goals	Management
Obesity	• Weight • BMI • WC	Age appropriate BMI and WC	• Diet and lifestyle to aim for weight maintenance or reduction as appropriate
Hypertension	BP measurement with appropriate cuff, after accounting for white coat hypertension	BP <95th centile for age, gender and height	• Weight loss, limiting excess salt intake, exercise • ACEI or ARB if BP >95th centile after 6 months
Dyslipidemia	Fasting lipid profile (after initial glycemic control)	LDL < 100 mg/dL TG < 150 mg/dL HDL>35 mg/dL	• Diet and lifestyle - limit simple carbohydrates and fatty food • Statin if persistently elevated LDL >130 mg/dL despite 6-12 months of lifestyle management • Consider fibrates if TG > 400-600 mg/dL after 6-12 months of lifestyle and glycemia management
PCOS	• Menstrual history • USG • Morning testosterone if suggestive symptoms	• Weight control • Regular menses	• Lifestyle management • Metformin • OCPs
NAFLD	Liver enzymes	Normal liver enzymes	• Lifestyle management • Metformin
Depression	Clinical screening		• Psychiatry referral
OSA	• History • Sleep studies in selected cases		• Weight loss • CPAP

Abbreviations: ACEI – Angiotensin converting enzyme inhibitors; ARB – Angiotensin 2 receptor blockers; BMI – Body mass index; BP – Blood pressure; CPAP – Continuous positive airway pressure; HDL – High density lipoprotein cholesterol; LDL – Low density lipoprotein cholesterol; NAFLD – Non-alcoholic fatty liver disease; OCP – Oral contraceptive pill; OSA–Obstructive sleep apnea; PCOS – Polycystic ovarian syndrome, TG –Triglyceride; USG – Ultrasonogram; WC – Waist circumference

MANAGEMENT

Unlike T1DM, lifestyle management is more important and is the cornerstone of treatment. Poor adherence to lifestyle modifications is the most important barrier in successful treatment of T2DM.

Goals of Management

- Normal height gain with weight maintenance/reduction as appropriate
- Commitment to healthy eating and lifestyle including reduction of sedentary activities
- Normal glycemic control
- Control of complications and comorbidities
- Cessation of smoking

Dietary Management

- A pediatric nutrition expert should review the diet in detail. An individualized plan should be made for each child taking into consideration the existing diet pattern, the family structure, cultural beliefs and the psychological state of the child. In general the focus is reduction of simple carbohydrates, refined cereals, processed food, sugary beverages, salted snacks, and Indian as well as western fried snacks.
- Attention should be paid to snacks in between meals, particularly as families often do not count these calories, which can be quite significant.
- The quality and quantity of homemade food should also be checked. Patients and families often believe that only "outside" or "modern" food causes obesity. Indian families often consume high amounts of carbohydrates (*roti,* rice, bread and biscuits) and low amounts of proteins and fiber.
- Large portion sizes or efforts to finish what has been cooked or served lead to overeating. Therefore, families should be encouraged to use smaller portion sizes and take only the necessary amount of food.
- Family dinners should be encouraged and other activities such as viewing or surfing television channels or internet, talking or texting on mobile phones and/or reading while eating should be discouraged.
- In addition to quality and quantity of food, healthy cooking and eating practices should be encouraged. Children should be encouraged to chew food slowly.
- It is necessary for all children and adults of the family to follow a similar diet routine.

- If the child is consuming school meals, attention to its quality is important as high calorie snacks and reheating of oils are some common unhealthy practices followed.
- Often foods like chips/fries are considered "modern" and "fashionable". It is not uncommon for a child to be teased or bullied in school for not bringing these items lunchbox. Therefore healthy eating should be an important component of the school curriculum, culture and practice.

Lifestyle Modification

Exercise is an important component of management of T2DM and helps in glycemic control, weight management and treatment of comorbidities like hypertension and dyslipidemia.

All patients (and family members) should be encouraged to do moderate to vigorous physical activity for 45-60 minutes daily. These can also be done in 2-3 segments in the day. Exercise should be an age-appropriate and enjoyable activity and monotony should be avoided by giving multiple options. Continuous motivation is necessary and is easier if family members serve as role models for the child. Involvement of peers is also beneficial. In addition, exercise should be incorporated in daily routine and activities including climbing stairs, walking or cycling to school, and doing household chores should be encouraged. Active participation in school sports and competitions should be strongly encouraged.

Sedentary activities involving television, internet, social networking, mobiles, Ipads and video games should be limited to less than 1-2 hour per day. Children should be encouraged to select only 1-2 programs of their liking and aimless surfing of channels be avoided.

A healthy sleep routine should be encouraged with fixed bedtimes and waking up times including on weekends. Late dinner followed by bedtime without an adequate gap lead to weight gain and gastro-esophageal reflux.

History of smoking and tobacco use should be recorded in all adolescents and proactive counseling should be done for smoking cessation.

Pharmacologic Management

Although lifestyle modification is the cornerstone of management of T2DM, when used alone it is ineffective in achieving glycemic control in more than 90% cases. Therefore, it is recommended that all patients with T2DM be started on pharmacologic management at the time of diagnosis.

Currently metformin and insulin are the only approved medications for management of childhood T2DM. Metformin is a biguanide that helps in improving insulin sensitivity and reducing hepatic gluconeogenesis, and has been shown to

be safe in children. Other medications which have been tried include sulphonlyureas (SU, effective, but cause weight gain), thiazolidinediones (TZD, effective and well tolerated), α-glucosidase inhibitors, and DPP-4 inhibitors. The GLP-1 receptor agonist, Exenatide also gave favorable results, but there is limited safety data. A survey of pediatric endocrine centers in the US and Canada found that 48% of children with T2DM was treated with insulin and 44% with oral drugs (of them, 71% were on metformin, 46% SU, 9% TZDs, 4% meglitinide). There is scant data on these drugs as they are subject to clinical trials; therefore they should be used only as part of well-designed clinical trials or in rare cases with due considerations to their safety.

Initial Pharmacologic Treatment

1. Patients presenting in a decompensated state (ketoacidosis, ketosis and dehydration) are managed with intravenous fluids, insulin infusion and potassium and electrolyte replacement as for T1DM. Due to underlying IR, the dose of insulin infusion required to control hyperglycemia may be higher.
2. Patients presenting with hyperglycemic hyperosmolar state (HHS) should be managed mainly with fluid replacement and cautious insulin infusion therapy (started after initial fluid resuscitation).
3. If the possibility of T1DM cannot be ruled out, it is better to start with basal-bolus insulin therapy with subsequent addition of metformin and tapering off of insulin if the diagnosis of T2DM is more likely on follow-up.
4. For stable patients with significant hyperglycemia (random plasma blood glucose (BG) ≥ 250mg/dL and/or HbA1c ≥ 9%), metformin (see below for dosage) along with basal insulin can be started. Long acting insulin analogs such as Glargine, Detemir or Degludec or intermediate acting NPH insulin can be started as single bedtime injection in a dose of 0.2-0.4 unit/kg and the dose adjusted, based on home monitoring of fasting BG levels. Twice daily NPH or premixed insulin can also be one of the options along with metformin for this group of patients.
5. For patients with milder hyperglycemia (HbA1c <9%), metformin alone can be started along with lifestyle modifications. Initial dose is 500 mg once daily after dinner and the dose can be then increased to 2000 mg/day in 2 divided doses after every 1-2 weeks in increments of 500 mg. The dose should be taken immediately after meals. Gastrointestinal side effects such as abdominal discomfort, diarrhea and bloating are common in the first month but usually subside with continued treatment.

Blood Glucose Monitoring

In the first few days all patients with T2DM and subsequently patients on basal bolus insulin should check BG levels at home 3-5 times daily. Principles of dose adjustment are the same as forT1DM.

Patients on basal insulin alone need to check fasting BG daily while dose titration is being done. They should be taught to adjust dose of basal insulin after every 3-5 days depending on fasting BG levels. Once a stable dose has been reached testing should be done at least 3-4 days in a week. Screening for nocturnal hypoglycemia should be done once in 7-10 days for all patients on basal insulin therapy.

Patients on metformin alone should be encouraged to check fasting and postprandial BG levels at least 1-2 times per week.

More frequent testing is required on sick days, with exercise and with variations in diet.

Targets for Blood Glucose

BG should be maintained in the range of 80-120 mg/dL for fasting and pre-meals and 100-160 mg/dL for post-meals and at bedtime. HbA1c should be maintained around < 6.5-7% and should be checked every 3 months.

Subsequent PharmacologicTreatment

The patient should be followed-up every 3 months with estimation of HbA1c. If target HbA1c is not achieved, intensification of therapy is done with the aim of treating to achieve the target. This includes review of diet, lifestyle, increasing the frequency of clinic visits and evaluation by psychologist/psychiatrist. If metformin alone fails to control glycemia, basal insulin should be added. If metformin and optimal dose of basal insulin (up to 1.2 unit/kg) fails to achieve control, next step is to consider twice-daily premixed or basal-bolus insulin therapy. In selected cases use of other oral antidiabetic medications maybe considered in consultation with adult endocrinologists and after due discussions with family. Frequency of insulin usage rises rapidly with diabetes duration.

The pharmacologic treatment approach is summarized in **Fig 1.**

Complication Screening

Microvascular complications can be present right at the time of diagnosis of T2DM; hence complication screening is recommended at diagnosis and repeated annually (or more frequently if abnormal).

- Fundus examination after pupillary dilatation

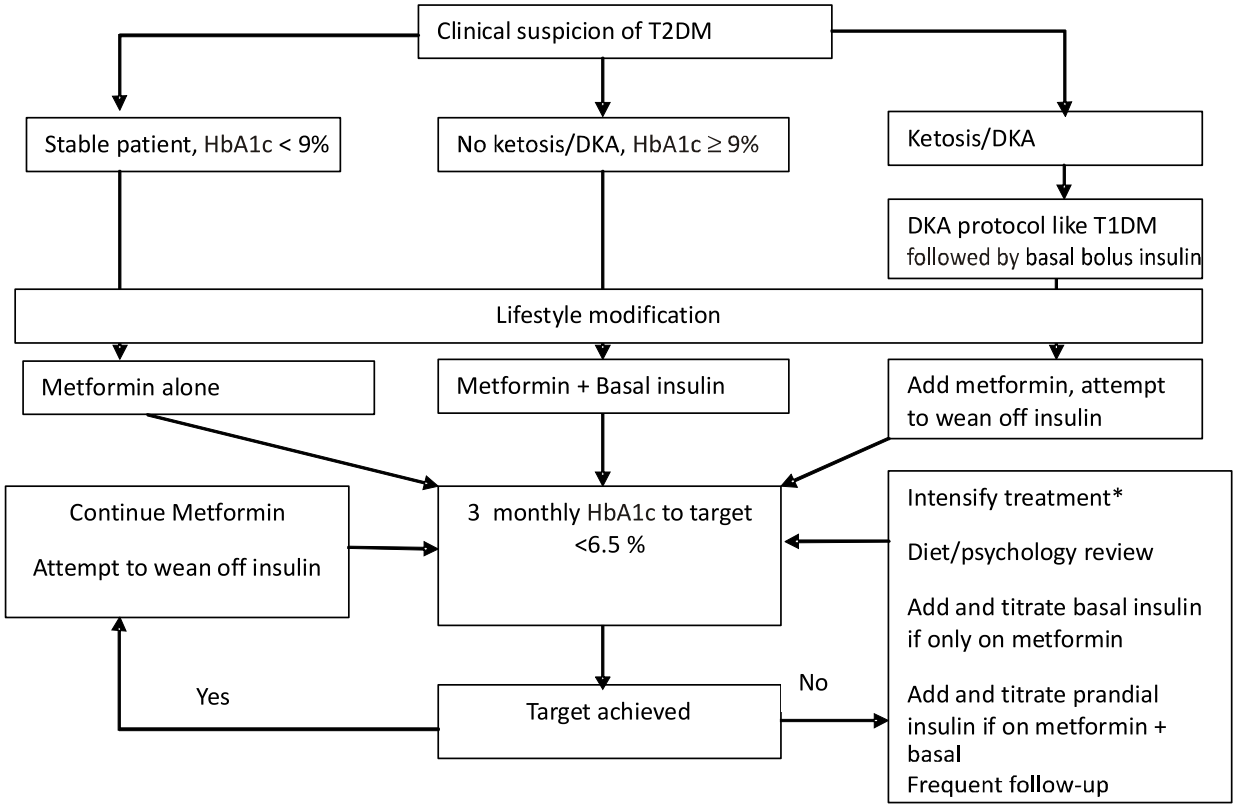

Fig 1. Pharmacologic management of type 2 diabetes in children and adolescents

Note: *In selected patients additional oral anti-diabetic drugs can be considered after discussion with family.

Abbreviations: DKA – diabetic ketoacidosis, HbA1c – glycosylated hemoglobin

- Clinical examination for peripheral neuropathy (microfilament, ankle jerk and vibration sense)
- Serum creatinine
- Fasting lipid profile
- Urine spot albumin to creatinine ratio – 3 consecutive days or a timed specimen to confirm if screening is positive (normal < 30 mg/g of creatinine, microalbuminuria 30-300 mg/g of creatinine, overt proteinuria > 300 mg/g of creatinine)

The rate of progression of microvascular complications is higher than in T1DM. The risk of nephropathy was 4 times the risk in T1DM, with 23 times increased risk of chronic renal failure and 39 times the risk of dialysis in a published study. Therefore timely recognition and aggressive management is necessary.

Bariatric Surgery

In severe obesity (BMI > 35-40 kg/m^2) with uncontrolled T2DM and other obesity-related comorbidities (e.g. hypertension and hypertriglyceridemia), bariatric surgery may be considered. Since the roux-en-Y gastric bypass might have significant morbidity, less aggressive procedures such as sleeve gastrectomy may be preferable. Long-term data on these surgical procedures is lacking; however in the short-term weight loss, remission of T2DM and improvement in other comorbidities have been reported in small observational studies.

Adherence to Therapy and Follow-up

Poor rates of follow-up and low adherence to treatment are extremely common. Available studies show that the disease presenting in childhood is more aggressive than in adults. With equal glycemic control, prevalence of microvascular and macrovascular complications and mortality is higher than T1DM or adult onset T2DM.

SCREENING FOR TYPE 2 DIABETES

Since T2DM in youth is an uncommon disease at least at present, generalized screening of youth is not recommended. However, since the Asian Indian phenotype is one of the high risk factor for T2DM, screening with glucose tolerance testing should be done for obese or overweight children (BMI> 85^{th} centile for age and gender) in the pubertal age group (>10 years of age) with one or more of the following:

- First or second-degree relative with T2DM.
- Signs of insulin resistance – acanthosis nigricans, skin tags, polycystic ovary syndrome
- Dyslipidemia
- Hypertension

In conditions that put a child at risk of diabetes, screening should be done as a part of evaluation. These include Down syndrome, Turner syndrome, Klinefelter syndrome, Cushing syndrome and syndromes associated with obesity (Prader-Willi, and Bardet-Biedl syndromes).

In all high-risk cases, screening should be repeated at least once in 2 years.

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NEONATAL DIABETES MELLITUS

Vijaya Sarathi

SUMMARY OF RECOMMENDATIONS

- The term neonatal diabetes mellitus (NDM) refers to diabetes in infants younger than 6 months of age.
- NDM may be transient or permanent; late recurrences are common with the transient form.
- Infants are typically born small for gestational age (SGA), and present with failure to thrive and dehydration and less often with ketoacidosis.
- Mutations in *KCNJ11* and *ABCC8* genes contribute to most cases (50%) of permanent neonatal diabetes mellitus (PNDM) while imprinting defects in chromosome 6q24 are responsible for most cases (~70%) of transient neonatal diabetes mellitus (TNDM).
- *KCNJ11* and *ABCC8* mutations are associated with DEND syndrome in around 20%, but more often with subtle neurological abnormalities like dyspraxia; majority of other genetic defects causing PNDM are associated with pancreatic agenesis or extra-pancreatic manifestations.
- Genetic testing of all NDM cases for *KCNJ11* and *ABCC8* mutations is cost-effective.
- Most of the cases with *KCNJ11* and *ABCC8* mutations can be successfully switched from insulin to sulphonylurea.

INTRODUCTION

The term neonatal diabetes mellitus (NDM) is traditionally used to describe diabetes mellitus in an infant younger than six months of age. It is a rare entity with an incidence of 1 in 100,000 births. More than 80% of the cases harbor a detectable cause on genetic testing. It can be either temporary with remission after an initial hyperglycemic phase (transient neonatal diabetes mellitus, TNDM) or permanent with hyperglycemia persisting throughout life (permanent neonatal diabetes mellitus, PNDM). NDM is often associated with other systemic manifestations, which may be identified either at diagnosis of NDM or later in life. Interestingly, some NDM cases with precise genetic defects respond to

sulphonylureas. Hence, the timely diagnosis of NDM and identification of its underlying genetic cause are very important to make appropriate management decisions (**Table 1**).

TABLE 1. Genetic Abnormalities Associated with Neonatal Diabetes, Mode of Inheritance, and Associated Features

Gene	*Inheritance*	*Type*	*Associated features*
PLAGL1	Imp	TNDM	Macroglossia, umbilical hernia
HYMA1	Imp	TNDM	Macroglossia, umbilical hernia
ZFP57	AR	TNDM	Macroglossia, umbilical hernia, congenital heart defects, developmental delay
KCNJ11	S, AD	PNDM, TNDM	DEND syndrome
ABCC8	AD, AR	PNDM, TNDM	Neurological symptoms
INS	S, AD	PNDM, TNDM	None
SLC2A2	AR	PNDM, TNDM	Fanconi-Bickel syndrome (Hypergalactosemia, liver dysfunction, proximal renal tubular acidosis)
GCK	AR	PNDM	None
SLC19A2	AR	PNDM	Roger syndrome (Thiamine-responsive megaloblastic anemia, sensorineural deafness)
EIF2AK3	AR	PNDM	Wolcott-Rallison syndrome (Epiphyseal dysplasia, hepatic failure, renal failure)
IER3IP1	AR	PNDM	Microcephaly, epileptic encephalopathy
FOXP3	XR	PNDM	IPEX syndrome (Enteropathy, eczema, hypothyroidism)
WFS1	AR	PNDM	Wolfram syndrome (Optic atrophy, diabetes insipidus, deafness)
HNF1B	AD	TNDM	Pancreatic hypoplasia, renal cysts
PDX1	AR	PNDM	Pancreatic agenesis
PTF1A	AR	PNDM	Pancreatic agenesis, cerebellar hypoplasia
PTF1A enhancer	AR	PNDM	Pancreatic agenesis
RFX6	AR	PNDM	Intestinal atresia, gall bladder agenesis
GATA4	AD	PNDM	Pancreatic agenesis, congenital heart defects
GATA6	AD	PNDM	Pancreatic agenesis, congenital heart defects, biliary abnormalities
GLIS3	AR	PNDM	Hypothyroidism, glaucoma, hepatic fibrosis, renal cysts
NEUROG3	AR	PNDM	Enteric anendocrinosis (Malabsorptive diarrhea)
NEUROD1	AR	PNDM	Cerebellar hypoplasia, visual impairment, deafness
PAX6	AR	PNDM	Microphthalmia, brain malformations
NKX2-2	AR	PNDM	Developmental delay
MNX1	AR	PNDM	Developmental delay

Abbreviations: AD– Autosomal dominant; AR– Autosomal recessive; DEND syndrome– Developmental delay, epilepsy and neonatal diabetes mellitus syndrome; Imp– Imprint; IPEX syndrome– Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PNDM– Permanent neonatal diabetes mellitus; TNDM– Transient neonatal diabetes mellitus; S– Sporadic; XR– X-linked recessive

TRANSIENT NEONATAL DIABETES MELLITUS (TNDM)

TNDM contributes to 50-60% of NDM cases in the Western countries; in contrast it accounts for a small proportion of NDM cases in India. Whether, this difference is due to missed diagnosis of TNDM in Indian patients is yet unclear. It typically starts within first month of birth and disappears at a median of three months, although rarely it can last up to 12-18 months. Neonates typically present with intrauterine growth retardation (IUGR), failure to thrive, lethargy, osmotic polyuria and dehydration. Ketoacidosis is usually absent indicating presence of some β cell reserve. After a period of remission diabetes recurs in a significant proportion, usually during periods of increased insulin demands like puberty or pregnancy, but it can recur as early as 4 years of age. Most of the TNDM patients have detectable genetic abnormalities.

6q24 Abnormalities

Around 65-70% of the cases can be attributed to abnormalities in chromosome 6q24. Chromosome 6q24 comprises of the genes *PLAGL1* and *HYMAI* and their overexpression due to paternal uniparental disomy or paternally inherited duplication of 6q24 have been proposed to cause TNDM. Hypomethylation of maternal 6q24 has also been seen to be associated with TNDM; few of these cases are associated with *ZFP57* mutations. 6q24 abnormalities are exclusively associated with TNDM. Most of the neonates are born small for gestational age (SGA) with 30% born preterm and usually present with non-ketotic hyperglycemia during the first week of life. Abnormalities in 6q24 are often associated with macroglossia (44%) and umbilical hernia (21%).

Genetic counseling for families with 6q24 TNDM depends on the underlying molecular mechanism. The risk of recurrence in siblings and offsprings of patients with uniparental disomy of chromosome 6q24 is less. For paternal duplication of the 6q24 region, males have a 50% chance of transmitting the disease to their children. In contrast, females will pass on the duplication, but their children will not develop the disease; but the disease may recur in the next generation as their asymptomatic sons pass on the duplication to their own children. Methylation defects are usually sporadic, but mutations in *ZFP57* show an autosomal recessive inheritance, and hence the recurrence risk is 25% for siblings.

KCNJ11 or *ABCC8* Mutations

Most of the remaining cases of TNDM patients have mutations of *ABCC8* or *KCNJ11. ABCC8* mutations (66%) are more likely to be associated with TNDM than *KCNJ11* mutations (10%). Compared to NDM associated with 6q24 abnormalities those associated with *ABCC8* or *KCNJ11* mutations present slightly later and go into remission later but relapse earlier.

Other Mutations

Rarely TNDM patients may have mutations in *INS, SLC2A2* or *HNF1B* genes (**Table 1**). While mutations in these genes are more likely to cause PNDM, some may present as TNDM.

PERMANENT NEONATAL DIABETES MELLITUS (PNDM)

PNDM patients are more likely to present with ketoacidosis than TNDM. Seventy percent of the PNDM cases have underlying genetic defects.

KCNJ11 or *ABCC8* Mutations

Heterozygous activating mutations in *KCNJ11* and *ABCC8* lead to a decrease in insulin secretion and account for around 50% of cases of PNDM. Potassium inwardly rectifying channel subfamily J member 11 gene (*KCNJ11*) encodes the Kir6.2 subunit of the beta cell K-ATP channel. Mutations in *KCNJ11* comprise the most common cause for NDM overall. Mutations are predominantly sporadic although autosomal dominant inheritance has been seen. ATP binding cassette sub-family C member 8 (*ABCC8*) encodes for sulphonylurea receptors of the ATP sensitive potassium channels. Mutations in *ABCC8* are inherited in autosomal dominant or recessive manner.

Around 20% of patients with mutations in K-ATP genes have associated neurological abnormalities on standard neurological evaluation. Most severe of these is the DEND (developmental delay, treatment resistant epilepsy with neonatal diabetes) syndrome, which is most often associated with *KCNJ11* mutation, p.Val59Met. Neurological abnormalities in patients with *ABCC8* mutations are considered milder; however, recent studies have demonstrated subtle neurological abnormalities in all patients with *KCNJ11* and *ABCC8* mutations.

Wolcott-Rallison Syndrome

The most common cause of NDM in children born to consanguineous parents, Wolcott-Rallison syndrome is an autosomal recessive condition caused by homozygous mutations in *EIF2AK3* gene. It is characterized by PNDM, recurrent liver failure, pancreatic exocrine insufficiency, epiphyseal dysplasia and renal failure. Skeletal dysplasia is evident after 1 to 2 years of age, while liver dysfunction can present at any time after the diagnosis of NDM.

FOXP3 Mutations

Autoimmune diabetes is generally not seen in infants less than 6 months of age. If autoimmunity is present the cause is most often a mutation in *FOXP3* and not T1DM. Mutation in *FOXP3* is associated with IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, and X-linked mode of inheritance).

Other Mutations

A minority (<10%) of cases of PNDM is accounted for by mutations in other genes. These are listed in **Table 1** along with their mode of inheritance, type of associated NDM and other associated features.

DIAGNOSIS

Neonatal diabetes is often diagnosed incidentally in the immediate newborn period. It should be differentiated from other conditions that cause stress hyperglycemia such as sepsis before work-up is started for NDM. Similarly, in preterm neonates diagnosis of NDM should be made with caution as many of them may have transient hyperglycemia. Diagnosis of NDM should be made after resolution of the stressor in such cases. A minimum of two elevated plasma glucose readings should be present to make a diagnosis of NDM.

When NDM is diagnosed in the neonatal period, it is difficult to determine if it is TNDM or PNDM. In general TNDM presents within the first two weeks of life while PNDM presents from third week onwards. Presence of features such as macroglossia and/or umbilical hernia may suggest TNDM associated with chromosome 6q abnormalities.

Genetic Testing

Checking for mutations in *KCNJ11* and *ABCC8* in all NDM cases and 6q24 abnormalities in patients who are already remitted will be cost-effective. With the recent advances in genetic testing and increasing availability of next-generation sequencing, universal screening of NDM patients for all NDM associated genes would be useful.

Genetic testing will be provided free of cost till the year 2020, for all patients with diabetes diagnosed before 9 months of age regardless of current age, at Exeter Medical School, Exeter. Further information on how to send the sample can be availed at 'http://www.diabetesgenes.org/content/genetic-testing-neonatal-diabetes'. Genetic screening panels for NDM are available in India at select labs.

Implications of Genetic Testing

Genetic testing has multiple implications for management of NDM. Firstly, it helps to predict the remission of NDM, especially when it is associated with 6q abnormalities. Secondly, it helps to identify patients who are most likely to respond to sulphonylurea therapy (*KCNJ11* and *ABCC8* mutations). Thirdly, associated extra-pancreatic features can be predicted by genetic defects identified. Lastly, it helps in assessing the risk of transmitting these genetic abnormalities and the disease to siblings and offsprings.

MANAGEMENT

Initial Management

Intravenous rehydration and insulin infusion should be started promptly after diagnosis in infants with ketoacidosis. Subcutaneous insulin is started when the infant is stable and able to take feeds. Therapy with insulin corrects the hyperglycemia and results in dramatic catch-up growth. Liberal caloric intake should be maintained for initial few weeks to achieve weight gain. The absence of fixed feeding timings however makes insulin therapy challenging in infants. Long acting analogs are preferred to NPH insulin. Rapid acting insulins should be used with caution.

When patients require very small doses of insulin, diluted insulin can be used (5-10 units/mL). Dilution of insulin is best done with compatible diluents provided by the manufacturers, preferably by a pharmacist. Diluents provided by manufacturers are not available in India. Alternatively, dilution of conventional insulins and rapid acting analogs can be done with normal saline or distilled water. Although manufacturer's data does not recommend dilution of Glargine, 1:10 or 1:100 dilution of Glargine with normal saline (by adding 0.1 mL of Glargine to 0.9 or 9.9 mL of normal saline respectively) has been used successfully, even in extremely low birth weight neonates (1:100 dilution). While using diluted insulin, extreme caution should be executed to avoid dosing errors.

Insulin pumps have also been used in few cases with good results. Further the low doses of insulin can be easily obtained with insulin pumps with provision for doses as low as 0.25 units. TNDM patients require lower insulin doses compared to PNDM.

Switch to Sulphonylurea

Approximately 90% of patients with NDM due to *KCNJ11* and *ABCC8* mutations can switch from insulin to sulphonylurea therapy and achieve good glycemic control. Low C-peptide levels or ketoacidosis at presentation do not preclude the response to sulphonylurea. When compared to insulin, sulphonylurea therapy is less costly, more comfortable and provides better glycemic control. It also brings some improvement in developmental delay and neurological abnormalities, especially if initiated before 6 months of age.

Glibenclamide is the preferred sulphonylurea in view of its non-specific action enabling binding to cardiac, muscle and brain receptors, but other sulphonlyureas have also been used with success. It is initially started in a dose of 0.2 mg/kg/day and increased slowly till 1 mg/kg/day. Fifty percent of responders do so at a glibenclamide dose of 0.5 mg/kg/day but some patients may require as high as 2

mg/kg/day of glibenclamide. The smallest dose of glibenclamide available in India is 2.5 mg (Semidaonil). For infants who require very low doses or those who are unable to swallow tablets, suspensions of glibenclamide can be prepared and used. Glycemic control improves with time and the dose may be decreased later. Side effects of glibenclamide are minimal and include discoloration of teeth, diarrhea and mild transient leukopenia.

The transfer of therapy from insulin to glibenclamide can be done either on an inpatient basis over 4-5 days or on an outpatient basis over 4-5 weeks with regular follow-up maintained over the phone. In both protocols, patients are hospitalized and baseline estimation to evaluate the progress of sulphonylurea including fasting plasma glucose, glycated hemoglobin (HbA1c), serum C-peptide, general physical examination, neurological examination, assessment of developmental age and EEG/MRI of brain if epilepsy/neurological features are present. After the testing, basal insulin is stopped or if on insulin pump basal rate is decreased by 50% and started on glibenclamide, 0.1 mg/kg/dose every 12 hours.

In the inpatient protocol, dose of glibenclamide is adjusted on a daily basis. If pre-meal GRBS (random blood sugar checked by glucometer) is > 126 mg/dL, the dose of glibenclamide is increased to 0.2 mg/kg/dose every 12 hours and if pre-meal GRBS is < 126 mg/dL, same dose of glibenclamide is continued and pre-meal insulin is decreased by 50%. Similar adjustments are done till either normal glycemia (pre-meal GRBS < 126 mg/dL) is achieved off insulin or a glibenclamide dose of 0.5 mg/kg/dose every 12 hours is reached. Patient can be discharged next day with regular monitoring of GRBS and weekly follow-up. In patients who still need insulin, the same glibenclamide dose is continued for next 4 weeks and insulin is gradually tapered off as glycemic improvement is noted to complete the switch. Patients in whom insulin requirement goes down by 60% of pre-sulphonylurea starting dose can continue glibenclamide for longer time and with higher doses (up to 1 mg/kg/dose every 12 hours). Patients are reviewed at 3 months and if there is no response, glibenclamide is stopped and insulin is continued. Patients managed on the outpatient basis are managed similar to inpatient protocol, except that patients are discharged on day 2 and with regular home monitoring of glucose values; glibenclamide dose is increased by 0.1 mg/kg/dose every 12 hours at weekly intervals.

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ECONOMICS OF THE CARE OF CHILDREN WITH TYPE 1 DIABETES MELLITUS

Vijaya Sarathi

SUMMARY OF RECOMMENDATIONS

- Families of children with type 1 diabetes mellitus (T1DM) from low socioeconomic group spend more than half, and those from middle-income group spend nearly one-third (32%) of their family income on the health care of the T1DM patient. Unfortunately, almost 90% of youth with T1DM in India are from low (58.7%) or middle (26%) socioeconomic status.
- Conventional insulins are as effective as costlier newer analogs; hence, there is no need to prefer the latter for children from low and middle socioeconomic status.
- Use of insulin vials and syringes instead of pen devices, and reuse of syringes and needles reduce the cost of T1DM care without significant side effects.
- Avoiding unnecessary hospitalization at diagnosis of T1DM in those who present with mild to moderate symptoms and preventing hospitalization for acute complications by insisting on home or self-monitoring of blood glucose (SMBG) and self-adjustments can reduce costs.
- Although ideally glucose monitoring should be done 4-6 times a day, even two tests per day gives much useful information.
- Alternative methods like cooling jars, *zeer* pot, earthen-wear pitcher (*matka)* or a cool wet cloth around the insulin vial can be used to store insulin where refrigeration facilities are not available.
- Empower T1DM children with good diabetes education to lead their life fully and assist them to complete their education and overcome discrimination in job opportunities.
- Governmental and non-governmental organizations and diabetes health care professionals should join hands together to ensure that no child is deprived for financial reasons of insulin and essential diabetes care accessories.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the second commonest chronic disorder of childhood, and can be life-threatening. Currently, there are more than half a million T1DM children worldwide; in addition, around 86,000 children under 14 years get diagnosed with T1DM every year. The prevalence of T1DM in children is increasing (3% every year) worldwide. India currently has the second highest (70,200) number of T1DM children, next only to United States. Although the data is not very precise, it has been estimated that around 10,900 new cases of T1DM get added every year in India. With the growing number of children living with insulin-dependent diabetes, there is an increasing need for insulin and other diabetes supplies. Nearly 100 years after the discovery of insulin, it is tragic that people still die because they cannot access insulin. Lack of finances or transportation is the most common reason to stop insulin therapy, resulting in diabetic ketoacidosis (DKA) and even death. Inadequate monitoring of blood glucose (BG) results in improper doses of insulin being given, resulting in poor glycemic control and greatly increased risk of hypo- and hyperglycemia. Hence, it is essential that every person with T1DM has an uninterrupted supply of effective insulin and glucose strips.

ECONOMIC BURDEN ON FAMILIES WITH A T1DM CHILD

In developed countries, most of the health care expenditure of children with T1DM is borne by government or health insurance. On the other hand, in developing countries like India, the cost of illnesses is mostly borne by families themselves. It has been estimated that families from low socioeconomic status (SES) spend more than half (59%) and those from middle SES spend nearly one-third (32%) of the family income on the health care of the T1DM patient. Unfortunately, almost 90% of youth with T1DM in India are from low (58.7%) or middle (26%) SES. T1DM can often impose catastrophic medical costs, especially if home BG monitoring is erratic, and these costs can push a family into poverty. Although government hospitals offer free treatment, they often do not have trained personnel familiar with T1DM care, and are not able to meet the increasing demands; none of the present health insurance policies in India cover ongoing health care expenses of children with T1DM. Hence, there is an absolute need for economic support for most children with T1DM in India. Indeed, most of these families who do manage, do so because they seek help from free/subsidized clinics run by government hospitals and non-governmental organizations (NGOs).

COSTS OF MANAGING A CHILD WITH T1DM

Treating a child with T1DM is not just the cost of insulin. The child needs daily multiple BG tests; routine visits to the diabetes clinic and routine monitoring of HbA1c and screening tests for complications and comorbidities; visits and

additional costs in case of emergencies; care of chronic complications when they occur; and costs of additional care during unusual circumstances. Understanding the total costs of various needs by diabetes care professionals is highly essential for choosing the best feasible treatment options. The costs of various types of insulin are listed in Chapter 4. An approximate cost estimation of care of a T1DM child weighing 30 kg using different methods of insulin delivery and glucose monitoring methods is summarized in **Table 1**. Patients often incur additional costs like ketone testing (blood ketone testing strip: Rs. 175 per strip, available to use with Optium® glucometers; urine ketone strip: Rs 20 per strip), glucagon injection (Rs 940 per 1 mg injection) and hospitalization for severe hypoglycemia or ketoacidosis or for concurrent illnesses not related to T1DM, and travel costs and work days lost to reach good diabetes care facilities. Approximate on-going costs of monitoring glycemic control, associated other autoimmune disorders, and microvascular complications, are listed in **Table 2**.

MANAGEMENT OF CHILD WITH T1DM IN A RESOURCE-LIMITED SETTING

Insulin: Type, Delivery and Storage

There are multiple options for insulin delivery. When compared to multiple dose insulin (MDI) therapy, continuous subcutaneous insulin infusion (CSII) pump may offer a few advantages like reduction in the incidence of severe hypoglycemia, reduction in the dose of insulin, better glycemic control and better quality of life. MDI analog therapy is associated with less episodes of severe hypoglycemia (especially less nocturnal hypoglycemia with basal analogs) than MDI therapy using conventional insulins (regular and NPH). However, there is limited data on the cost-effectiveness of 'CSII vs. MDI therapy' and 'MDI analog therapy vs. MDI with conventional insulins'. Fortunately, good glycemic control can be achieved with the use of conventional insulins (regular and NPH). In poor families, other family members may have to skip some meals to buy insulin. Moreover, food insecurity would interfere with the T1DM child's glycemic control. So, undue pressure on parents to use costlier analog therapy or CSII should be strongly discouraged for T1DM children from low-middle SES.

Use of pen devices may seem less painful than syringes, but are costlier (higher cost of insulin cartridges used for pen devices and higher cost of pen needles). Reuse of insulin syringes, pen needles and fingerpick lancets is not recommended by the manufacturers owing to the slightly increased pain and small risk of infections with reuse of these sharps. However, most often our patients reuse these sharps a few times comfortably, with no discernible increase in discomfort or infection rates. This reduces the cost burden for the family, as also the country (and also reduces environmental damage).

TABLE 1. Cost comparison of various methods of insulin delivery and glucose monitoring in a child weighing 30 kg

Mode of insulin delivery and glucose monitoring	*Insulin requirement per day*	*Essential needs for the care of T1DM child*	*Expenditure per unit (Rs)*	*Expenditure per month (Rs)*	*Total expenditure per annum (Rs)*
MDI Regular and NPH, Vials and syringes	1 U/kg/day	Insulin Syringes Glucometer Strips FP needles	0.35/U 7 1500 15 5	0.35*900 7*25 12.5 15*120 5*20	Rs 28,830
MDI Regular and NPH, Pen and Cartridges	1 U/kg/day	Insulin Syringes Glucometer Strips FP needles	0.75/U 11 1500 15 5	900*0.75 11*25 12.5 15*120 5*20	Rs 34,350
MDI Rapid acting and basal analogs, Pen and Cartridges	1 U/kg/day	Rapid analog Basal analog Pen needles Glucometer Strips FP needles	1.65/U 2.95/U 11 1500 15 5	1.65*600 2.95*300 11*25 12.5 15*120 5*20	Rs 48,750
CSII 640G Medtronics	0.8 U/kg/day	Insulin Pump device Transmitter Sensor Accessories Glucometer Strips FP needles	1.65/U 500000 60000 3256 5282 1500 15 5	1.65*720 8333 2500 3256*5 5282 12.5 15*60 5*10	Rs 414,550
CSII 754	0.8 U/kg/day	Insulin Pump device Transmitter Sensor Accessories Glucometer Strips FP needles	1.65/U 329000 68890 3256 5282 1500 15 5	1.65*720 5483 2870 3256*5 5282 12.5 15*60 5*10	Rs 384,795
CSII 722 Medtronics	0.8 U/kg/day	Insulin Pump device Transmitter Sensor Accessories Glucometer Strips FP needles	1.65/U 229000 68890 3256 5282 1500 15 5	1.65*720 3816 2870 3256*5 5282 12.5 15*60 5*10	365,065
CSII 715 Medtronics	0.8 U/kg/day	Insulin Pump device Accessories Glucometer Strips FP needles	1.65/U 159000 5282 1500 15 5	1.65*720 159000 5282 12.5 15*120 5*20	132,390
Freestyle Libre Pro		Reader Sensor	4999 1999*2	83 1999*2	49,976
Real time monitor Medtronics		Monitor Sensor	1,30000 3256	2166 3256*5	221,360

Abbreviations: CSII – Continuous subcutaneous insulin infusion; FP – Fingerpick; MDI – Multiple daily injection regimen

TABLE 2. Approximate costs of laboratory investigations for periodic monitoring of glycemic status, complications and comorbidities, in a private lab, in 2016

Laboratory investigations	*Approximate cost (Rs.)*
Fasting plasma glucose	70
Glycated hemoglobin (HbA1c)	500
Lipid profile	675
Spot urine microalbumin/creatinine ratio	450
Thyroid stimulating hormone (TSH)	200
IgA tissue transglutaminase antibodies (tTG)	1200
Anti-thyroperoxidase (TPO) antibody	1000

Buying a refrigerator to preserve insulin at home is often an economic burden to parents of T1DM children. However, where refrigeration is not available or electricity is erratic, cooling jars, thermos with few cubes of ice, earthen-wear pitcher (*matka*), *zeer* pot (double earthenware pot system with wet sand in the space between the 2 pots) or a cool wet cloth around the insulin vials, all help to preserve the insulin activity **(see Chapter 4)**.

Monitoring for Glycemic Control and Comorbidities

BG monitoring is essential for the safe management of T1DM, to adjust insulin doses, thus empowering the child and family, and helping to prevent acute and chronic complications. Ideally BG should be tested 4-6 times a day; more frequent testing may be needed during sick days or pregnancy. Even two tests per day give much useful information. However, this substantially adds to the cost; many T1DM children end up having suboptimal glucose monitoring, which leads to poor glycemic control. Educating patients and families about the importance of regular self-monitoring of BG (SMBG) can also save costs, in the short-term by preventing acute complications (hypoglycemia and DKA), infections and school absenteeism; and in the long-term by preventing or decreasing chronic complications.

Standard guidelines recommend regular checking of weight, height, blood pressure, sexual maturity rating, foot examination and checking for neuropathy. Ideally HbA1c is measured four times per year and retinal examination, testing of serum lipids, thyroid function, and renal function including microalbuminuria annually, with initial screening for gluten enteropathy. Other tests may be needed. Due to relatively higher cost of tests for periodic screening of comorbidities (**Table 2**), they should be used judiciously. If resources are limited, less frequent measurements are still helpful. Monitoring and tracking anthropometry to ensure age-appropriate progression poses no additional cost, and can provide significant information, so that more focused tests can be done. For example, if the child is

growing slowly, it is important to rule out celiac disease and hypothyroidism. However, by avoiding costly testing for thyroid antibodies (which rarely help to make decisions about therapy) and just checking serum thyroid stimulating hormone and if necessary total or free thyroxine, the cost can be minimized. Similarly, fundus photographs are a permanent record but cost money; meticulously done retinal examination, which is carefully recorded, can provide useful information about retinopathy.

Minimize Hospitalizations

Provision of initial T1DM education and care to new-onset non-critically ill children in a hospital setting increases health care costs. Hence, in all children older than 5 years of age, with mild to moderate symptoms at diagnosis, hospitalization and the consequent expenses could be avoided with management being done on outpatient basis. Increasing awareness among health care personnel and the general public about symptoms of diabetes has been shown to increase early diagnosis. This in turn can help reduce the incidence of DKA at diagnosis and thus reduce not just morbidity and mortality, but also costs.

Insulin is no doubt the lifeline for these children, but T1DM cannot be managed only by taking insulin. It is very important that the children and their families also learn more about the disorder and its management since it has to be managed 24×7. Initial and ongoing education of families on how to manage sick days, and provision of contact numbers of the health care personnel to the patients, for telephonic suggestions during sick days and hypoglycemic episodes, may help in avoiding hospitalizations and the consequent costs. This will also help to minimize the loss of earning for parents and earning patients, which can account for almost one-third of the cost of T1DM care.

Socioeconomic Support

Youngsters with T1DM often face difficulties in education, marriage, and job opportunities. Hence, there is a need to motivate children to continue their school and further education, which is essential to enable them to sustain themselves in the future. Ensuring they are provided necessary support for self-care in school, and where needed, provision of educational scholarships, schoolbooks and other necessary material, will help them to continue their education. The dual burden of diabetes combined with un- or under-employment can push families more deeply into poverty and poor health. There is a risk that T1DM patients may face discrimination because of their condition; perhaps being excluded from certain jobs. Hence, there is a need to bring in special policies to prevent this discrimination.

There is a need for more support from governmental and non-governmental organizations. Firstly, the government and other agencies could ensure adequate training facilities for pediatricians who are interested in taking care of T1DM

children. Continuous, affordable and adequate supply of insulin (at least regular and NPH insulin) in a proper cold chain, syringes and glucose strips, should be available to all T1DM children. To execute this, public-private partnership initiatives are needed, involving the central and state governments, civil society, diabetes foundations, city corporations, and local non-governmental organizations.

It should be the endeavor of diabetes care professionals and health authorities to provide suitable facilities and resources (insulin, glucose strips, testing for early diagnosis of complications) to all patients with T1DM. The diabetes care team and professionals should help families of the T1DM children to locate the resources for free/subsidized insulin and other diabetic care supplies, whether local organizations or individuals or larger programs such as "NOVOAID".

It is useful to encourage families to form self-help groups. Bulk purchase of supplies or buying near-expiry supplies can enable the members of the group to reduce costs. Similarly, prices can be negotiated for conducting tests in "bulk" by holding camps. Group members can pool other resources like sharing information, and offering job or marriage opportunities to each other.

Equally importantly, diabetes care team members should be involved in increasing awareness of the condition in the general public, join hands with NGOs who provide free/subsidized health or other care to persons with T1DM (e.g. jobs, educational opportunities, etc.), and put strong pressure on government agencies to ensure adequate and effective supplies to all children with T1DM. Over the past decade a large decline in medication costs and subsequent patient expenditure has been noticed in the field of HIV/AIDS as a result of strong pressure from HIV activists and NGOs. A similar movement is required to ensure that no child with T1DM has to compromise on basic treatment due to financial constraints.

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HOPE FOR THE FUTURE

Anurag Bajpai

SUMMARY OF RECOMMENDATIONS

- A structured program should be developed for transition of adolescents with type 1 diabetes mellitus (T1DM) to adult care.
- Young adults with T1DM should be counseled against risk-taking behaviors like smoking and consumption of alcohol and illicit drugs.
- Counseling on reproductive health, academics and career are integral to management of young adults with type 1 DM.
- Although the patients should be educated about the latest developments in the treatment of diabetes, the need for long-term insulin should be emphasized.

INTRODUCTION

The future of children with type 1 diabetes mellitus (T1DM) is bright thanks to the tremendous advances in management. There are ever-expanding hopes for disease prevention, near-physiological insulin replacement, minimally invasive insulin delivery systems and potential cure. However, despite this leap in the science of diabetes, the art of managing children with diabetes remains a challenge. Central to this is the need to tailor the management according to the changing requirements of different phases of life. This section elaborates the key aspects of post-adolescent management of T1DM and makes an attempt to gaze through the crystal ball.

THE FUTURE OF A CHILD WITH TYPE 1 DIABETES

T1DM is a life-altering disease affecting all aspects of life. Advances in management have however provided the opportunity of achieving lifetime goals for affected children. This requires ongoing interaction with the patient with a continuing age-appropriate education program.

Ongoing Medical Care

Continuation of quality medical care is central to successful outcome for the young adults with T1DM. The transition from family-oriented pediatric care to individualized targeted adult care is often disconcerting and frequently results in

the interruption of medical care. The transition should therefore happen only after the achievement of physical, social and psychological maturity by the young adult. This is often subjective and should not entirely depend on the age of the patient. Stabilization of insulin regimen and screening for complications should be performed prior to transfer to the adult care. Transition provides an opportunity for re-education for the young adult about self-management of diabetes. Adult health care providers (HCPs) willing to and equipped for the management of young adults with T1DM should be identified. Shared care by both pediatric and adult HCPs should be done in the initial phase.

Academics

Children with T1DM should be encouraged to achieve their full academic potential. This requires a close interaction between the HCPs, parents and the educational institutions. *Information about the disease, special needs of the child/adolescent, and identification and management of hypoglycemia should be provided to the school authorities.* In particular, the need for carrying snacks and glucometer during examinations and trips should be emphasized. Physiological regimens (basal-bolus or insulin pump) are important, to accommodate day-to-day variations in eating and activities.

Career

Occupational counseling is integral to T1DM management. Children should be informed at an early stage that while almost all careers are possible, in some like armed forces, commercial driving, flying and firefighting, T1DM would be an impediment. Letters of support may be required to allay the anxieties of academic institutions and the employers.

Risk-taking Behaviors

HCPs should strive for early identification and rectification of risk-taking behaviors in young adults with T1DM. Smoking increases the risk of microvascular complications and should be discouraged. The adverse effects of alcohol consumption including hypoglycemia and dyslipidemia should be addressed. Consumption of illicit drugs should be identified and rectified.

Reproductive Health

Reproductive health forms an important aspect of the long-term care for T1DM, with information provided about appropriate methods for prevention of reproductive tract infections and unwanted pregnancies. Contraceptive needs should be addressed in a confidential and non-judgmental manner. Barrier contraception should be encouraged, as it also provides protection from reproductive tract infections. Oral contraceptives may be associated with adverse metabolic effects and increased risk of microvascular complications. However,

the adverse effects of not using contraception are far greater than any of the potential adverse effects of contraception. The need for careful pre-pregnancy planning with good glycemic control, folic acid supplementation and discontinuation of ACE inhibitors and statins need to be emphasized to young girls with T1DM.

THE FUTURE OF TYPE 1 DIABETES MELLITUS MANAGEMENT

Tremendous changes are happening in the management of children with diabetes, and it is important for HCPs to keep abreast with them. Some of these advances are highlighted below.

Hope for Prevention

The efforts for prevention of T1DM have almost completed a full circle. Large studies have failed to show benefit from oral and subcutaneous insulin, nicotinamide and immunosuppressive agents in preventing its development. The outcome of ongoing research using inhaled insulin, vitamin D analogs, delayed cow milk exposure and newer immunosuppressants also appears far from encouraging. Subgroup analysis of DPT-I study showing beneficial effects of oral insulin in delaying onset of T1DM in children with high titers of islet cell antibodies has reinvigorated studies assessing the preventive role of oral insulin in this subset of individuals (Trialnet Trial). INIT II trial is evaluating the preventive effect of inhaled insulin in relatives of patients with T1DM.

Hope for Monitoring

Severe hypoglycemia remains a major hindrance in achieving good glycemic control. Continuous glucose monitoring (CGM) with real-time sensors has added a new dimension to T1DM management, since they provide information about impending hypo- and hyperglycemia, and glycemic variability. They are expected to play an important role in reducing acute as well as chronic complications in the future. Early identification and management of diabetic complications is a desirable goal. Prediction of long-term complications using advanced glycation products is expected to provide opportunity to prevent and treat them at an early stage.

Hope for Treatment

The aim of T1DM management is to provide near physiological insulin replacement using minimally invasive measures. Insulin analogs and continuous subcutaneous infusion of insulin (CSII) have gone a long way in achieving this goal. However, the need for parenteral administration represents a formidable barrier. Inhaled insulin, considered a big breakthrough, was withdrawn due to market considerations. Despite its reintroduction, inhaled insulin has very few

takers in children with T1DM due to variability of action profiles, and potential for local adverse effects. Phase III trials of oral insulin IN-105 (Tregopill) are ongoing, and if successful would be a welcome development. Recent successes in the development of sensor-augmented dual pump therapy with both insulin and glucagon have brought us closer to the long sought goal of an artificial pancreas, though the cost is very high.

Insulin has remained the mainstay of treatment for T1DM for over a century. A variety of non-insulin options as adjuncts to insulin have been explored in experimental settings (**Table 1**).

Pramlintide, an amylin analog, reduces gastric emptying, inhibits glucagon secretion and induces satiety. It is approved as an add-on treatment with insulin in adults with T1DM.

Glucagon-like peptide 1 (GLP-1) plays an important role in regulation of glucagon secretion, gastric emptying and satiety. GLP-1 analogs have emerged as effective options for treatment of type 2 diabetes mellitus (T2DM) with obesity, since they offer the advantage of weight loss. The glucagon inhibition and weight loss might make them an attractive option for treatment of selected obese adolescents with T1DM, though so far, studies have failed to reveal any benefits.

Sodium glucose linked transporter 2 (SGLT2) is the major transporter responsible for tubular resorption of glucose. Inhibition of SGLT2 lowers the urinary glucose threshold, inducing urinary glucose loss. This provides an insulin-independent blood glucose lowering mechanism, making SGLT2 inhibitors a possible option in obese T1DM. However, the side effect of euglycemic DKA mandates the need for compelling evidence before the use of the drug in T1DM.

Metformin, a biguanide, acts predominantly on hepatic glucose production and improves insulin sensitivity. The drug has been used in adolescents with T1DM and polycystic ovarian syndrome (PCOS), and with non-alcoholic fatty liver disease. The drug is currently being studied in obese adolescents with high insulin requirements.

TABLE 1. Non-insulin agents in the treatment of T1DM

Drug	*Class*	*Mechanism of action*	*Status*
Pramlintide	Amylin analog	Reduced gastric emptying	Approved in adults
Liraglutide	GLP-1 analog	Reduced gastric emptying Glucagon inhibition	Experimental
Canagliflozin	SGLT2 inhibitor	Urinary loss of glucose	Experimental
Metformin	Biguanide	Insulin sensitization	Trials in selected adolescents with T1DM

Artificial Pancreas

As this *'Guidelines'* goes to the press, the US FDA has approved an artificial pancreas for commercial sale. The product is expected to be available in 2017. Continuous glucose measurements from a CGMS will be directly fed into an insulin pump, and a computer chip will calculate (from the rate of change of antecedent glucose readings and response to previous doses), the dose to be released from the pump minute to minute. The system has been tested in limited environments under strict observation such as diabetes camp, and then in recent years safety has been demonstrated in less restricted settings.

Hope for Cure

It is understandable that patients seek a permanent cure from the malady. Unfortunately, no such cure is available at the moment. The efforts at developing a cure for T1DM are directed towards reversing the autoimmune process or restoration of beta cell mass. Immunosuppressive agents (e.g. steroids, cyclosporine A, azathioprine, anti-thymocyte globulin and anti-CD3 antibody) have resulted in only partial and transient responses. Moreover, significant adverse effects limit these strategies. Autologous stem cell transplants after high dose immunosuppression have been utilized to reset the immune process with some success in young adults with T1DM. These strategies are limited by the fact that over 95% of beta cell mass is destroyed by the time of diagnosis of the disease.

The other, more appealing, approach for cure involves restoration of beta cell mass using pancreatic, islet cell or stem cell transplantation (**Table 2**).

Pancreatic transplantation is a major endeavor requiring long-term immunosuppression and has been reserved to patients who are contemplating or have already received renal transplant, since they would anyway receive immunosuppression for the renal transplant. Pancreatic transplantation in this setting improves glycemic control, reduces the frequency of hypoglycemia, and provides protection to the transplanted kidney. The duration of functional pancreatic transplant is 9 years for simultaneous transplant, and 6 years for subsequent transplant. Advances in surgical procedures with lower perioperative risk have resulted in the guarded recommendation for pancreatic transplant in adult patients without renal transplant with highly erratic glycemic control despite all efforts. The obvious limiting factor of course is that pancreas transplant can only be cadaveric, which is a major constraint in developing countries.

Islet cell transplantation is a more attractive approach, accomplished by injection of islet cells, so surgery is not required. Non-steroid-based immunosuppressive therapy has lowered the complication rates. Islet cell transplantation is associated with remission for a period of three years, with persisting beta cell effects for a few more years.

The most logical solution to the T1DM cure puzzle remains the use of ***stem cells*** as a never-ending source of beta cells, but *there is currently no evidence for the efficacy of stem cell therapy as a cure.* Recent encouraging results of differentiation of stem cells into functional beta cells in murine models form the basis of ongoing optimism about the use of stem cell therapy in T1DM.

TABLE 2. Current status of beta cell replacement therapy in T1DM

Procedure	*Indication*	*Period of remission*
Pancreatic transplant	In the setting of renal transplant	6-9 years
Islet cell transplant	Experimental	3 years
Stem cell therapy	Experimental	Unclear

SUMMARY

T1DM is going through an exciting phase. Advances in management over the last 100 years have enabled the transition of this fatal disease to a manageable condition, with hope for long-term cure. At the moment, however, insulin represents the one and only treatment. Thus while parents should be counseled about the feasibility of cure in the future, they should be cautioned about the tall claims of cure by mushrooming stem cell centers.

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