GUIDELINES FOR MANAGEMENT OF TYPE 1 DIABETES

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Guidelines for Management
of
Type 1 Diabetes

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Preface

The ICMR type 1 diabetes guidelines come at a time when the SARS-CoV-2 pandemic has disproportionately affected people with diabetes population, exposing them to a high risk for severe illness and mortality. Globally, diabetes was responsible for over four million deaths in the year 2019. It was the leading cause of end-stage kidney disease, adult-onset blindness and cardiovascular diseases. Further, there was a considerable heterogeneity in the prevalence of complications and deaths associated with diabetes across the countries.

India is home to world's second largest adult diabetes population and every sixth person with diabetes in the world is an Indian. The past three decades witnessed 150% increase in the number of people with diabetes in the country. The growing prevalence of pre diabetes indicates a further increase in diabetes in the near future. Diabetes, in India, has traversed from high to the middle income and underprivileged sections of our society. The first nationwide diabetes prevalence study (INDIAB), funded by the ICMR reported a narrowing of urban rural difference in the burden of diabetes. A matter of immense concern is the progressive lowering of age at which type 2 diabetes is presenting, with an inflection in disease prevalence becoming apparent in the age group of 25–34 years in both urban and rural areas.

Over one million children and adolescents in the world have type 1 diabetes, and recent estimates from the International Diabetes Federation suggest that India has the highest number of incident and prevalent cases of type 1 diabetes in the world. Individuals with type 1 diabetes need support to survive, using insulin and other therapies, and to live their entire life without stigma, restrictions, or disabling complications due to their illness. Intensive management of all aspects of diabetes, especially glycemic control, is now the gold standard in type 1 diabetes management. At the same time, there is significant advancement in technology for diabetes care including newer insulin analogues, pumps, automated insulin delivery systems and sensors. Further, a multidisciplinary team of providers is essential for comprehensive diabetes management. This has considerably increased the cost of diabetes care and made it exorbitant to a large section of people with diabetes, even in countries with access to manpower and technology.

In India, there exists a considerable variability in the quality of diabetes care, which depends upon various factors such as accessibility to services, affordability of drugs, attitude and perceptions of care providers, lack of specialists and diabetes educators, standardized laboratories and treatment guidelines. Although several international guidelines are available for type 1 diabetes management, a context specific culturally adaptive guideline that ensures affordable diabetes care is the need of the hour to inform the diabetes care providers in low and middle income countries such as India.

The ICMR type 1 diabetes guidelines is a comprehensive document providing advice on care of diabetes in children, adolescents and adults with type 1 diabetes. All chapters in this guideline have been provided with formation to reflect advances in scientific knowledge and clinical care that have occurred in the recent past. ICMR is committed to update this document periodically to inform clinicians and diabetes care providers on future advances in type 1 diabetes care.

Chapter-1

Epidemiology, Diagnosis and Guide for Differential Diagnosis

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Definition and diagnosis

Type 1 Diabetes mellitus (T1DM) is an autoimmune disease characterized by insulin deficiency and hyperglycemia in people with underlying genetic susceptibility[1,2]. The diagnosis is established based on the tests, fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c) or random plasma glucose (along with characteristic signs and symptoms of hyperglycemia), using cut-offs recommended by American Diabetes Association[1,3].

Epidemiology of T1DM

There are nearly 1.1 million people below 20 years of age estimated to be affected by T1DM globally and 0.13 million are diagnosed with the disease each year, as per the International Diabetes Federation (IDF) Atlas, 9th edition[4]. A recent study found an incidence of 4.9 cases/100000/year in India, which is much lower than the incidence of 21.2 cases/100,000/year observed in the SEARCH registry of USA[5]. The peak incidence for T1DM is seen between 10-14 years of age, though it can affect an individual at any age[6].

Pathogenesis of T1DM

Genetic factors play a significant role in the etiology of T1DM. The concordance rate in monozygotic twins is around 30%[7,8]. The risk of T1DM is 3%, 5%, and 8%, respectively, when mother, father, and sibling have T1DM[9]. The HLA haplotypes with a strong association with T1DM are DR3-DQ2 and DR4-DQ8, present in 30-40% patients with T1DM compared with 2.4% in the general population[10,11]. There are more than 50 non-HLA loci, which increases the susceptibility for T1DM, though the association is weaker than for the HLA region[1,6,7]. The identified genes play a significant role in immune function or pancreatic β-cell function. Though the environmental risk factors have been proposed in the etiopathogenesis of T1DM, understanding is still low. The factors with the most substantial evidence include enteroviral infections, older maternal age, rapid weight gain in early life, and β-cell stress[12].

Natural history of disease evolution

In a genetically susceptible individual, T1DM is preceded by the autoimmunity phase without clinical diabetes. A joint statement from professional organizations proposed a staging classification system that defines the early stages of T1DM with prognostic significance[13]. The recommended classification is mainly for research rather than for clinical practice.

Staging

The various stages are defined as follows[13]:

i)   Stage 1 (pre-symptomatic): Presence of β-cell autoimmunity with normoglycemia. This stage is evident by the presence of two or more islet cell autoantibodies.

ii)   Stage 2 (pre-symptomatic): β-cell autoimmunity is present along with dysglycemia.

iii) Stage 3 is the onset of symptomatic disease.

A study found that in children with two or more islet autoantibodies, 43.5%, 69.7%, and 84.2% developed symptomatic type 1 diabetes at 5, 10, and 15 years of follow- up[14]. T1DM occurred in 12.7%, 61.6%, and 79.1% of children with a single, two, and three autoantibodies, respectively, after 15 years of follow-up. The progression was faster in those who developed autoantibodies at less than three years of age and had HLA DR3- DQ2/DR4-DQ8 genotype[14]. The magnitude of the autoimmunity titer, the autoantibody's affinity, and the type of autoantibody also determine the rates of progression[6]. Higher titers of insulin and IA-2 autoantibodies are associated with earlier onset of disease. The presence of IA-2 or ZnT8 autoantibodies is associated with faster progression to T1DM[15]. The two and five year risk for T1DM is approximately 60% and 75%, respectively, for those who have reached stage 2 (prediabetes)[13]. The β-cell function is reduced at presentation and shows partial recovery with control of hyperglycemia. Patients may go in a so-called honeymoon period after diagnosis and may have minimal or no exogenous insulin requirement. However, residual cells are subsequently lost. The beta-cell damage may not be complete in certain individuals. With sensitive C-peptide measurements, 30–80% of people with long-term T1DM are insulin micro-secretors[1].

Classification of diabetes

World Health Organization came out with a recent classification system in 2019. The WHO 2019 classification system has removed the subtypes for T1DM and T2DM. A new entity called 'hybrid forms of diabetes' is introduced, including a) slowly evolving immune-mediated diabetes of adults and b) ketosis-prone type 2 diabetes. WHO has also introduced a category called 'unclassified diabetes' which is a temporary label, when it is difficult to make a precise diagnosis regarding the type of diabetes, especially close to the time of diagnosis. 'Diabetes mellitus in Pregnancy' is included as a distinct entity, and 'Gestational Diabetes Mellitus' is placed under 'Hyperglycemia first detected during pregnancy'[16].

Spectrum of T1DM

T1DM is associated with autoantibodies in 70-90% of the individuals with the disease. In the classification system of the American Diabetes Association, this entity is called immune-mediated T1DM. T1DM without evidence of autoimmunity is known as idiopathic T1DM[3]. In 2019, WHO removed these subtypes, as insulin need is determined clinically rather than based on autoimmunity.

T1DM can have variable presentations[17-21]. Children often present acutely, with severe symptoms of polyuria, polydipsia, and ketonemia, and approximately a third of them present with diabetic ketoacidosis (DKA). Older children may have a hyperacute presentation so-called fulminant T1DM. In them, autoimmunity is absent, and there is a complete loss of beta-cell function. Japan and Korea have predominantly reported cases of fulminant T1DM. Adults usually present with a more gradual onset, and the initial clinical presentation may

appear consistent with type 2 diabetes mellitus (T2DM). However, they may have an acute presentation similar to children. The reasons for different clinical presentations seen in children and adults may be due to the more severe nature of the disease in childhood T1DM and less frequent blood testing for unrelated indications. WHO has renamed 'Latent autoimmune diabetes in adults' (LADA) as 'slowly evolving immune-mediated diabetes of adults' in their new classification. It is characterized by presence of islet antibody (predominantly GAD65), in individual older than 35 years at diagnosis, and with no insulin requirement for the first 6-12 months after diagnosis. The individuals retain greater beta-cell function and have higher chances of having metabolic syndrome features than individuals with T1DM[16,22]. We have tabulated the salient differences between T1DM and slowly evolving immune-mediated diabetes of adults in Table I.

Table I: Comparison of features between slowly evolving immune-mediated diabetes of adults and Type 1 Diabetes mellitus

Characteristic	T1DM	Slowly evolving immune- mediated diabetes of adults
Age at diagnosis	Childhood to adolescence, rarely in adulthood	> 35 years
Body mass index	Underweight to normal	Normal to overweight
Onset	Acute	Rarely acute
Autoimmunity	Severely increased	Increased
Ketosis	Frequent	Rare
Insulin dependence	At onset	> 6 months after onset
Insulin resistance	No change	Increased or no change

Abbreviation: T1DM-Type 1 diabetes mellitus

Differentiation from other types of diabetes

The age group of 20-40 years has the highest heterogeneity and is at risk of misclassification[23]. In this regard, the category of 'unclassified diabetes' in the new WHO 2019 classification is a significant addition. The precise label for a type of diabetes can be given at a later stage, once the diagnosis is clear. T2DM and monogenic diabetes are two common entities from which T1DM needs to be differentiated. The other forms of diabetes seen in the younger age group and from which T1DM needs to be differentiated upon include neonatal diabetes, mitochondrial diabetes, and fibrocalculous pancreatic diabetes (FCPD). There is a vast list of conditions that can give rise to or are associated with diabetes. Diabetes can be seen in context to diseases of the exocrine pancreas, endocrinopathies, infections, and drugs. It may also result in the context of other genetic syndromes or due to genetic defects in insulin action. Given their rarity in youth, these conditions are not discussed in detail but are essential to recognize, as they may be the first clue to underlying syndrome or disease[3].

Differentiation from T2DM

T2DM has emerged as a new type of diabetes in childhood due to an increase in obesity[24]. The incidence and prevalence of youth onset T2DM are increasing. In the Registry of people with diabetes with young age at onset (YDR) from India, 25.3% of individuals developing diabetes under the age of 25 years had a diagnosis of T2DM[24]. Dabelea et al. provided an etiologic approach for the classification of recently diagnosed diabetes

in youth less than 20 years[25]. They described four categories using autoimmunity and insulin sensitivity (IS). Most individuals (54.5%) had autoimmune markers and were insulin sensitive. This group had characteristics of T1DM. There were 15.9% of individuals who did not have autoimmunity and were insulin resistant. This group had characteristics of T2DM. The third group (19.5%), who had autoimmunity and were insulin resistant had similar prevalence and titers of diabetes autoantibodies, and distribution of HLA risk genotypes to those in the autoimmune plus insulin sensitive group. This suggests that it includes individuals with T1DM who are obese. The last group classified as nonautoimmune plus IS (10.1%) may include those with monogenic diabetes. Nearly 50% of insulin-sensitive individuals had diabetes onset before the age of ten years, compared to 5 to 11% for insulin-resistant individuals. The mean age of diabetes onset reported in YDR is 10.5 years for T1DM and 16.5 of T2DM. There were 15.7%, 30.7%, 32.7% and 20.9% individuals with T1DM in age groups 0-4, 5-9, 10-14 and 15-19 years. The corresponding figures for T2DM were zero, 4.4%, 25.6%, and 70%. The individuals with T1DM who were overweight/obese in YDR were 11.9% compared to 58.2% with T2DM[26]. DKA at diagnosis was present in 28.7% of individuals with T1DM and 6.6% with T2DM[27]. There were 30.6% of individuals with T2DM who were on insulin alone or in combination with oral glucose-lowering drugs in YDR[28]. These data suggest that discriminating T1DM from T2DM on isolated features based on the age of onset, overweight/obesity, autoantibody positivity, insulin requirement, or presentation with ketoacidosis is difficult[23]. The initial differentiation between T1DM and T2DM requires considering multiple factors rather than relying on a single parameter. It is relatively easy to make a diagnosis of T1DM for a patient who is younger than ten years, is normal weight, has evidence of autoimmunity, and presents with DKA[23]. Key features are tabulated that may help in differentiating between T1DM and T2DM in Table II.

Differentiation from Maturity Onset Diabetes in the Young (MODY)

MODY is due to a single gene defect resulting in compromised insulin secretion[29-31]. The mutations in the genes encoding the enzyme glucokinase (GCK), the nuclear transcription factors hepatocyte nuclear factor 1α (HNF1A), and hepatocyte nuclear factor 4α (HNF4A) are the most common causes of MODY30. There are more than ten different types of MODY described so far. It should be considered in a patient without obesity, who develops diabetes before 25 years of age and has two or three generations of diabetes in the family[23,30,31]. MODY's other features are insulin independence (although insulin may be needed for optimal control), absence of features of insulin resistance, and absence of β cell autoimmunity.

Patients with MODY may be misdiagnosed as T1DM or T2DM. The diagnosis may be revised in those who show persistent C peptide production, low insulin dose (<0.5 units/kg/day), and with no tendency for DKA on insulin omission, especially three to five years after diagnosis of apparent T1DM[31]. Patients with T2DM who are less than 45 years, and who do not have features of insulin resistance (acanthosis nigricans, central obesity, hypertension, and dyslipidemia) may have MODY[30]. Genetic testing can help in the precise diagnosis of MODY. There is a 50% probability for a first degree relative to have the genetic mutation and 95% probability of getting the disease in those having the genetic mutation.

Neonatal Diabetes Mellitus

The term neonatal diabetes is used for cases presenting with diabetes within the first six months of life. Full-term infants usually present around six weeks of age. Preterm infants

Table II: Differential diagnosis between Youth onset T1DM, T2DM and MODY

Key features	T2DM	T1DM	MODY
Age at diagnosis	Rarely younger than 10 years	Peak in presentation occur between 5-7 years of age and at or near puberty	Younger than 25 years
Causes and genetic factors	Obesity; genetic and ethnic predisposition	Autoimmune; genetic predisposition {HLA and other genes}	Autosomal dominant: HNF1A, HNF4A, GCK are predominantly affected genes
Body mass index	Usually overweight / obese at onset	Lean or weight loss at diagnosis	Lean or weight loss at diagnosis
Associated features	Acanthosis nigricans, polycystic ovarian syndrome, hypertension, hyperlipidemia, fatty liver disease	Thyroid autoimmunity; coeliac disease	No such features as seen in T1DM or T2DM are associated with MODY
Diabetic ketoacidosis at presentation	Yes; 5-10%	Yes; about 25%	No
Family history	Strong family history	An individual presenting without a first degree relative is generally suggestive of T1DM	Strong family history with autosomal dominant inheritance
Insulin deficiency	Mild to moderate	Severe	Moderate
Insulin resistance	Moderate to severe	None or mild	None or mild

Abbreviations: T1DM-Type 1 diabetes mellitus, T2DM- Type 2 diabetes mellitus, MODY-Maturity onset diabetes of the young , HLA-human leukocyte antigen, HNF1A-Hepatocyte nuclear factor 1-Alpha, HNF4A-Hepatocyte nuclear factor 4-Alpha, GCK-Glucokinase

can present around one week of age[32,33]. Neonatal diabetes mellitus (NDM) occurs in approximately 1 in 90,000 to 160,000 live births. There are more than 20 known genetic causes for NDM[32]. Mutation in KCNJ11, INS and ABCC8 accounts for more than 50% of NDM[33]. NDM can be transient or permanent and can be isolated or part of a syndromic presentation. The data of 11 infants reported by Jain et al. found permanent neonatal diabetes in eight infants[34].

When should neonatal diabetes be suspected?

There may be stress hyperglycemia in neonates, especially in those who are premature or had very low birth weight. Therefore, consider neonatal diabetes (and genetic testing) in cases[32]:

-   With persistent hyperglycemia (glucose > 250 mg/dl) without an alternative explanation.
-   When true serum glucose levels exceed 300 mg/dl, regardless of the time course.
-   Requiring insulin before 6 to 12 months of age.

Why is it crucial to differentiate neonatal diabetes from T1DM?

Differentiating neonatal diabetes from T1DM is helpful, as individuals with mutations in KCNJ11 and ABCC8 may be treated with oral sulfonylureas. They account for about 40% of these patients[32,33]. In a large genetic screening study from India, 12 mutations were

identified (seven in ABCC8, three in KCNJ11, and two in the INS gene) in 33 neonatal diabetes cases. This study also reported some novel mutations. The patients carrying the KCNJ11 (Cys42Arg, Arg201Cys) and ABCC8 (Val86Ala, Asp212Tyr) were successfully treated with sulfonylurea[35]. Early sulfonylurea treatment in responsive patients, in contrast to insulin, may improve neurodevelopmental outcomes, quality of life, is safer, and also more effective in achieving good glycemic control. Another Indian study has reported the mechanism behind the effectiveness of sulfonylurea[36]. Early diagnosis helps explain additional clinical features in syndromic forms, and guide appropriate management for patients. The proportion of monogenic diabetes was 85% in infantile-onset diabetes (n=40) if onset was in the first half of infancy and 55% if it was in the second half of infancy[37]. Genetic testing for NDM is suggested for all cases of diabetes diagnosed in infancy. Wolcott-Rallison syndrome (WRS) is recognized as the most frequent cause of neonatal diabetes in children with consanguineous parents, and the mutations in the EIF2AK3 gene should be studied[38]. For patients presenting between 6 and 12 months of life, antibodies for T1DM should be tested[32,33].

Fibrocalculous Pancreatic Diabetes (FCPD)

Fibrocalculous pancreatic diabetes is due to idiopathic non-alcoholic chronic pancreatitis characterized by recurrent bouts of abdominal pain, steatorrhoea, and pancreatic calcification[40]. The pancreatic calculi develop late in the disease course. It is reported predominantly from tropical countries in a lean adolescent or young adult of either sex. The diagnostic criteria for FCPD are listed in Table III.

Table III: Diagnostic criteria for Fibrocalculous Pancreatic Diabetes[39]

1. The patient should be from a tropical country.
2. Diabetes should be present.
3. Evidence of chronic pancreatitis must be present—pancreatic calculi on abdominal X-ray or at least three of the following
   - Abnormal pancreatic morphology on sonography/CT scan
   - Recurrent abdominal pain since childhood
   - Steatorrhoea
   - Abnormal pancreatic function test
4. Absence of other causes of chronic pancreatitis.

Abbreviation: CT scan-Computerized tomography scan

The salient features which may help in differentiating it from youth onset T1DM are presented in Table IV.

Kerala and Tamil Nadu have reported most of the cases in India. Malnutrition and low socioeconomic status are thought to be major predisposing factors, and with improvements in socioeconomic status and nutrition, the prevalence of FPCD has decreased from 1.6% (1991-95) to 0.2% during the years 2006-2010[40].

The patients require multiple doses of insulin for control of glycemia, and management can still be challenging. Despite hyperglycemia, ketosis rarely develops. The reasons for this could be: a) enough endogenous insulin to prevent ketogenesis, but not hyperglycemia, b) decreased glucagon reserve, and c) reduced availability of non-esterified fatty acids (substrate for ketogenesis), due to lack of subcutaneous fat.

**Table IV: Differential diagnosis between Youth onset T1DM and
Fibrocalculous pancreatic diabetes (FCPD)**

Key features	FCPD	Type 1 diabetes
Age at diagnosis	Most patients are diagnosed between age of 10 to 30 years.	Peak in presentation occur between 10-14 years of age and at or near puberty.
Clinical presentation	While some patients present with the classical symptoms of polyuria, polydipsia and polyphagia, most are asymptomatic and are detected incidentally.	Presentation is usually acute with the classical symptoms of polyuria, polydipsia and polyphagia or even with DKA.
Geographical variation	Reported predominantly from Kerala and Tamil Nadu.	Reported through India
Causes and genetic factors	Exact etiology remains elusive. Malnutrition, chronic consumption of cassava, deficiency of trace elements/ antioxidants, certain genetic factors have been implicated.	Autoimmune; genetic predisposition {HLA and other genes}
Body mass index	Most patients are lean, some are of normal weight and few may be obese.	Lean or weight loss at diagnosis.
Associated features	Abdominal pain, Steatorrhoea Physical examination may reveal bilateral parotid enlargement and abdominal distension.	Thyroid autoimmunity; coeliac disease
Diabetic ketoacidosis at presentation	They are usually ketosis resistant.	Yes; about 25%
Family history	FCPD occasionally occurs in different members of the same family, which may reflect shared environmental risk factors .	An individual presenting without a first degree relative is generally suggestive of T1DM.
Insulin requirement	Require insulin for control of glycaemia right from time of diagnosis. May require insulin for prevention of DKA in latter stage.	Require insulin for control of glycaemia and prevention of DKA.
Insulin resistance	Moderate to severe	None or mild

Abbreviations: T1DM-Type 1 diabetes mellitus, FCPD-Fibrocalculous pancreatic diabetes, DKA-Diabetic ketoacidosis, HLA-Human leukocyte antigen

Mitochondrial Diabetes

Mitochondrial diabetes is also known as maternally inherited diabetes and deafness. It is a monogenic form of diabetes, as are MODY and NDM[41]. The average age of onset is between 35 and 40 years, in contrast to T1DM or other monogenic forms of diabetes that usually present much earlier. It can present like T1DM or T2DM. Initially, patients with phenotypes like T2DM can be treated by diet or sulfonylurea[41]. Metformin should not be prescribed due to the risk of lactic acidosis. Most patients will require insulin treatment due to progressive insulinopenia.

It should be suspected where there is robust familial clustering of diabetes, the characteristic also seen with MODY. However, in mitochondrial diabetes, there is a maternal transmission

and a bilateral hearing impairment in most of the carriers. The precise diagnosis can be established by genetic analysis. A range of mutations in mitochondrial DNA (mtDNA) has been implicated. However, in many patients, it is associated with A3243G mutation in mtDNA[41].

Summary

Type 1 Diabetes mellitus (T1DM) is an autoimmune disease characterized by insulin deficiency and hyperglycemia in people with underlying genetic susceptibility. The incidence of T1DM in India is 4.9 cases/100000/year. The peak incidence for T1DM is seen between 10-14 years of age, though it can affect an individual at any age. Genetic factors play a significant role in the etiology of T1DM. The risk of T1DM is 3%, 5%, and 8%, respectively, when mother, father, and sibling have T1DM[9]. The HLA haplotypes with a strong association with T1DM are DR3-DQ2 and DR4-DQ8, present in 30-40% patients with T1DM than 2.4% in the general population. There are more than 50 non-HLA loci, which increases the susceptibility for T1DM, though the association is weak than the HLA region. T1DM is associated with autoantibodies in 70-90% of the individuals with the disease. T1DM can have variable presentations[17-21]. Children often present acutely, and adults usually present with a more gradual onset. World Health Organization proposed a recent classification system of diabetes in 2019. The WHO 2019 classification system has removed the previous subtypes for T1DM and T2DM. A new entity called 'hybrid forms of diabetes' is introduced, including a) slowly evolving immune-mediated diabetes of adults and b) ketosis-prone type 2 diabetes. T1DM needs differentiation from other forms of diabetes seen in a younger age group. The age group of 20-40 years has the highest heterogeneity and is at risk of misclassification. WHO has also introduced a category called 'unclassified diabetes' which is a temporary label, when it is difficult to make a precise diagnosis regarding the type of diabetes, especially close to the time of diagnosis.

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Chapter-2

Lifestyle-Diet and Exercise

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Introduction

Lifestyle management (LSM) plays an essential role in managing type 1 diabetes mellitus (T1DM). Understanding the effect of diet and physical activity on glycemia is essential for optimal management of T1DM.

Aims of Nutritional Management

1) Maintain glycemia in the normal to the near-normal range with minimal/no hypoglycemia.

2) Maintain optimal blood pressure, weight, and lipid levels.

3) Ensure adequate nutrition to facilitate healthy growth and development in children and adolescents.

4) To prevent the development or progression of diabetes-related microvascular and macrovascular complications.

5) Address individual nutrition needs, incorporating personal, social, and cultural preferences.

6) Improve overall health through appropriate food choices.

Concepts of energy and proximate principles of diet

Individualize the diet plan for each patient with diabetes, considering his/her socio-cultural environment, food habits, preferences, and work schedule to facilitate proper compliance. The energy requirement for children and adults with T1DM (Table I) is similar to the general population. Consider reduction in the caloric intake for obese and overweight individuals.

Table I: Nutritional recommendations for individuals with T1DM
• Carbohydrate: 50–55%
Sucrose intake < 10%
• Fat 25–35%
Saturated fat + trans fatty acids: < 10% Trans fatty acids < 1%
Polyunsaturated fat: < 10% Monounsaturated fat: 10-20%
• Protein 15–20%

Abbreviations: TIDM-Type 1 diabetes mellitus

Carbohydrates

The recommended carbohydrate intake is 50-55% of total calories. Too much carbohydrate restriction may hamper growth in children and adolescents and hence, should be

discouraged1. Even in adults, ensure a minimum of 130 g of carbohydrate per day to provide sufficient glucose as fuel for the brain. The effects of carbohydrate restriction below 130 g/day are not clear. In pregnancy, the minimum recommended carbohydrate intake is 175 g/day[2]. However, in the Indian Subcontinent, approximately two-third of calories are obtained from carbohydrates in individuals with diabetes, which is higher than the recommended amount[3]. Hence, it is essential in Indians with diabetes to monitor carbohydrate intake and reduce if possible.

Moreover, Indian (especially South-Indian and East-Indian) diets are rich in simple carbohydrates. The intake of complex carbohydrates should be encouraged to constitute at least 70% of the total carbohydrates. The use of sucrose should be limited to less than 10%, and preferably less than 5% of total calories. Although sugar is not much different from isocaloric amounts of starch for glycemic excursions, consuming high amounts of sugar in sugary drinks may not be adequately covered with insulin, and hence, should be avoided. Healthy sources of carbohydrate foods include wholegrain bread and cereals/ millets, legumes (peas, beans, and lentils), fruits, vegetables, and low-fat dairy products. With a reduction in the intake of carbohydrate components in the diet, the intake of fat increases. In this situation, execute caution to ensure the consumption of good quality fat.

Fiber

Dietary fiber is a non-digestible complex carbohydrate derived from foods of plant origin. The recommended dietary fiber intake for children ≥ one year of age is 14 g per 1000 kcal. Another way of calculating the daily dietary fiber requirement in children over two years is 'Age in years + 5 g'. Encourage consumption of foods such as legumes, fruits, vegetables, and wholegrain cereals to ensure adequate fiber intake. Higher fiber foods may help to improve satiety and replace more energy-dense foods. Soluble fiber helps moderate postprandial blood glucose levels and lower serum cholesterol levels to prevent cardiovascular disease. Good sources of soluble fiber include oats and oatmeal, legumes (peas, beans, lentils), barley, fruits, and vegetables (especially oranges, apples and carrots). Insoluble fiber also offers several benefits to intestinal health, including a reduction in the risk of hemorrhoids and constipation. Most of the insoluble fibers come from the bran layers of cereal grains. It is good to increase fibers gradually to avoid bloating and discomfort.

Fat

Recommended daily intake for fats is up to 30% of total calories. Infants and children younger than two years of age may have a higher daily fat intake of up to 35%. Dietary fats are of two kinds: visible fats, like that in cooking medium or invisible fat, which is inherently present in the foods. Take into consideration the calorie consumption of both these fats. Excess consumption of saturated fats and cholesterol increases serum LDL cholesterol associated with increased cardiovascular disease risk. Hence, the daily intake of saturated fats should be limited to less than 10% of the total calories and dietary cholesterol to less than 300 mg/day. In patients with raised LDL cholesterol, restrict the daily saturated fat intake to below 7% of total calories and cholesterol intake to less than 200 mg/ day. The common foods rich in saturated fats and cholesterol include egg yolk, ham, bacon, red meats, whole milk, cheese, butter, ghee, cream, and cream-based desserts, vanaspati, coconut oil, palm oil and it is best to limit their consumption. The right options for low cholesterol and low saturated fat foods are fish, lean chicken, low-fat milk and curd, low-fat cheese, buttermilk, and cooking oils rich in healthy fatty acids.

Unsaturated fatty acids are essential components of lipid membranes and comprise polyunsaturated and monounsaturated fatty acids. They are derived mainly 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 and glycaemic control. These help to reduce the risk of cardiovascular disease.

Monounsaturated fatty acids (MUFA) are there in olive, canola, groundnut, peanut, sesame, rice bran, mustard oils, almonds, and avocados. This form of fat (particularly MUFA with *cis*-configuration) is most lipid-friendly, and 10-20% of the total daily calories should be from their intake.

Polyunsaturated fatty acids (PUFA) should be less than 10% of total daily calories. Significant components of PUFA are ω-6 PUFA and ω-3 PUFA. Omega-3 PUFAs lower serum triglycerides. Encourage regular ω-3 intake from natural food sources rather than supplements. Coldwater fatty fishes (mackerel, salmon, sardine, herring, and tuna) are good non-vegetarian sources of ω-3 PUFA whereas flaxseeds, walnuts, chia seeds, soybean oil, canola oil, kidney beans, tofu, broccoli, spinach, cauliflower, and Chinese cabbage are good vegetarian sources of ω-3 PUFA. Omega-6 PUFA helps to reduce serum LDL cholesterol and is found in various vegetable cooking oils (safflower, sunflower, soy, cottonseed, corn, canola, peanut, and sesame), pulses, vegetables, cereals, walnuts, seeds, eggs, and poultry. However, do not recommend consumption of ω-6 PUFA > 10% of the total daily fat. A higher ω-6/ω-3 PUFA ratio of > 5-10 may promote several diseases, including cardiovascular disease. ω-6/ω-3 PUFA ratio in Indian diet is much higher than optimal; hence, a mix or alternate oils rich in ω-6 PUFA and ω-3 PUFA to attain the lower ratios is preferred. Similarly, mixing and alternating oils should also focus on allowing the recommended MUFA in the diet.

Plant **sterol and stanol esters**, typically found in enriched foods, may modestly reduce total and LDL cholesterol and may be considered for children ≥ five years with high serum total or LDL cholesterol.

Trans-fatty acids, though unsaturated fatty acids, are structurally different and have adverse health effects. They not only increase LDL cholesterol but also reduce HDL cholesterol. Hence, the use of trans-fats should be limited as much as possible, ideally to less than 1% of total caloric intake. They form when vegetable oils are processed to make them solid (partial hydrogenation). They are scarce in nature but are commonly found in packaged baked goods (cakes, cookies), snack foods (potato chips), fried food (French fries, doughnuts, fried chicken) and margarine (stick margarine, vanaspati as a cooking medium).

Proteins

The protein requirement in children and adolescents varies from 2 g/kg at one year, 1 g/kg at ten years to 0.8-0.9 g/kg in adolescence. Recommended protein intake is 15-20% of the caloric requirement. Protein promotes growth only when calorie intake is sufficient, and high protein intake may compromise growth by reducing calorie intake and may also reduce vitamin and mineral intake.

Proteins from animal sources (fish, milk, egg white, poultry, and meats) are of better quality as they provide all essential amino acids, but their use is associated with higher salt and saturated fat content. Remove the skin and visible fat while consuming the animal sources of proteins. On the other hand, proteins from vegetarian sources (soy, beans, and lentils) contain less saturated fat and are rich in fiber and complex carbohydrates. Hence,

the consumption of proteins from both vegetarian and low-fat non-vegetarian sources, preferably in equal amounts, is recommended.

In patients with diabetic nephropathy, daily protein intake should not be restricted to less than 0.8 g/kg body weight to avoid the risk of malnutrition. There is no benefit of protein intake less than 0.8 g/kg body weight on glycemia, cardiovascular risk, or decline in glomerular filtration rate.

Vitamins and Minerals

Vitamin and mineral requirements in children with diabetes are the same as in other healthy children. There is no clear evidence to suggest that routine vitamin or mineral supplementation in children with diabetes is beneficial. Ensure the RDA of all vitamins and minerals in the diet by appropriate choice of macronutrients.

Salt

Recommendations for salt intake in children with diabetes are similar to that of healthy children. Daily salt intake should be limited to 1000 mg (2.5 g salt) in 1–3 years old children, 1200 mg (3 g salt) in 4–8 years old children, 1500 mg (3.8 g salt) for children and adolescents aged ≥ nine years and 2300 mg (6.0 g salt) in adults. Processed foods are rich in salt, and hence their intake should be limited.

Sweeteners

The commonly used non-nutritive and hypocaloric sweeteners include saccharin, neotame, aspartame, acesulfame K, stevia, alitame, and sucralose. They are commonly used in low sugar, 'light' or 'diet' products to improve sweetness and palatability and are also used to replace table sugar in cooking at home. Intake of sweeteners not exceeding acceptable daily intakes (ADI) is considered safe[4]. They have the potential to replace caloric or carbohydrate intake if substituted for caloric sweeteners. However, the benefits of their use for better glycemia, weight reduction, or reduction of cardiometabolic risk factors are limited.

Carbohydrate assessment, Glycaemic Index (GI), Glycaemic Load (GL) and carbohydrate counting

The GI is an indicator of the quality of carbohydrates in food and measures the rapidity of increment in plasma glucose after ingestion of a food item. GI is evaluated by calculating the area under the curve for blood glucose rise for 2 hours after consuming 50 g of a test-food compared to that of 50 g of oral glucose (preferably) or white bread (reference food). A value of 100 represents, rise in blood glucose similar to pure glucose. The GI of foods varies from 0 to 100. Foods with a low GI produce a lower rise in blood glucose during the first 2-3 hours after their ingestion. Table II presents the classification of common Indian foods as low (≤ 55), medium (56-69), and high (≥ 70) glycaemic index. Remember, GI is not a sole criterion for deciding diet composition as there are certain limitations to its use. Some food products (such as ice cream) may have a large amount of fat, delaying the absorption of carbohydrate and rendering a relatively low GI value but may have adverse health effects in the long term.

GL is a measure of both the quality (GI value) and quantity (g per serve) of a carbohydrate in a meal. Determine foods GL by multiplying its GI by the amount of carbohydrate the food contains in each serve and dividing the product by 100. Therefore, the GL provides a summary measure of the relative glycaemic impact of a "typical" serving of the food. Classify foods with a GL < 10 as low GL and those with ≥ 20 as high GL value.

Table II: Classification of commonly used foods based on the Glycemic index (GI)

Low GI (≤ 55)	Medium GI (56-69)	High GI (≥ 70)
Peanuts (14±8), Prunes (29±4), Soy Boiled (18±3), Rajma (19), Cherries (22), Fructose (19±2), Grapefruit (25), Barley (28±2), Whole milk (31), Low-fat milk (37±4), Skimmed milk (37±4), Yogurt (28), Red Kidney beans boiled (19), Apple (38), Green gram dal (29), Rye, Pinto beans (39), Pear (30), Plum (24), Black-eyed beans (38), Peach (34), Black beans (30), Orange (40), Boiled Carrots (33), Kiwifruit (50), Horse gram (51), Sweet Potato (41), Peas boiled (51), Buckwheat (55), Banana (51)	Apricot (57), Mango (60±16), Papaya (60±16), Whole green gram (57±6), Basmati Rice (57±4), Oatmeal (69), Ice cream (61±7), Honey (55±5), Bajra (67), Pineapple (59±8), Raisins (64±11), Cream of wheat (66), White rice (64), Beets (64±16), Boiled potatoes (58), Table sugar (63), Coca-Cola (regular) (63), Grapes (59), Brown Rice (68±4),	Watermelon (76±4), Jowar (77±8), Pumpkin (75), Ragi (84), White Baked Potato (78±4), Parsnips (97±19), Glucose (99±3), Dates (103±21), Corn flakes (81±6), White bread (75±2),

Abbreviations: GI-Glycemic Index

Carbohydrate counting

For patients using continuous subcutaneous insulin infusion (CSII), carbohydrate counting is essential. Carbohydrate counting is also beneficial for patients on a basal-bolus regimen. There are three levels of carbohydrate counting. In level 1, consistent carbohydrate intake is encouraged using an exchange or portion lists of measured quantities of food. The level 1 carbohydrate counting is useful for patients on twice daily insulin doses for whom a consistent carbohydrate intake from day-to-day is essential. Level 2 (pattern management principles) is an intermediate step. In this, patients use a consistent baseline insulin dose, continue to eat regular carbohydrates, and frequently monitor blood glucose (BG) levels to recognize patterns of BG response to carbohydrate intake and the impact of insulin doses and exercise on it. Based on this knowledge, insulin doses are adjusted for food and exercise to achieve BG goals. However, it is less commonly used primarily by the pediatric teams. Level 3 [insulin to carbohydrate ratios (ICRs)] is the most commonly recommended one and is the most appropriate for patients using multiple daily injections (MDI) or CSII. ICR varies from patient to patient based on age, sex, pubertal status, duration of diagnosis, and activity. Initially, ICR can be calculated using the formula 500 divided by total daily dose (TDD) of insulin and represents the g of carbohydrate that would be covered by 1 unit of rapid-acting insulin. Replace the number 500 with 450 for regular insulin. ICR helps to adjust the prandial insulin dose according to carbohydrate intake. Fine-tune the ratio by checking BG level before and 2 hours after the meal to maintain a BG increment of less than 60 mg/dl.

The various carbohydrate counting methods involve gram increments, 10–12 g carbohydrate portions, and 15 g carbohydrate exchanges (listed in Appendix-1). None of the methods are superior over the other. Cover all major meals and snacks containing more than 10-15 g of carbohydrates with a bolus insulin.

Dietary recommendations for specific insulin regimen

Divide daily calorie intake in 6-7 meals (3 major meals, and 3-4 snacks). In general, represent breakfast with 20% of total caloric needs, lunch, and dinner with 25- 30%, and each snack

with 10% of daily calorie inputs. Each meal should be taken at a particular time during the day with no significant and frequent deviations. A bedtime snack is considered an essential part of the regimen to prevent nocturnal hypoglycemia and should include at least 7-8 g of protein.

Most of the T1DM patients will have absolute insulin deficiency. Hence, nutritional intake should match that of a specific insulin regimen that patient is receiving. CSII and MDI provide flexibility in eating patterns, whereas pre-mix preparations and fixed insulin regimens demand food intake at fixed quantity and time. In patients on MDI with analogs or CSII, relatively higher GI major meals can be allowed, but the inter-meal snacks should contain relatively fewer carbohydrates. On the other hand, while using a basal-bolus regimen with regular insulin, relatively low GI major meals with moderate carbohydrate-containing inter-meal snacks should be encouraged.

Exercise Physiology

Exercise has multiple benefits in individuals with T1DM. Regular physical activity increases the feeling of general well-being and helps prevent obesity and mitigate increased cardiovascular risk in T1DM patients[5]. Also, although results vary across studies, regular physical activity may modestly improve glycaemic control and reduce microvascular complications[6,7]. Hence, regular physical activity should be encouraged in individuals with type 1 diabetes. Moreover, many T1DM patients may be interested in sports; instead, few may like to have sports as their careers. Hence, T1DM should not limit the ability to excel in a chosen sport.

Normal exercise physiology

The two types of exercises (aerobic and anaerobic) have diverging effects on glucose homeostasis[8]. During moderate-intensity aerobic exercise, glucose production by the liver increases 5 to 10 fold to meet the peripheral glucose supply into working muscles, in the absence of which blood glucose levels diminish below the normal range. In healthy individuals, glucose production increases up to 10-fold during maximum aerobic activity, and glucose homeostasis is maintained. During anaerobic activity, a 15-fold increase in glucose production occurs[9]. Besides, with normal islet cell function, insulin level decreases in response to diminishing BG level.

Mechanisms for exercise-associated hypoglycemia and hyperglycemia in T1DM

Exercise can cause perturbation in glucose homeostasis in T1DM individuals, hence often discouraged in them. It is difficult to predict the effect of exercise onglycemia accurately. Significant inter-individual variations are observed though intra-individual variability is less, primarily when consistency in the timing and dose of insulin, carbohydrate intake, duration, and intensity of exercise is maintained.

During aerobic exercise in T1DM, an increase in glucose disposal into skeletal muscle is often not compensated well by an increase in glucose production from the liver. Elevated insulin levels enhance the entry of glucose into muscle cells as a result of previously administered exogenous insulin (whose levels cannot be decreased unlike in those with significant endogenous insulin production) and insulin-independent mechanism (GLUT4 translocation). Moreover, elevated insulin levels effectively suppress glycogenolysis and gluconeogenesis from the liver, combating the compensatory mechanisms of hypoglycemia. Often the counter-regulatory hormone function may be compromised in T1DM individuals,

further contributing to hypoglycemia occurrence and its severity. Prior exposure to either aerobic exercise or hypoglycemia further blunts glucose counter-regulatory responses (i.e., glucagon and catecholamines).

In contrast, during anaerobic exercise, a more substantial rise in catecholamines occurs, and the pancreas in T1DM patients is not able to increase insulin secretion to offset the action of catecholamines. These factors increase glucose production by the liver while limiting glucose disposal into skeletal muscle leading to a mismatch in glucose production, utilization, and consequent hyperglycemia.

Factors affecting glucose response to exercise

Various factors such as intrinsic factors of exercise, type, and timing of insulin and food consumption, metabolic control, environmental factors affect BG response to exercise. Table III summarises these factors and their effect on the BG response.

Normal day-to-day exercise

Normal day-to-day activities are essential and part of almost every child's daily routine. Aerobic fitness may improve glycemic control. On the other hand, good glycaemic control maximizes exercise capacity.

Usually, children indulge in short periods of intense activity interspersed with periods of resting. However, occasional extra physical activity may require insulin adjustments. Once the individual gets accustomed to activities and performs them as per a predictable and regular schedule, the adjustments in diet/insulin are easier.

Hypoglycemia including late hypoglycemia and insulin adjustments

Blood glucose disposal significantly increases during aerobic exercise. Hence, when exercise is anticipated within few hours after bolus insulin (especially within one hour while on rapid-acting insulin and within three hours on regular insulin), it is advisable to reduce the pre-meal bolus dose. In children with obesity, regular administration of carbohydrates before physical activity may not help to reduce weight. Hence, especially for regular physical activities, reduced insulin dosage of previous short-acting insulin should be preferred instead of carbohydrate supplementation. However, exercise may often be spontaneous, and some patients may develop postprandial hyperglycemia with anticipatory reduction of pre-meal insulin, leading to a decrease in exercise performance. In such cases, carbohydrate consumption before an activity is the preferred strategy to maintain blood glucose levels. In patients using CSII, setting a temporary lower basal rate (50% to 80% reduction in basal dose depending upon the duration and intensity of the exercise, which should be done at least 90 min before the initiation of activity and lasting till the activity stops) may be considered.

Insulin sensitivity increases during and immediately after the exercise and again 7-11 hours after the completion of the exercise. Glucose requirement increases during these periods of heightened insulin sensitivity and increases the risk of hypoglycemia for 24 hours after the exercise. Hence, reducing the basal insulin by 10-20% or extra-low GI snacks at bedtime should be considered on the day of exercise. Consider a 30-50% reduction in the basal insulin of the previous day and on the day of activity for all-day or prolonged activities. The use of continuous glucose monitoring (CGM) during exercise in patients who are on CSII with low glucose suspension facility is beneficial in preventing hypoglycemia. Even

Table III: Factors affecting and their effect on the BG response to exercise

Factor	Effect on glycemia
Duration of exercise	Nearly all forms of activity lasting >30 min require some adjustment to food or a reduction in insulin.
Intensity of exercise	Increase in the intensity of exercise increases the risk of hypoglycemia requiring more significant insulin decrements.
Type of exercise	Anaerobic efforts increase the BG level due to the release of epinephrine and glucagon. On the other hand, aerobic activities can lower BG levels during (usually within 20–60 min after the onset) and after the exercise. Combining intermittent bouts of anaerobic exercise with aerobic forms may prevent hypoglycemia during long-duration aerobic activities. Weight-bearing activities may cause hyperglycemia due to the release of growth hormones, and the performance of these activities before aerobic activities may prevent hypoglycemia.
Timing of exercise	Morning activity, done before insulin administration, is less likely to result in hypoglycemia as circulating insulin levels are typically low, and glucose counter-regulatory hormones may be high.
Conditioning	Hypoglycemia is less with regular conditioning. It may be due to the reduction of insulin in anticipation or the better utilization of lipids as fuel.
Degree of stress/ competition in the activity	Like high-intensity activity, stress may also increase catecholamine release and elevate BG levels, requiring corrective insulin administration.
Muscle mass/ number of muscles used in the activity	Exercises that involve a higher number of muscles during aerobic exercise lead to a higher drop in BG. More significant energy consumption occurs during weight-bearing activities than non- weight-bearing activities.
The long term metabolic control	Suboptimal control may reduce aerobic capacity and may cause easy fatigability.
Hyperglycaemia during exercise	May reduce exercise tolerance.
Type and timing of insulin	Rapid-acting insulins typically cause hypoglycemia 60-90 min after administration, whereas regular insulin does so at 2-3 hours.
Choice of injection site	Injection of insulin in the exercising muscle leads to the rapid absorption of insulin.
Ambient temperature	Insulin absorption is increased by high temperature and decreased by low temperature.

Abbreviations: BG: Blood Glucose

otherwise, the use of CGM and appropriate management of down trending BG levels can reduce hypoglycemia. Suggest monitoring BG levels at regular intervals in patients not using CGMS and performing unaccustomed activities and act accordingly. Supplement carbohydrates adequately in patients in whom regular BG monitoring cannot be done, and any person who develops clinical features of hypoglycemia should receive glucose tablets or other forms of quick-acting carbohydrates.

Ketones

Significant hyperglycemia (random BG level > 250 mg/dl) with any degree of ketonuria indicates under insulinisation. These patients are likely to experience a further rise in blood glucose with exercise due to the unopposed action of counter-regulatory hormones and impaired glucose uptake by the muscles. The latter also compromises the exercise performance. Ketone production may also increase rapidly and may precipitate ketoacidosis, which may manifest with pain in abdomen and vomiting. Hence, do not recommend exercise in all individuals with type 1 diabetes who have hyperglycemia with any degree of ketonuria (small or more) or ketosis (blood β-hydroxybutyrate is > 0.5 mmol/L).

Parents often believe that prolong exercise does not require insulin. Unless long-acting insulin provides cover, monitor blood glucose levels carefully during exercise, because skipping the previous dose of short-acting insulin could be dangerous. If the previous insulin dose is skipped, the child's monitoring should include ketone testing, preferably blood ketone levels using glucometer devices, equipped to measure blood ketones. The latter provides an excellent method for rapid detection and exact measurement of ketones. Blood ketone measurement is also a better marker of resolution of ketosis than urine ketones.

On the other hand, few patients are afraid that reducing the pre-exercise insulin doses may lead to ketosis during or after exercise; however, reducing insulin down to 25% of pre-exercise doses does not increase the risk of ketosis.

Nutritional management of exercise and physical activity

Individuals with T1DM should receive some carbohydrate snacks before physical activity. If pre-exercise insulin doses are appropriately reduced, a carbohydrate intake of 0.3-0.5 g/kg/h of moderate physical activity may be sufficient. A relatively lower BG level at the initiation of physical activity and not adjusting the insulin doses before physical activity increases the hypoglycemia risk despite being in the fed state. The occurrence of hypoglycemia on the previous day blunts the autonomic and counter-regulatory response to hypoglycemia. Hence, in all these situations, 2-3 times more carbohydrates (1.0-1.5 g/kg/h) need to be supplied to prevent hypoglycemia. Table IV summarises the suggestions for carbohydrate intake during physical activity.

For activities lasting more than 30-60 min, prefer slow-releasing carbohydrates, whereas for activities lasting less than 30-60 min moderately fast releasing carbohydrates should be administered. Prefer administration of foods containing fat or protein with carbohydrates (e.g., chocolates, milk, curd, etc.) for the former situation and prefer predominant carbohydrate foods (e.g., fruits, a cereal) for the latter. It is essential to maintain adequate hydration before, during, and after the exercise to achieve optimal exercise performance.

Exercise recommendations for individuals with T1DM

For adults with T1DM, recommend 150 min or more of moderate-to-vigorous intensity activity per week spread over at least three days/week but without more than two consecutive days of no activity. Adults with T1DM should also engage in 2-3 sessions per week of resistance exercise on non-consecutive days.

Table IV: Suggestions for carbohydrate intake during physical activity

< 90 mg/dl	Ingest 0.3-0.5 g/kg/h of quick-acting carbohydrate and increase BG level to ≥ 90 mg/dl before initiating exercise. For prolonged activities, consume additional carbohydrate (0.5–1.0 g/kg/h of exercise) based on BG testing results.
90–150 mg/dl	Consume carbohydrates (0.8–1.0 g/kg/h) starting from the onset of exercise.
150-250 mg/dl	Start an exercise and avoid consumption of carbohydrates until BG levels are < 150 mg/dl.
> 250 mg/dl	Check for ketones and avoid exercise if ketones are moderate-to-large. If BG 250-350 mg/dl and ketones are negative, initiate mild-to-moderate intensity exercise but delay intense exercise until BG level is < 250 mg/dl. If ketones are negative but BG > 350 mg/dl consider insulin correction by ~ 50% depending on the active insulin.

Abbreviations: BG- Blood Glucose

For children and adolescents with T1DM, recommend 60 min/day or more of moderate or vigorous-intensity aerobic activity. Besides, recommend vigorous, muscle-strengthening, and bone-strengthening activities at least three days a week.

Precautions for exercise

T1DM individuals with signs and symptoms of cardiovascular disease (CVD), any diabetes-related complications (microvascular or macrovascular), or previously sedentary patients older than 30 years of age (and those who have had diabetes for ten years or longer) should undergo evaluation for CVD before starting new exercise programs. Vigorous exercise is contraindicated in patients with severe NPDR or PDR to reduce the risk of vitreous hemorrhage.

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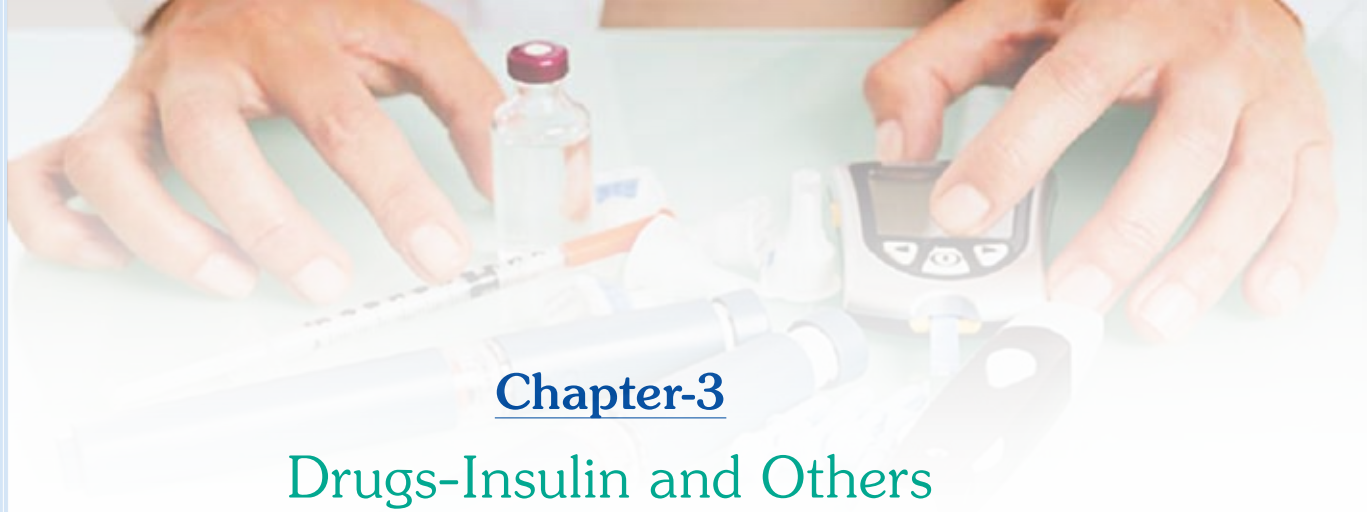
Chapter-3

Drugs-Insulin and Others

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Introduction

All children and adults with type 1 diabetes (T1DM) require insulin as soon as they are diagnosed and continuously thereafter throughout life. Short-acting bovine insulin was first used in the treatment of a 14-year-old child with T1DM in 1922. Since then, there have been many improvements in available insulin formulations, and also in the regimens of insulin therapy. These include the availability of recombinant human insulin since 1982 and bio-engineered insulin with rapid-action (insulin lispro, insulin aspart, and insulin glulisine), ultra-rapid action (fast-acting insulin aspart) as well as specially designed insulins with longer duration and relatively "peakless" action (insulin glargine U-100, insulin glargine U-300, and insulin degludec). In addition, the previous regimens using twice daily "split-mix" insulin regimens have been mostly superseded by more physiological "intensive" regimens with multiple daily insulin injections (MDII) or continuous subcutaneous insulin infusion (CSII). It has been clearly shown in the Diabetes Control and Complications Trial (DCCT) study that intensive glycemic control, using either MDII or CSII, improves hemoglobin A1c (HbA1c) and reduces progression of diabetic microvascular complications in patients with T1DM[1].

Whatever the insulin regimen, their optimal use depends on the painstaking care taken by a diabetes team, including the physician, diabetes educator and nutritionist to educate and support the patient and his/her family regarding their best use as well as insulin dose adjustment. In addition, while it is essential to strive for the best HbA1c feasible (< 7.5% in children and < 7% in adults), the type of insulin used and insulin regimen will differ from patient to patient. Factors such as motivation, education, and financial resources of the family should be considered while making this decision. The co-operation of the patient, and support of the family members, are key to achieving good glycemic control in T1DM.

Types of insulin

The different types of insulin available and their action profile have been shown in Table I[2-4].

Short-acting recombinant regular human insulin (plain, soluble) is the most commonly used bolus (or prandial) insulin to prevent post-meal glucose elevation. The earlier used insulin formulations which were derived from other sources (such as porcine and bovine insulin) are no longer available in India.

Conventional insulin formulations

Regular insulin is used along with intermediate actingor long-actinginsulin in "split-mix", "pre-mix" and "basal bolus" regimens. Regular insulin should be administered 20-30

Table I: Action profiles of different insulin preparations on subcutaneous administration

Type of insulin	Onset of action	Peak action (h)	Duration (h)
Regular	30-60 min	2-4	6-8
Rapid-acting analog (aspart, lispro, glulisine)	5– 15 min	1-2	3-5
Ultra-rapid acting analog (fast-acting insulin aspart)	3-5 min	1	3-4
NPH	1-3 h	5-7	12-16
Detemir	2-3 h	6-8	12-24
Glargine U-100	2-3 h	Peakless	20-24
Glargine U-300	4-6 h	Peakless	>24 (about 36 h)
Degludec	1-4 h	Peak less	>24 (about 42 h)

Abbreviation: NPH: Neutral Protamine Hagedorn

minutes before meals for optimum effect; its effect peaks at 3-4 hours and total duration of action is approximately 6-8 hours. It can be used via the intravenous route in diabetic ketoacidosis, during perioperative period or labor.

Intermediate-acting insulin (NPH) is used as a basal insulin in split-mix or pre- mix (twice daily insulin) regimens and in basal-bolus regimens. This preparation cannot be given by intravenous route or in insulin pumps. In contrast to newer basal insulin formulations, NPH insulin does not have a uniform action and has a pronounced peak after 6-8 hours and the effect tails off in 12-14 hours.

Insulin analogs

Rapid-acting insulin analogs have quicker onset and shorter duration of action as compared with regular insulin (Table I). The currently available preparations include aspart, lispro and glulisine insulin. They have essentially similar properties, and are given 5-10 minutes before food because of their quicker action as compared with regular insulin. Also, they have an earlier and higher peak compared with regular insulin and thus are useful in diminishing immediate post-prandial hyperglycemia. Their shorter duration of action decreases the risk of subsequent delayed hypoglycemia. Recently introduced ultra-rapid acting insulin analog, that is, "fast acting insulin aspart" (Fiasp, Novo Nordisk) has an onset of action at 3-5 minutes and duration of action of 3-4 hours, compared to 10-15 minutes and 3-5 hours, respectively with rapid acting analogs. Ultra-rapid acting insulin analog (administered immediately before meal or up to 20 minutes after meal) and rapid acting insulin analogs (may be administered immediately before meal in selected cases) offer special advantages in toddlers with T1DM who are moody and refuse to eat or throw up after a meal, compared to regular insulin (which carries an increased risk of hypoglycemia in such a scenario). Besides, these formulations are also helpful in school or college going children and teenagers, and office going adults with T1DM who have limited recess time and therefore, observing a gap of 30 minutes before a meal is not feasible. A latest development in this field is "ultra-rapid acting insulin lispro" (Lyumjev, Elli Lilly) which has been approved for use in adults with T1DM and T2DM by the US FDA.

Basal insulin analogs include insulin glargine (U-100 and U-300), insulin detemir and recently introduced insulin degludec. These preparations (especially, insulin glargine and

insulin degludec) are relatively "peakless" and have a sustained action over 24 hours (except for detemir which has a slightly shorter action of 12-24 hours). Most studies show a reduced risk of nocturnal hypoglycemia with basal insulin analogs compared to NPH, though there is only a modest improvement in HbA1c levels in patients with T1DM[5]. Detemir is often used as twice daily injection, while glargine and degludec are frequently utilized as a single daily injection.

Insulin mixing

Regular and NPH insulin can be mixed together for use in a syringe (split-mix regimen). For this purpose, regular insulin should be drawn in syringe first, followed by NPH insulin (see Box 1).

Box 1: Preparing an injection of regular and NPH insulin using insulin vial for split-mix regimen

1. Allow insulin vials to reach room temperature and check that there are no clumps or particles.

2. Turn the NPH bottle on its side and gently roll it between the palms. Do not shake vigorously.

3. Clean the top of the vial with an alcohol swab.

4. Take the NPH insulin vial and inject an amount of air equal to the dose of NPH insulin required. Do not draw insulin. Remove the needle from the vial.

5. Take the vial with regular insulin, clean top with alcohol, and inject air of an amount equal to the regular insulin dose.

6. With the needle still in the vial, turn the vial upside down and pull the plunger to fill the syringe with the desired dose. Remove any air bubbles from the vial.

7. Re-insert the needle into the vial of NPH insulin, slowly draw the correct amount of insulin and remove the needle from the vial.

8. The syringe is ready for injecting.

Abbreviation: NPH: Neutral Protamine Hagedorn

Similarly, rapid acting analogs can be mixed with protaminated regular insulin (NPH) or protaminated analog insulin. Insulin glargine cannot be mixed with any other insulin due to its acidic pH. Pre-mixed formulations of regular insulin and NPH (such as Huminsulin 30/70, Mixtard 30/70, Mixtard 50/50), rapid acting insulin analog and protaminated analog insulin (such as Novomix 30/70, Humalog Mix 25/75, Eglucent Mix 25/75), and insulin aspart and insulin degludec (Ryzodeg 30/70) are readily available in the market.

Insulin strengths

In India, human regular and NPH insulin are available in strengths of 40 units/ml and 100 units/ml in vials. All insulin (regular, NPH, analogs) in pen cartridges have a strength of 100 units/ml.

Insulin color coding

There is a universal color coding for each insulin preparation which has been standardized worldwide. This means that a given preparations of insulin should have a fixed color on the label, regardless of the manufacturer. The color coding for various preparations of insulin has been described in Table II.

Table II: Color coding of different insulin preparations

Insulin preparation	Color code
Rapid-acting insulin analog Aspart Lispro Glulisine	 Orange Dark brown Dark purple
Short acting insulin Regular	Yellow
Intermediate acting insulin NPH	Green
Basal insulin analog Glargine Detemir	 Purple Dark green
Premix Insulin conventional 30/70 50/50 25/75	 Brown Grey Sky blue
Premix insulin analog Aspart plus protaminated aspart (30/70) Lispro plus protaminated lispro (25/75) Lispro plus protaminated lispro (50/50)	 Deep blue Golden yellow Red

Abbreviation: NPH: Neutral Protamine Hagedorn

Storage and stability of insulin

At the time of purchasing the insulin, the expiry date should be checked and it should be ensured that there are no clumps or discoloration of the insulin. Extra vials or cartridges of both short/rapid-acting as well as intermediate/long-acting insulin should always be available at home.

At room temperature (25^0C), insulin will lose < 1% of its potency over a month, while at higher temperatures there will be a greater loss of potency[6]. Exposure to direct sunlight or heat damages insulin and it will lose its potency. Insulin should never be frozen. The unopened insulin vial or cartridge should be kept in the refrigerator shelf for long-term use, where it will retain its potency till the expiry date. Once opened, the insulin vial can be kept at room temperature for up to 1 month in cooler climates or during winter months. In all other circumstances, it would be best to store the opened insulin vial in a refrigerator where it will be stable for 1 month. In hot climates, when a refrigerator is not available, the vials can be kept in an earthenware pot with wet sand or cooled thermos flasks. While travelling, it is convenient to use ready-made "cool packs" which are previously frozen in the ice compartment of the refrigerator. Alternatively, the vials should be kept in plastic wrapper and placed in a cold thermos. During travel, insulin (and other supplies) should always be stored in the personal luggage. During a flight, insulin should not be placed in the check-in luggage since it may be exposed to extremes of temperature (see chapter on "Special group-Pregnancy, Travel and Surgery"). It should be always be checked that the electrical supply is adequate and insulin is appropriately stored at the medical shop from where insulin is procured.

Unopened insulin cartridges/disposable pens can be stored in the refrigerator until their expiry date. Once in use, they can be stored at room temperature (below $25\text{-}30^0$C) for 1 month. In warmer climates, they can be stored in the refrigerator (without needles attached)

for up to 1 month. Insulin pens should never be stored with the needles attached since air may be drawn in.

Insulin needles

The thickness of skin (epidermis plus dermis) has not been found to vary significantly with age, body mass index, ethnicity and gender in adults with diabetes. The mean skin thickness by ultrasound measurements is about 2.2 mm. However, since subcutaneous tissue thickness varies with body mass index, lean individuals are at increased risk of intramuscular injections with longer needles. The needle length should therefore be selected accordingly and in selected individuals, the risk of intramuscular injection may be further minimized by: a) lifting a fold of skin before injecting, and b) injecting at an angle of 45-60^{0}C instead of 90^{0}C. The length of needles recommended for injecting insulin in most children and adults is 4-6 mm. For extremely lean individuals, a skin fold should be raised even with 4 or 5 mm needles. The needles for insulin syringes are available in lengths of 6,8 and 12.7 mm (29-31 G) while pen needles are available in lengths of 4,5,6 and 8 mm (30-32 G)[7].

Injection sites

In most clinical circumstances, insulin is injected subcutaneously. Care should be taken to avoid an intradermal injection, since it is painful and insulin is not well absorbed. In addition, intramuscular injections should be avoided since absorption occurs more rapidly compared to a subcutaneous injection, increasing the risk of hypoglycemia. Preferred sites for injection are abdomen (at least four finger breadths away from umbilicus), anterolateral aspect of thigh, deltoid region and upper-outer quadrant of buttock. Injecting on deltoid region and buttocks require the help of another person, while the patient alone may inject on abdomen and thigh. The forearm and calves should never be used for insulin injections. In general, the same region should be used for injection at different times of the day, but the exact sites should be changed daily (e.g. moving 0.5-1.0 inch from a previous site in a clockwise or anticlockwise manner on one quadrant of the abdomen or one half of the thigh). In young children, the deltoid region and buttocks should be avoided. This is because of the small muscle mass in the arms and proximity to sciatic nerve in the gluteal region. Injections in abdomen result in faster absorption and are less affected by exercise. Hence, the site is suitable for injecting faster-acting insulin preparations. Absorption from the thigh is slower, but can increase if the legs are involved in exercise. Hence, injection at this site should be avoided when it is likely that the running or similar vigorous exercise will be performed, since this may lead to hypoglycemia.

Injection site pain

Pain from insulin injection can be reduced by using smaller and narrow gauge needles, changing needles after a single use (where possible), avoiding injection of cold insulin (taking insulin out of refrigerator about 30 minutes before injecting) and using insulin injection aids and distraction techniques. Insulin needles are coated with silicone to make the injection virtually painless; use of an alcohol swab for cleaning the site and injecting before the area is dry may lead to loss of needle's silicone coating and make the injection painful. The site chosen for insulin injection should be clean and dry; if visibly dirty, it can be cleaned with soap and water, however, use of alcohol swab to clean the site is not recommended. Besides, while changing needle after a single use is helpful to reduce

the pain associated with the repeated use of a blunt needle, it may not be cost-effective, especially in a resource constrained setting like ours. Therefore the cost-effective practice of "multiple use of needles till the tips feel blunt" may be employed.

Side effects of insulin therapy

1. *Hypoglycemia:* Hypoglycemia is the most frequent side effect of insulin treatment and is a major deterrent in achieving tight glycemic control. While prescribing insulin, patient should be clearly explained about the symptoms of hypoglycemia, its management and possible factors (such as exercise, delayed or skipped meals) which can cause hypoglycemia.

2. *Weight gain:* Weight gain may occur due to improved glycemic control, recurrent hypoglycemia leading to increased hunger, and direct lipogenic effects of insulin on adipose tissue.

3. *Lipohypertrophy and lipoatrophy:* Lipohypertrophy occurs due to injection of insulin at the same site and repeated use of a blunt needle. Since the lipohypertrophic site is relatively painless, patient prefers to inject insulin at the same site, leading to further hypertrophy and variable insulin absorption. Injection sites should be examined periodically by both physician and patient, especially in setting of unexplained blood glucose variability. Rotation of sites should be strictly adhered to and needle changed periodically (ideally after each injection) to prevent this condition. Lipoatrophy, defined as localized loss of fat is a rare phenomenon in the current day due to introduction of purified insulin preparations.

4. *Insulin site infection* (see chapter on "Acute complications-Diabetic Ketoacidosis, Hypogycemia and Infections").

Insulin delivery devices

Insulin syringes: In India, insulin syringes with two different markings viz. 40 IU/ ml (U-40) and 100 IU/ml (U-100) are available. U-40 syringe has a red cap and markings upto 40 at interval of one unit, while U-100 syringe has an orange cap with markings upto 100 at interval of two units (each division of U-40 and U-100 syringe equals one unit and two units of insulin respectively). It is important to ensure that the patient uses the correct insulin syringe- 40IU/ml for U40 insulin vial and 100IU/ml for U100 insulin vial.

Disposable plastic insulin syringes are designed for single use. Reuse should be avoided as far as possible since it may result in infections. If this is not feasible due to high cost, the syringes should be changed daily. Used needles and syringes should always be cut and then discarded into a tin or plastic container which cannot be tampered with.

Injection aids include subcutaneous indwelling catheters which are useful to overcome multiple pricks and resulting pain. Automatic injection devices and jet injectors are other options for insulin injection in children. These are only required in special cases where the child or adult is very apprehensive of conventional injections.

Pen devices: Pen devices contain insulin in pre-filled cartridges. Pens may be re-usable with separate insulin cartridges, or may be available as pre-filled disposable pens. Half unit pens are available and are useful for giving small doses in young children. With a pen device, there is no need to draw up insulin; hence chances of inadvertently taking a

wrong dose are minimized. Also, the risk of contamination of insulin is reduced. It is far more convenient to carry the pen device to school, work place or travel compared with syringes and insulin vials. The main disadvantage is higher costs compared to insulin vials. In addition, administering regular and NPH insulin in a single injection (in the context of split- mix regimen) is not possible with a pen device.

Insulin infusion device: An insulin infusion pump essentially consists of an insulin reservoir and a pump[8]. The insulin reservoir is connected to a cannula with a needle which is inserted subcutaneously at one site in abdomen for 2-3 days. Most insulin infusion pumps use rapid acting insulin analogs (aspart, lispro and glulisine) for continuous insulin delivery by subcutaneous route. The rate of insulin infusion is programmable by the patient, using the in-built software. The patient (in discussion with treating physician) can set and adjust insulin infusion rate for basal coverage which can be further divided into multiple segments and administer bolus doses of rapid acting insulin via the pump device immediately before a meal (or snack). The device can be worn by the patient e.g. on a belt. The newer insulin pump devices are able to communicate with a continuous glucose monitor system (CGMS) and utilize CGMS glucose values to temporarily suspend insulin delivery before an episode of hypoglycemia (threshold suspend insulin pump, Medtronic MiniMed 530 G) and adjust basal insulin infusion rates via an in-built algorithm (hybrid closed loop insulin pump, Medtronic MiniMed 670G).

Insulin injection technique

Insulin taken out from the refrigerator should be allowed to come to room temperature before injecting (approximately 30 minutes). Before injection, it has to be ensured that no air bubbles are sticking in the needle. Insulin should never be given through clothing, a practice not uncommon among young adolescents. Cleaning of the skin with an alcohol swab is not essential since most insulin preparations contains anti-bacterial agents which inhibit growth of bacteria commonly found on skin and the use of alcohol may lead to loss of silicone coating of insulin needles (see above). However, if the site is visibly dirty, it should be cleaned with soap and water and allowed to dry before injecting. Insulin injection devices should never be shared. The details of the drawing insulin and the injection technique are provided in boxes 1-3.

Box 2: Preparing an insulin pen for injection

1. Attach a fresh pen needle to the pen. Remove the cap from the needle.
2. In case of pen with NPH insulin, slowly mix the insulin by inverting 5 times.
3. Remove 2 units of insulin and inject into the air to prime the pen.
4. Turn the dial on the pen to the prescribed dose.

Abbreviation: NPH: Neutral Protamine Hagedorn

Insulin dose

An optimal insulin dose is one which will achieve good glycemic control without frequent hypoglycemic episodes. With an appropriate dose, a child should be able to have appropriate growth and development. During the initial presentation, total daily insulin dose may be high due to increased counterregulatory hormones and the suppression of insulin secretion due to glucotoxicity. A few weeks or months after diagnosis, the dose may decrease ("honey moon phase"), with a requirement < 0.5 IU/kg/day. This phase lasts for

> **Box 3: Insulin injection technique**
>
> 1. Select an appropriate injection site (always rotate sites).
> 2. Make sure that the skin is clean. In case, the site is visibly dirty, clean with soap and water and allowed the area to dry before injecting.
> 3. Pinch 1-2-inch portion of skin and fat between the thumb and first finger.
> 4. With the other hand, hold the syringe or pen like a pencil, insert into the skin at a 45^0 angle (children and adolescents) or perpendicularly (most adults), and inject with one motion.
> 5. Push the plunger steadily with the thumb until the insulin is fully injected. Keep the needle in the skin for 10-15 seconds.
> 6. Remove the needle. If needed, press the injection site for 5-10 seconds to prevent the insulin from leaking out.
> 7. Remove the needle from the syringe/pen and dispose in tin or plastic box.

some weeks or months, after which requirement increases and a pre-pubertal child requires nearly 0.7-0.9 IU/ kg/day. During puberty, the requirement often increases (1.2-2 IU/kg/day), due to increasing insulin resistance resulting from higher levels of growth hormone and sex hormones and gradually reduces after puberty. In addition, insulin requirement differs in each individual and varies at different times of the day and in relation to meals and exercise.

Other major factors which can affect insulin requirements are body weight, stress, underlying infections, renal impairment and adrenal insufficiency and concomitant autoimmune disorders, hypothyroidism and celiac disease.

Insulin regimens

The aim is to mimic as closely as feasible the physiological action of insulin in relation to the time of the day, including meals, snacks and exercise, and to avoid hypoglycemia. This can be achieved by different insulin regimens:

1. Split-mix regimen

In this regimen, both short acting (regular) insulin and intermediate acting (NPH) insulin are given in the morning before breakfast and before dinner. Approximately half of the total daily dose (TDD) is given as basal insulin and remaining as prandial insulin. Patients on this regimen require approximately 2/3rd of TDD in the morning and the remainder at night. This regimen has the advantage of reducing insulin injection pricks to 2 times/day. However, the morning NPH insulin peak is often inadequate to cover lunch and tea time snacks, while there is frequent pre-lunch hypoglycemia (due to combined effect of both regular and NPH insulin). In addition, the scope for adjustment of insulin is limited and it is essential that snacks and meals, specially lunch, do not vary in time or quantity. Hence, this regimen is not ideal for most children and adults with T1DM.

2. Pre-mix regimen

Pre-mixed insulin preparations containing short acting insulin (or rapid-acting insulin analog) and NPH insulin (or protaminated insulin analog) in a fixed ratio (30:70; 25:75; 50:50) are ready to use, commonly available, cheap and effective. However, because of a fixed ratio, the dose of short and intermediate acting insulin cannot be adjusted

separately, making them a less preferred choice in patients with T1DM. Despite this major limitation, premixed insulin given twice daily before breakfast and before dinner along with a short acting insulin administered before lunch is a reasonable option in a large number of patients with T1DM. This is especially relevant in a resource poor country like India, as a well as a needle phobic society. This regimen brings down the prick count from 4 to 3 per day (compared to basal-bolus regimen) and also results in better compliance and significant reduction in treatment costs. It is a good practice to resuspend the premixed insulin preparation by gently shaking or rolling the pen or vial before injection.

3. Intensive insulin regimens

These regimens aim to replicate normal insulin secretion by providing separate basal and prandial insulin doses, and are now recommended in all age groups, even young children with T1DM. Patient education and motivation is essential for their success.

a) Basal bolus regimen: multiple daily insulin injections (MDII)

Here basal insulin (intermediate-acting or long-acting analogs) is injected once or twice a day and short-acting insulin (regular or rapid-acting analogs) is given before each major meal (and whenever a large snack is eaten). Nearly 40-60% of TDD is given as the basal analog (preferable if patient can afford) or as intermediate- acting NPH insulin. The remaining dose is given as multiple boluses of regular insulin or rapid-acting insulin analog in 3-4 or greater number of divided doses. The dose of basal insulin is adjusted depending upon the fasting glucose while the bolus doses are adjusted by levels of post-meal glucose and postprandial glucose excursion. The control achieved with this regimen is close to that with continuous subcutaneous insulin infusion (CSII) and there is considerable flexibility in the timing and quantity of meals and exercise[9,10]. However, the frequency of severe nocturnal hypoglycemia may be higher than CSII. The expenses involved in MDII are considerably lower than for CSII. With patient/family education and motivation, it can be successfully used in smaller towns and even in rural areas, where lesser resources are available and technical back-up required for CSII is not available.

b) Continuous subcutaneous insulin infusion (CSII)

This topic will be discussed only in brief. CSII provides the most physiological insulin replacement for patients with T1DM, especially when it is combined with CGMS input. It has been recommended for all age groups, including children[11], but should only be used if the patient and family is motivated, willing to test glucose frequently by finger-prick or CGMS, and if adequate resources are available. Studies and meta-analyses suggest that it provides slightly improved glycemic control and, importantly, a reduced frequency of severe nocturnal hypoglycemia[9,10,12] compared with MSI. A Cochrane review suggests that CSII provides improved HbA1c when compared with MSII [-0.3% (-0.1-0.5%)] in children and in adults with T1DM[10].

Careful selection of patients, constant education and regular monitoring are essential for the success of pump therapy. Unless the patient and family are motivated and agree to monitor capillary glucose 4-6 times per day by finger prick or by CGMS, and to adjust insulin doses by giving appropriate boluses, glycemic control is unlikely to improve on CSII. Patients who may be selected for CSII include those with brittle diabetes, recurrent hypoglycemia and/or hypoglycemic unawareness, persistent fasting hyperglycemia due to "dawn phenomenon", women planning pregnancy or pregnant women with type 1

DM (to intensify glycemic control) and children/adolescents who desire greater flexibility in their lifestyle while being on insulin therapy. The costs of CSII should be discussed with the patient and family since it considerably greater than MSII, especially if used along with CGMS. In addition, technical resources for CGMS are not available in many cities in India and there is a paucity of pediatricians or physicians who are familiar with CSII use.

All insulin pumps currently use rapid-acting insulin analogs. Insulin is delivered continuously at a basal rate throughout 24 hours, though the rate is changed at different times. Higher doses are required in early morning after 4 AM (due to insulin resistance caused by release of counter regulatory hormones), while lower doses are required earlier at night, during the day, and at times of exercise. Insulin boluses are given before each meal and snack (meal bolus) in quantities which are decided by the patient or care-giver depending upon the pre-meal glucose level, carbohydrate content of the meal, and exercise being considered.

In general, pumps to deliver CSII may be either "open-loop" or "closed-loop". In the former, insulin is infused at variable basal and bolus rates which are set by the user. Glucose is measured separately either using multiple finger pricks or using CGMS, and rates of bolus insulin are decided by the patient using various "bolus calculators" which may be incorporated into the pump or available separately. Newer pumps can use information received from CGMS to automatically suspend insulin infusion for a short time period once the glucose has a decreasing trend or approaches hypoglycemic levels. More recently, "hybrid closed loop" insulin pumps are available, which utilize the glucose values available through CGMS to automatically increase or decrease basal insulin delivery rates. However, the bolus insulin dose is still decided by the patient. Recent studies suggest that their use may results in lower frequency of hypoglycemic episodes[13].

The risks associated with use of CSII per se are diabetic ketoacidosis (DKA) and catheter site infection/contact dermatitis. It should be remembered that DKA may occur rapidly in setting of interruption of insulin supply due to technical failure in CSII, since the action of rapid acting insulin used in the pump lasts for only few hours. It is therefore recommended that a patient using CSII should have back-up insulin for subcutaneous injection in case of pump malfunction.

Insulin dose adjustments

Insulin dose adjustments should be performed to achieve target blood glucose and HbAIc levels. Adjustments should be made based on daily pattern of blood glucose levels, food consumption and exercise (see chapter on "Monitoring of metabolic control"). Adjustment of doses should be carefully done during exercise and sick days. During the times of acute illness, in addition to other aspects of therapy (increased fluids, frequent monitoring of blood glucose, testing urine ketones), increased regular or rapid-acting insulin (5-10% of TDD) at 4-6 hourly intervals is often required, in addition to the daily insulin dose (also see "Sick Day Guidelines" in on "Education").

Insulin-carbohydrate ratio (ICR) and insulin sensitivity factor (correction factor):

The carbohydrate content of meal is the major dietary component which will produce rapid elevation in blood glucose. Hence, the insulin dose has to be adjusted to deal

with differing amounts of carbohydrate intake in a meal. The approximate amount of carbohydrate which will be covered or disposed of by 1 unit of short acting insulin (ICR) can be calculated as: 450 or 500 divided by TDD for regular insulin or rapid acting insulin analogs, respectively. In addition to carbohydrates, fat and protein content of the meal also affect late post-prandial glucose levels, though to a lesser extent. Insulin sensitivity factor, defined as amount of blood glucose reduction (mg/dl) expected with 1 unit of short acting insulin, is calculated as: 1500 or 1800 divided by TDD for regular insulin or rapid- acing insulin analogs, respectively. The glucose level above the desired pre- meal glucose level is calculated (ambient blood glucose-desired pre-meal blood glucose) and divided by the insulin sensitivity factor to derive the supplemental (or correctional) insulin required.

Summary

All children and adults with T1DM require insulin as soon as they are diagnosed and continuously thereafter throughout life. Insulin therapy has constantly evolved over the last 100 years. While insulin analogs provide increased flexibility and probably a reduced risk of hypoglycemia, their use is associated with significantly increased treatment costs. The usage of these agents should therefore be individualized to settings where there is a distinct advantage associated with their use such as in toddlers with fussy eating patterns, school or college going children and teenagers with limited recess times, and patients with nocturnal or delayed hypoglycemia on conventional insulin preparations. Physiological insulin regimens, either MDII or CSII, should be used as far as feasible in all age groups, including young children. CSII provides the most physiological insulin delivery, but it its use in Indian setting is limited by cost, technical expertise and healthcare provider awareness. The level of motivation and education and financial resources available with the patient and family should be taken into account when deciding which insulin and regimen to use.

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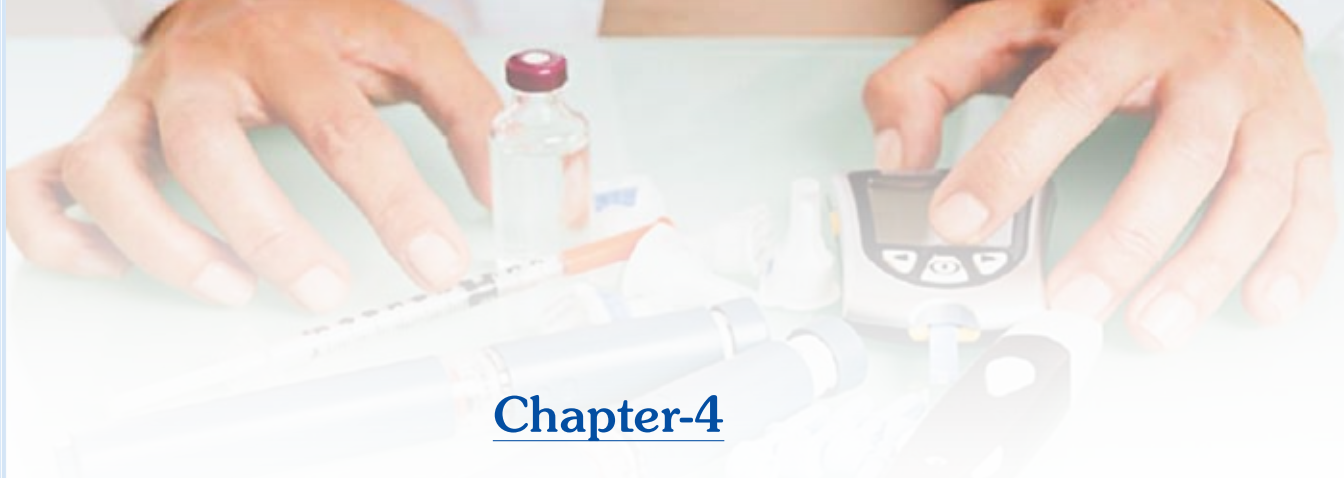
Chapter-4

Monitoring of Metabolic Control

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Introduction

Blood glucose monitoring is a key factor that predicts glycemic control in patients with type 1 diabetes mellitus (T1DM). Diabetes Control and Complications Trial (DCCT) trial provides evidence that achieving good glycemic control in the initial years of T1DM results in reduced incidence of macrovascular and microvascular complications. This foregrounds the importance of achieving near-normal glycemic status, especially during the early years. This chapter highlights the various aspects of monitoring in patients with T1DM.

Self-monitoring of blood glucose (SMBG)

Glycemic control for patients with T1DM of any age should be assessed based on frequent SMBG. SMBG is an intrinsic part of intensive therapy in T1DM. The rewards of SMBG are manifold: a) it helps to supervise immediate and daily blood glucose control, b) it aids to ascertain immediate and daily insulin requirements, c) it guides insulin adjustments to decrease fluctuations in blood glucose levels, and d) it facilitates timely management of hypoglycemia and hyperglycemia. SMBG not only allows modulation of doses and timing of insulin, but also timing and content of meals and snacks based on blood glucose results. It is also important for patients with T1DM not managed with intensive insulin therapy, although, such patients may require somewhat less frequent testing[1,2].

The American Diabetes Association (ADA) recommends that patients with T1DM should monitor capillary blood glucose prior to meals and snacks, at bedtime, occasionally postprandial, prior to exercise, when they suspect low plasma glucose, after treating low plasma glucose (till blood glucose is normal), and before starting any critical tasks such as driving[3]. In addition, blood glucose should be checked intermittently (every 1-2 weeks) at 1-3 am for nocturnal hypoglycemia, and frequently during intercurrent illness and travel. SMBG helps to identify hypoglycemia much before the appearance of symptoms, thereby avoiding overcorrection-related hyperglycemia. SMBG enables patient (and physician) to understand the response to treatment, and make appropriate treatment decisions.

Frequent SMBG has been demonstrated to improve glycemic control, and to reduce the absolute frequency of severe hypoglycemic episodes in children[4-6]. It is important to remember that frequent SMBG may translate into improved glycemic control only when these values are used in a systematic manner (by patient and physician) for making decisions on insulin dose adjustments, and/or meal/snack timing and content. Zieger et

al. found that the frequency of SMBG is highest in children under the age of six years, which decreases as the child grows older[4]. The predictors of lower frequency of SMBG include low self-esteem, higher levels of stress, and inadequate parental support. The presence of psychosocial support and parental supervision has been found to improve the frequency of SMBG in older children.

Equipment

A wide variety of glucometers are available in the market for SMBG testing. The use of a glucometer does not require much technical expertise and can be used easily by adults as well as children. Impedance-based glucometers are considered to be more accurate compared to colorimetric-based glucometers. Most glucometers utilise one of the three enzymatic reactions-glucose oxidase, hexokinase and glucose dehydrogenase. Glucose dehydrogenase may give false positive readings with non-glucose sugars present in pharmaceutical preparations such as peritoneal dialysis solution (icodextrin) and intravenous immunoglobulin[7,8]. Such erroneous readings may result in potentially fatal dose calculation errors.

Accuracy of glucometers

Although glucometers analyze glucose in whole blood, many meters provide a plasma equivalent value using a built in algorithm (to convert whole blood glucose to plasma glucose). Their readings are most accurate when blood glucose ranges from 60-160 mg/dl. For blood glucose values both above and below this range, larger deviations from venous blood glucose values have been observed. Additionally, SMBG values approximate the venous glucose values better in the fasting state; in the postprandial state, the capillary values may be higher by around 10–20%. It is advisable to cross-check SMBG values with venous plasma glucose values, when in doubt. ADA has recommended an intermediate goal of limiting error (for 95% of glucometer values) to < 15% at glucose concentrations $\geq$ 100 mg/dl and < 15 mg/dl at glucose concentrations < 100 mg/dl[9].

Coded versus non-coded meters

There may be a lot-to-lot variation in the amount of enzymes in blood glucose strips, resulting in variation in amount of electric current produced per unit of glucose[10]. To minimize this variation, a code is provided that calibrates the meter for that batch of strips. However, miscoding errors are frequent, and about 16% patients miscode, leading to errors as high as 30%. This may result in incorrect insulin dosing, and hypo or hyperglycemia. With improved enzyme purification methods, and better quality control, the blood glucose strip standard variation has reduced dramatically. This has resulted in decline in availability of coded meters and emergence of non-coded meters, which are accurate and patient- friendly.

Control Solution (CS)

CS contains a known amount of glucose, and when applied to the test strip it aids in assessing the working status of glucometer. Although the usage of CS is clearly stated to improve accuracy of SMBG, storage and prevention of decline of glucose in the solution is itself an issue of concern[11,12.] Additionally, it is not readily available for all glucometers.

Analytical and pre-analytical variables

Analytical variables (intrinsic to glucometer and glucose strips) and pre-analytical variables (related to patients) could affect accuracy of SMBG. Briefly, the common causes for inaccurate readings by glucometer include use of expired tests strips, improper condition of strip storage (extremes of temperature or humidity), unwashed hands, and low or high hematocrit and hypotension. Blood volume required for glucometers is as low as 0.3 µl[13]. For the visually impaired, size of the screen and font sizes need to be adjusted. The option of using a talking meter that provides verbal guidance on the process is also available. Dexterity is another important issue that needs to be considered in patients advised SMBG.

Reducing pain with SMBG testing

Pain with SMBG may be reduced by rotating fingers, using side of fingers rather than the central fat pad, using fresh lancet for each prick, using lancet with depth gauge and adjusting it to a minimal setting which gives an adequate blood drop, using smaller gauge lancet and using alternate sites for testing (discussed in next section).

Sites for testing

Alternate testing sites have been advised for minimising pain associated with lancing for blood drop. These include the palm of the hand, the forearm and the thigh. Compared to the fingertip, the density of pain receptors at these sites is much lower, resulting in reduced pain with testing. Fineberg et al. demonstrated that alternative site testing (using arm) provides accurate results, while being less painful compared to the finger prick testing[14]. In the fasting state, glucose readings from alternative sites are nearly similar to the fingertip. However, these sites should not be relied upon at times when blood glucose is expected to change rapidly (such as after meals, insulin and exercise). Additionally, hypoglycemia identification is difficult, and these sites should also not be used at the time of suspected hypoglycemia.

Timings of SMBG

Both pre-meal and post-meal (2 hours after beginning of the meal) blood glucose values should be monitored, however, their significance may vary from one patient to another. Individuals with HbA1c of less than 8-8.5% need to check their postprandial glucose levels more often, since these contribute disproportionately to the dysglycaemia. On the other hand, patients having HbA1c above this threshold should concentrate on normalizing the fasting and pre-prandial values before attempting control of postprandial hyperglycemia[15,16]. Blood glucose should be checked whenever hypoglycemia is suspected, and with re-evaluation after correcting the hypoglycemia (till the time normal blood glucose level is achieved). Additionally, monitoring of blood glucose at 1-3 am (for nocturnal hypoglycemia), before and during exercise, before performing critical tasks (such as driving), frequently during an intercurrent illness and travel is important.

Targets for SMBG

The blood glucose targets recommended (Table I) by International Society of Pediatric and Adolescent Diabetes (ISPAD) are: pre-meal: 70-130 mg/dl, post- meal: 90-180 mg/dl and pre-bed: 80-140 mg/dl[17].

Table I: Blood glucose targets in children and adolescents with T1DM according to various professional bodies

	ISPAD [17]	NICE [18]	ADA [19]
Pre-prandial (mg/dl)	70-130	70-126	90-130
Post-prandial (mg/dl)	90-180	90-162	-
Pre-bed (mg/dl)	80-140	70-126	90-150

ADA: American Diabetes Association, ISPAD: International Society for Pediatric and Adolescent Diabetes, NICE: National Institute of Clinical Excellence, T1DM: Type 1 Diabetes Mellitus

National Institute of Clinical Excellence (NICE) recommends pre-meal, post-meal and pre-bed blood glucose targets of 70-126 mg/dl, 90-162 mg/dl and 70-126 mg/dl respectively, while ADA recommends pre-meal and pre-bed blood glucose targets of 90-130 mg/dl and 90-150 mg/dl respectively[18,19]. However, it should be remembered that these blood glucose targets need to be individualised, and less stringent targets may be suitable for certain group of individuals (such as those with recurrent hypoglycemias, hypoglycemia unawareness and other comorbidities).

Maintaining and interpreting a blood glucose log

The frequency of SMBG may vary from 4-6 times per day in young children, especially the ones with poor glycemic control. A more liberal SMBG of 2-3 times per day may be advocated in children with a better glycemic control. Patterns, as opposed to intermittent problems, are best identified if there are a relatively large number of measurements every day. However, due to the substantial financial burden associated with regular 7-point blood glucose charting, less frequent glucose charting, with rotation of timings of blood glucose charting should be provided as an alternative option, especially in stable patients with T1DM[20]. In a subgroup of patients, cost constraints may hamper monitoring of even 1-2 blood glucose readings. In such a scenario, the Indian Society of Pediatric and Adolescent Endocrinology (ISPAE) recommends that testing could be reserved for sick days and episodes of hypoglycemia, and a "bare minimum" testing of 2 to 4 times per day for 2 to 3 consecutive days in a month could be used to evaluate blood glucose patterns[21]. In a setting where patient cannot even afford to perform the "bare minimum" testing, one may have to rely upon monitoring using urine glucose strips. The colour obtained on the urine strip should be indicated against the time of performing test on a standard blood glucose monitoring chart. For an illiterate patient who may have difficulty in writing the colour name, coloured pencils could be provided to indicate the appropriate colour. Urine glucose will be positive only if blood glucose is more than 180-200 mg/dl, and it will not be able to detect hypoglycemia. It should be remembered that urine glucose provides an extremely crude method of evaluating glycemic control that should only be used as a last resort in patients with significant financial constraints.

The documented SMBG readings should be reviewed during each hospital visit. Apart from blood glucose readings, the log should contain a column for remarks and insulin dose injected on a given day. The remarks should address the possible reasons for aberrant glucose values-both hyperglycemia (such as eating outside, less dose of insulin injected, lack of physical activity, fever) and hypoglycemia (such as delayed meal timings, decreased food intake, vomiting, excessive exercise, increased dose of insulin injected). It is also important to correlate SMBG log with HbA1c values. A lack of correlation between

the two may be indicative of faulty glucometer/strips, incorrect documentation by the patient and/or family members, or presence of factors decreasing the utility of HbA1c as a marker of glycemic control (such as iron deficiency anemia, hemoglobinopathy, hemolysis). Many patients check blood glucose using a glucometer, but fail to enter these values in SMBG log or only enter values which are near-normal. It is important to counsel such patients on importance of SMBG documentation in achieving good glycemic control.

Apart from logbooks, today's technology offers other options such as use of downloadable software available with the meter that displays the data in a usable format. Some smart phone apps are available to enter glucose readings and other useful diabetes information (such as food intake and exercise). These include- mySugar (iPhone and Android), Glucose Buddy (iPhone and Android), On Track Diabetes (Android), and Glucool Diabetes (Android). Patients and/or caregivers can also be trained to look for patterns and also be encouraged to make minor alterations in their insulin dosage accordingly.

Patient education strategies are crucial in assuring successful management of SMBG feedback. The frequency of SMBG testing often decreases over time, because patients do not know how to respond to a high value, and may perceive that the treating doctor is more interested in HbA1c values than glucose logs[22]. In a study, the use of SMBG was successful in reducing A1C values when accompanied by training of patients and clinicians to collect and interpret SMBG profiles[23].

Insulin algorithms

Once a basic regimen of eating, exercise, and insulin dosing has been established, there could still be a day-to-day variability in blood glucose values. This may be effectively treated using an insulin algorithm in which the pre-meal dose of short-acting insulin is adjusted according to the blood glucose value and, for patients who use carbohydrate counting, anticipated carbohydrate content of the meal. Any changes in exercise can also be included in this calculation. The adjustments should be small in patients who are very sensitive to insulin or who are taking low doses of insulin (as with a subcutaneous continuous insulin infusion via a pump).

Monitoring and interpretation of urine and blood ketones

Urine ketones

Strips and tablets may be used for quick monitoring of urine ketones at the bedside. Nitroprusside test is commonly used for ketonuria; however, it can only estimate acetone and acetoacetate, and not beta-hydroxybutyrate. Presence of ketonuria in association with hyperglycemia serves a clue for metabolic decompensation. IDF recommends that in limited care settings, urine ketone test strips should be available and testing performed during illness with fever and/or vomiting, persistent polyuria with elevated blood glucose (more than 250 mg/dl), especially with abdominal pain or rapid breathing. Urine ketones may also be elevated in patients with T1DM as a physiological metabolic response to low carbohydrate diet (e.g. Atkins diet), during pregnancy, following prolonged exercise, and in those with alcohol intoxication. False positive ketonuria may be encountered in those using drugs like penicillamine, captopril and mesna. False negative ketonuria is rarely encountered in patients with DKA and shock, as liver is the site of conversion of ketones to beta-hydroxybutyrate[24].

Blood ketones

The ratio of beta-hydroxybutyrate to acetoacetate, which is approximately 1:1 in normal subjects, can soar to as high as 10:1 in DKA[25,26]. Therefore, in ketosis, it is preferable to measure beta-hydroxybutyrate directly, whenever feasible. This can be accomplished either in the laboratory or by using the point-of-care ketone meters[27,28]. Home blood ketone monitoring is now possible with some glucometers (such as Abbott Freestyle), where the ketone strip is used (in a way similar to blood glucose strip) to provide blood ketone (beta-hydroxybutyrate) value (in mmol/L). Blood ketones should be always be interpreted along with concurrent blood glucose values. Blood ketones level <0.6mmol/L is considered normal. A level between 0.6 and 1.5 mmol/L indicates mild elevation. In such a scenario, increased fluid and carbohydrate intake should be advised if blood glucose is less than 180 mg/dl, while if blood glucose is more than 180 mg/dl, additional dose of insulin may be required. If the ketone levels are between 1.5 and 3 mmol/L, there is a high risk for ketosis. Such patients need more fluids and additional dose of rapid acting insulin immediately. Blood ketone level more than 3 mmol/L is usually associated with acidosis, and warrants emergency admission and management for DKA.

It is important that patients with T1DM keep blood ketone (or urine ketone) strips at home for use during a sick day, and periodically check that these are not beyond the expiry date.

HbA1c and other glycated products

HbA1c measurement should be performed at least every 3 monthly in patients with T1DM[17]. The measurement should be performed using an assay which is certified by National Glycohemoglobin Standardisation Program (NGSP), and standardised to the DCCT reference assay. For children and adolescents with T1DM, a HbA1C target of <7% is recommended by ISPAD, while NICE and ADA recommend a target of <6.5% and <7.5% respectively[17-19]. However, these targets need to be individualised, and each patient should be treated to achieve a value as close to normal as possible whilst avoiding severe hypoglycemia as well as minimising frequent mild to moderate hypoglycemia. The aim is to avert the long- term microvascular and macrovascular complications of diabetes, while also avoiding abnormalities associated with acute hypoglycemia and the associated neurological consequences.

Children below six years of age are at especially high risk of having adverse neurologic outcomes with severe hypoglycemia. Because they cannot self-identify hypoglycemia, caution need to be exercised in achieving target HbA1c in such individuals. In fact, many paediatric centres report that the average HbA1c is lowest in this age-group, reflecting the more complete caregiver involvement at younger ages. As teens advance towards adulthood, targets alike to those of the adult population should be approached, while recognizing that the hormonal alterations and psychological adjustments of adolescence make achieving these targets difficult. Of all age-groups, adolescents are currently the farthest from achieving HbA1c target of < 7.5%, reflecting the diabetes mismanagement that frequently accompanies the increased independence in diabetes care during the adolescent years, along with the effect of psychological and hormonal challenges of adolescence.

Hemoglobinopathies may interfere with HbA1c measurement due to the presence of haemoglobin variants [false high or low result with ion-exchange high-performance liquid

chromatography (HPLC)] or reduced red cell life span (false low result with any HbA1c method[29,30]. Certain hemoglobinopathies such as hemoglobin S (HbS), hemoglobin E (HbE) and β-thalassemia are relatively common in certain population groups in India[31,32]. While HbE is predominantly restricted to tribal population belonging to North-Eastern states, West Bengal, Odisha and Andaman and Nicobar Islands, the distribution of HbS is more extensive, being especially prevalent in central India. Similarly, the prevalence of β-thalassemia is known to be higher in Punjabis who have migrated from West Pakistan. The interference caused by a haemoglobin variant can be addressed by using alternative methods of HbA1c measurement, namely immunoassays (especially for HbE) and boronate affinity HPLC. On the other hand, for accelerated red cell turnover, an alternative non-HbA1c method of estimating intermediate to long-term average glycemic control such as fructosamine, glycated albumin and 1-5 anhydroglucitol should be relied upon. Among these, fructosamine is the most popular; it assesses the glycation of blood proteins such as albumin and reflects glycaemia over the past 2–4 weeks. Although useful in monitoring glucose control, these biomarkers are limited by cost, lack of availability and standardization[30].

Continuous glucose monitoring system (CGMS)

Subcutaneous glucose sensors that continuously measure interstitial fluid glucose levels (CGMS) are available, and approved for use in children. While SMBG provides a snapshot of glycemic data at a given point of time, CGMS provides comprehensive longitudinal data for a given day. CGMS can be of two types- retrospective (professional, masked) and real-time (personal, unmasked)[33]. The data from retrospective CGMS can be downloaded subsequently and reviewed in clinic while real-time CGMS allows real-time assessment of blood glucose fluctuations allowing remedial action to be taken by the patient or caregiver. The term "continuous" and "real-time" are relatively inaccurate since CGMS records glucose every 5 to 15 minutes (not continuous) and interstitial fluid glucose results lag behind blood glucose by approximately 7-15 minutes (not real-time). The CGMS sensor measures glucose in interstitial fluid based on the "glucose oxidase" enzymatic reaction. CGMS can be used alone (in patients on multiple subcutaneous insulin injection (MSII) or with continuous subcutaneous insulin infusion (CSII or insulin pump). Although the use of CGMS benefits patients using MSII and CSII both, the benefit is likely to be higher when used along with insulin pump (CSII), especially a sensor-augmented insulin pump.

CGMS is useful for optimizing glycemic control in motivated patients, and also for management of patients with a history of hypoglycemia unawareness. The improvement in glycemic control with use of CGMS has been shown to occur only in those patients who are committed to wear the device. Patient should be willing to use the device for at least 70% of the time. Therefore, like continuous subcutaneous insulin infusion (CSII) therapy, appropriate patient selection is very important. CGMS is useful for those with any of the following: hypoglycemia unawareness, more than 1 episode per year of severe hypoglycemia with no obviously preventable precipitating cause, frequent (more than 2 episodes a week) asymptomatic hypoglycemia, those with extreme fear of hypoglycemia, hyperglycemia (HbA1c level of 9% or more) that persists despite frequent testing, and pregnancy-associated hyperglycemia. CGMS is also helpful in assessment of glycemic variability, a parameter known to correlate with vascular complications, independent of HbA1c.

The procedure of CGMS sensor insertion is very simple, rapid and painless. The sensor, in the form of a membrane-clad, needle-shaped enzyme electrode, is inserted through the skin (usually upper abdomen) into the subcutaneous fatty tissue to have access to interstitial fluid. The device can be fixed, and usually remains in place for therapeutic monitoring for a period of seven days (varies from 3-14 days depending on the model). For most CGMS devices, the sensor needs to be calibrated with capillary blood glucose readings either four times a day (Medtronic iPro2) or two times a day (Medtronic Guardian Connect, Dexcom G4 Platinum, Dexcom G5 Mobile). The calibration should be done a time when blood glucose is expected to be relatively stable (fasting and pre-meals). Recently, a new CGMS sensor (Dexcom G6) which does not require calibration with capillary blood glucose values has been introduced in the market.

The real- time values can be readily accessed using a reader device and, a detailed assessment of the glucose variability can be analyzed by feeding the data to a computer. The alarm in the device (when using real-time CGMS along with an insulin pump or as a standalone device used along with a mobile app) helps in identifying and predicting low or high blood glucose levels based on the target level set.

The use of CGMS has been found to improve glycemic control, with higher time in target, and reduced number of hypoglycemic events. In the Juvenile Diabetes Research Foundation (JDRF) CGMS study, 322 children and adults with T1DM on intensive insulin therapy (predominantly CSII, 80% of the study participants) were randomly assigned to the use of CGMS or SMBGas a tool for blood glucose monitoring[34]. The primary outcome, change in HbA1c level over 26 weeks period, varied according to the age group (8-15 years versus 15-24 years versus ≥25 years). HbA1c change (0.53%, 95% CI: 0.35%-0.71%) was only found to be significant in adults aged ≥25 years, who also had significantly higher sensor use, compared to the participants belonging to the two other age groups. Similarly, in the DIAMOND study, the use of CGMS (versus SMBG) was associated with greater reduction in HbA1c (1% versus 0.4%, $p<0.001$) and lesser time spent in hypoglycemia (median time with glucose concentration <70 mg/dl: 80 minutes versus 43 minutes, $p=0.002$)[35]. In the HypoDe study, the use of real-time CGMS (n-75) was compared against conventional SMBG (n-74) in individuals with T1DM treated with MSII who had history of impaired hypoglycemic unawareness or severe hypoglycemia during the past one year[36]. The use of real-time CGMS was associated with a significant reduction in number of hypoglycemic events (mean number of events over 28 days reduced from 10.8 to 3.5 in real-time CGMS group versus reduction from 14.4 to 13.5 in SMBG group). Additionally, CGMS use has been found to be associated with decreased fear of hypoglycemia, lower diabetes-related distress and improved quality of life in various studies[37-40].

The lack of accuracy is an issue with CGMS sensors, especially when glucose concentrations are rapidly changing, ascribed to the retarded equilibration between the different physiologic compartments. Most CGMs are least accurate on day 1 of use (owing to the local inflammation) and when blood glucose in the hypoglycemic range[41,42]. Therefore, when taking a decision based on a CGM reading (such as taking extra insulin or else treatment for hypoglycemia), it is advisable to do a finger-prick blood glucose to confirm it. Nevertheless, the accuracy of CGM is acceptable in terms of clinical monitoring of patients with T1DM.

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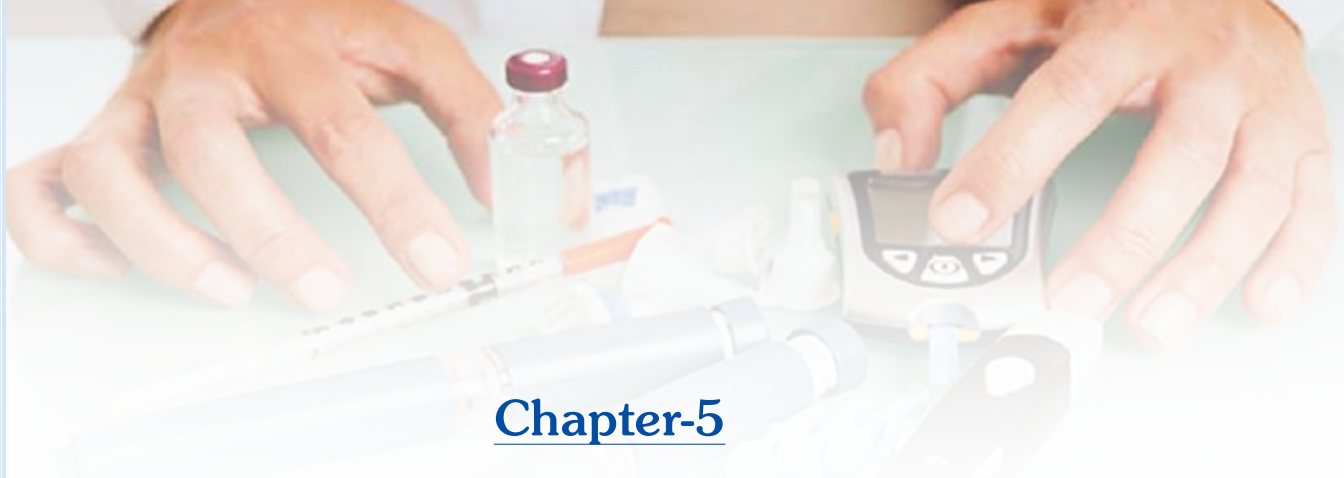
Chapter-5

Acute complications-Diabetic Ketoacidosis, Hypoglycemia and Infections

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Section A - Diabetic ketoacidosis (DKA)

Epidemiology of DKA

Diabetic ketoacidosis (DKA) is a composite metabolic state of hyperglycemia, ketosis and acidosis occurring predominantly in the setting of severe uncontrolled diabetes. Euglycemic DKA, characterized by the presence of ketoacidosis in absence of hyperglycemia (blood glucose <250 mg/dl) has been reported in the setting of pregnancy, alcohol intake, reduced carbohydrate intake and treatment with sodium-glucose contransporter-2 (SGLT-2) inhibitors. DKA is the leading cause of morbidity and mortality in children with type 1 diabetes mellitus (T1DM), with a case fatality rate ranging from 0.15-0.30%[1-3]. In two pediatric intensive care unit (PICU)-based retrospective studies from India involving 68 and 55 children with DKA, mortality was reported at 12.7% and 13.2%, respectively[4,5]. Cerebral edema is the major contributor to morbidity and mortality in DKA. Due to the absence of adequate cerebral autoregulatory mechanisms and increased severity of presentation, young children are predisposed to this potentially fatal complication. Cerebral edema occurs in 0.5-1% of children with DKA and carries a mortality rate of 20-25%, accounting for about 60-90% of all DKA-related deaths in children[6-8]. According to data from developed countries, about 15-70% patients have DKA at the time of diagnosis of T1DM[9-14]. DKA at onset of diagnosis is especially common in children <5 years of age and in children with poor socioeconomic background. The prevalence of DKA at diagnosis was reported to be 28.7% among 2335 Indian youth with T1DM enrolled in the Registry of People with Diabetes with Youth Age at Onset in India (YDR)[15]. The risk of DKA in youth with T1DM varies from 1-15% per patient per year across various studies[16-18]. Omission of insulin is the most common cause of recurrent DKA and such patients (predominantly adolescents) need detailed psycho-social assessment apart from the management of the acute episode[14]. The possibility of using non-injectable "alternate systems of medicine" is a potential contribution to insulin omission in India.

Pathophysiology of DKA

Insulin deficiency coupled with glucagon excess is largely responsible for development of DKA and hyperosmolar hyperglycemic state (HHS) in patients with uncontrolled diabetes[19,20]. A decreased insulin: glucagon ratio results in reduced hepatic activity of phosphofructokinase-2 (PFK-2) and increased activity of fructose-2,6-bisphosphatase. The concentration of fructose-2,6-bisphosphate, a key activator of phosphofructokinase-1 (PFK-1, an enzyme that regulates glycolysis) is thus reduced, resulting in inhibition of

glycolysis and stimulation of gluconeogenesis. Additionally, elevated secretion of other counterregulatory hormones (such as catecholamines, cortisol, and growth hormone) oppose the actions of insulin and contribute to the development of hyperglycemia and ketosis. Since inhibition of lipolysis and ketogenesis is more sensitive to insulin rather than the inhibition of gluconeogenesis, the residual insulin secretion and its systemic action in HHS is enough to prevent the development of significant ketoacidosis but not hyperglycemia[21]. In patients with absolute or relative insulin deficiency, DKA and HHS are usually precipitated by stressful conditions that act in part by increasing the secretion of counterregulatory hormones.

The plasma glucose concentration in HHS is often > 1000 mg/dl, whereas in DKA, it is by and large <800 mg/dl and frequently in the range of 350-450 mg/dl[22]. There are two factors responsible for the lesser degree of hyperglycemia in DKA. Firstly, in DKA, patients present relatively early with symptoms of acute ketoacidosis like dyspnea, abdominal pain, and nausea and vomiting, whereas patients with HHS present late with symptoms of hyperosmolality. Secondly, patients with DKA are relatively young and have a high glomerular filtration rate (GFR), resulting in greater glucosuria than older patients with HHS. The pathogenesis of DKA has been illustrated in figure 1.

Figure 1: Pathophysiology of diabetic ketoacidosis and hyperglycemic hyperosmolar state
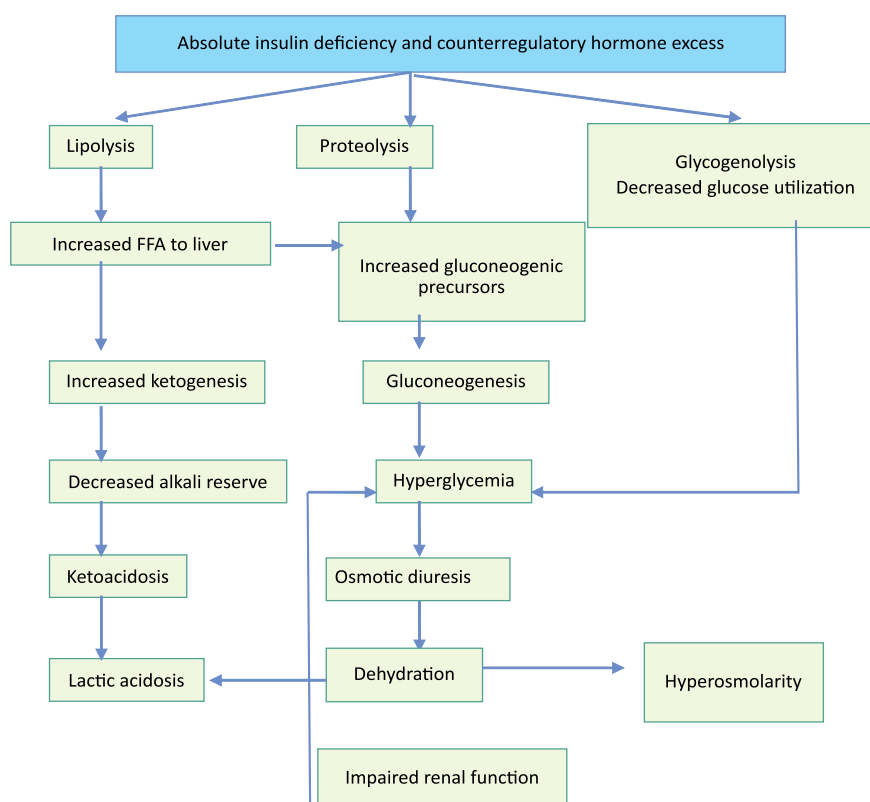
FFA: Free fatty acid

Clinical presentation and precipitating factors

Signs and Symptoms

A history of classical triad of hyperglycemia (polyuria, polydipsia and polyphagia), nocturia, generalized weakness, weight loss despite a good appetite, recurrent vaginal candidiasis

and a history of ants collecting around the child's urine may be present in the days-months prior to the acute episode. As ketoacidosis sets in, nausea and vomiting, abdominal pain, acidotic breathing with peculiar fruity odor and signs of dehydration appear. The patient is often drowsy at the time of presentation, though coma is rare. Infants tend to present with decreased energy and activity, irritability, weight loss, and physical signs of dehydration. A severe diaper dermatitis due to candidal infection is common in infants presenting with DKA.

Physical examination may disclose the following:

- Altered sensorium
- Tachycardia, tachypnea or hyperventilation (Kussmaul's breathing)
- Hypotension, very rarely hypertension
- Increased capillary refill time, poor perfusion
- Acetone odor of the breath reflecting ketosis

Precipitating Factors

A precipitating event can generally be discovered in patients with DKA. Most common precipitating factors are omission of insulin and acute infection. Omission of insulin usually occurs during an inter current illness in patients with poor awareness of sick day guidelines. Intentional omission of insulin is also possible, especially to try non-injectable "alternate systems of medicine". This may also be done with suicidal intent, as an attention seeking measure or as a manifestation of an eating disorder, especially in adolescents with T1DM. In patients using continuous subcutaneous insulin infusion (CSII), mechanical pump failure may be an important cause of DKA, especially in patients using the pump without adequate training and information.

Diagnosis and baseline assessment

DKA is defined by the presence of following[3]:

- Hyperglycemia – blood glucose of $\geq$ 200 mg/dl and
- Metabolic acidosis – venous pH < 7.3 or plasma bicarbonate < 15 mmol/L AND
- *Ketonemia (blood β-hydroxybutyrate $\geq$ 3 mmol/L) and ketonuria (typically urine ketones $\geq$ 2+)

  *A blood ketone (β-hydroxybutyrate) level between 0.6 and 1.5 mmol/L indicates mild elevation, while a level between 1.5 and 3 mmol/L suggests high risk for ketosis. Blood ketone level more than 3 mmol/L is usually associated with acidosis and warrants emergency admission and management for DKA.

Initial laboratory investigations should include plasma glucose, serum electrolytes, blood urea nitrogen, serum creatinine, venous blood gas analysis, and hematocrit. Measurement of blood β-hydroxybutyrate (BHB) should be performed, if possible. Point-of-care blood ketone test meter could also be used for this purpose. Several biochemical parameters may have fallacious readings in the setting of DKA. Plasma glucose may not be elevated in patients with repeated episodes of vomiting, reduced carbohydrate intake or those who have already received some treatment before presentation. Serum sodium can be falsely low due to dilutional hyponatremia resulting from hyperglycemia induced fluid shift from cells. An elevation of serum amylase and rarely, serum lipase may be present, unrelated to acute pancreatitis. Leucocytosis is common in DKA and does not always indicate infection.

Anion Gap (AG) is a very useful measure in calculating the severity of ketosis, and normalization of the anion gap is an indirect measure of the resolution of ketoacidosis. However, it cannot be used as a surrogate for blood pH since it fails to reveal the state of normal anion gap hyperchloremic metabolic acidosis, which may develop during treatment of DKA as a result of administration of chloride containing fluids and loss of potential bicarbonate precursors as ketoanions in urine.

AG is calculated as: AG (mmol/L) = Serum sodium (mmol/L) – [Serum chloride (mmol/L) + serum bicarbonate (mmol/L)] (normal value is 12 ± 2 mmol/L).

The severity of DKA is categorized by the degree of acidosis and is outlined below[3]:

- Mild: pH 7.20-7.29; serum bicarbonate 10-15 mmol/L
- Moderate: pH 7.10 -7.19; serum bicarbonate 5-10 mmol/L
- Severe: pH < 7.1; serum bicarbonate < 5 mmol/L

Differential diagnosis

The differential diagnoses of high anion gap metabolic acidosis have been outlined in Table I.

Table I: Differential diagnosis of high anion gap metabolic acidosis

Diabetic ketoacidosis
Uremia
Lactic acidosis
Methanol, ethylene glycol, ethanol ingestion
Salicylate toxicity

Management of DKA

Management of DKA broadly involves administration of intravenous fluids, intravenous insulin infusion and good supportive management (Table II)

Table II: Broad principles of DKA management

A (airway), B (breathing), C (circulation) of resuscitation
Intravenous fluids (normal saline)
Intravenous regular insulin infusion (after confirming normal serum potassium)
*Intravenous potassium supplementation (after confirming normal urine output) Serum potassium: < 3.3 mmol/L: correct potassium before starting intravenous insulin Serum potassium: 3.3-5.3 mmol/L: potassium supplementation along with intravenous insulin
Serum potassium: > 5.3 mmol/L: potassium supplementation not needed; monitor at regular intervals
Look for and treat the acute precipitating factor (such as infection)
Monitor vitals, hydration status, intake-output, neurological status at regular intervals Monitor blood glucose 1-2 hourly; urea, creatinine, sodium, potassium, bicarbonate, venous pH, urine or blood ketones every 4-6 hourly
Intravenous insulin infusion needed for both hyperglycemia and ketosis once BG <200-250 mg/dl, continue intravenous insulin infusion and replace intravenous normal saline with dextrose based intravenous fluid (DNS or D5W)
Once DKA resolved, and patient accepting orally, shift to subcutaneous insulin with adequate overlap

*Electrocardiography can be used as a surrogate for assessment of tissue potassium levels
 Abbreviation: DNS: Dextrose normal saline, D5W: 5% dextrose

These measures are aimed at correction of ketoacidosis, hyperglycemia, hyperosmolality, hypovolemia and electrolyte disturbances. Like any other emergency, the first principle of resuscitation i.e. the ABCs (airway, breathing, circulation) apply to DKA as well. A decreased level of consciousness may lead to an unprotected airway and compromised breathing. Osmotic diuresis can cause a significant loss of fluid, leading to severe dehydration and circulatory collapse. Furthermore, severe electrolyte derangements significantly increase the risk of life threatening cardiac arrhythmias. Clinical assessment of degree of dehydration and level of consciousness is important and reader is directed to excellent reviews on these topics[23-25].

Fluid management

Fluid management in DKA involves the use of isotonic saline infusion to restore and expand extracellular volume and stabilize cardiovascular status. It should precede administration of intravenous insulin infusion. The use of fluids in the first hour before insulin administration has many advantages: a) it provides an opportunity to check potassium value, b) it prevents worsening of hypotension in a dehydrated patient (due to insulin-mediated shift of fluid from intravascular compartment) c) it decreases serum osmolality, reduces the counterregulatory hormone concentration, and improves hyperglycemia.

A bolus dose of isotonic (0.9%) normal saline is administered at a rate of 10 ml/kg intravenously over an hour or less, and may be repeated if necessary. A simple way of calculating total fluid requirement is outlined here. The sum of maintenance requirement (1500 ml/m2/day) + fluid deficit (calculated as 3%, 6% and 9% of body weight according to severity of dehydration) should be given evenly over 24-48 hours. Isotonic saline is recommended for the first 5-6 hours after which 0.45% saline can be used, provided serum sodium is rising. When the blood glucose falls below 200-250 mg/dl, 5% dextrose is added and at blood glucose levels below 150 mg/dl, 10% dextrose can be added. Addition of 5% dextrose to normal saline may be considered earlier (i.e., after the initial two hours of treatment), if blood glucose drops at a rate exceeding 90-100 mg/ dl/ hour.

Potassium replacement

Potassium deficit in children with DKA is around 3-6 mmol/kg of body weight. Despite the deficit, serum potassium may be elevated at presentation due to hypertonicity, insulin deficiency and metabolic acidosis. In most situations, potassium replacement should be started after initial fluid resuscitation and concurrent with insulin therapy. In case of hypokalemia, potassium replacement may be started after initial fluid resuscitation, but insulin therapy should not be initiated till serum potassium is >3.3 mmol/L. If immediate serum potassium measurements are not available, a bedside ECG may help determine the presence of significant hyperkalemia or hypokalemia at tissue level. Hypokalemia is indicated by the flattening/inversion of T waves, ST segment depression, wide QT interval, and presence of U waves. Tall and peaked symmetrical T waves, prolongation of PR interval, wide and flat/absent P wave, widened QRS complex and sine wave pattern are indicators of hyperkalemia. Initial potassium concentration in the infusate should be 40 mmol/L with subsequent potassium replacement rates based on serum potassium measurements (Table III).

Table III: Potassium replacement in diabetic ketoacidosis

Serum Potassium (mmol/L)	Potassium replacement (mmol/L)
< 3.3	40 – 60
3.3 – 4.3	30 – 40
4.3 – 5.3	20 – 30
> 5.3	0 – 20

Insulin therapy

Although fluid replacement by itself lowers blood glucose, insulin therapy is required to lower it further, and suppress lipolysis and ketogenesis. Intravenous insulin bolus at start of the therapy is not recommended, since it may increase the risk of cerebral edema[26,27]. Intravenous insulin infusion should be administered to all patients with moderate to severe DKA with serum potassium >3.3mmol/L. Regular insulin should be initiated at 0.05 to 0.1 U/kg/h intravenously by continuous infusion, at least 1 hour after starting intravenous fluids. To prepare the insulin drip, 50 units of regular insulin should be dissolved in 50 ml of normal saline. The usage of regular human insulin is recommended as short acting analogues offer no added advantage over regular insulin, when using the intravenous route for DKA management. The dose of insulin infusion should be titrated to achieve blood glucose reduction of 50-75 mg/dl/hour. The initial infusion rate may be kept at 0.05 units/kg/hr for patients with mild DKA, in infants or those with severe hypokalemia. Initial insulin infusion rate should be continued till resolution of diabetic ketoacidosis (BG <200 mg/dl, pH >7.3, bicarbonate>15 mmol/L and normalization of AG). It should be remembered that target of therapy is not merely normalization of hyperglycemia, but also resolution of ketoacidosis (which takes longer to correct than hyperglycemia).

Bicarbonate therapy

Acidosis in patients with DKA improves with insulin and fluid therapy, and the use of bicarbonate therapy for correction of acidosis remains controversial. Bicarbonate use in DKA is based on the theoretical assumption that severe acidosis could contribute to vital organ malfunction and prompt correction of acidosis may be beneficial. However, controlled trials have failed to show clinical benefit from bicarbonate therapy. On the other hand, therapy is associated with following risks:

a) A heightened risk of hypokalemia
b) Induction of paradoxical central nervous system acidosis
c) Worsening of intracellular acidosis owing to increased carbon dioxide production
d) Prolongation of ketoanion metabolism
e) Hyperosmolarity due to added sodium load

The only valid indications of administration of bicarbonate therapy are severe acidosis with arterial pH<6.9 and presence of life-threatening hyperkalemia[14].

Transition to subcutaneous insulin

The tapering of IV insulin infusion and initiation of a multiple-dose subcutaneous insulin regimen is recommended when the plasma glucose is <200 mg/dl (11.1 mmol/L), and at least two of the following parameters are achieved:

AG <12 mmol/L

Serum bicarbonate ≥15 mmol/L Venous pH >7.30

Beta-hydroxybutyrate < 1mmol/L

Insulin infusion should be continued for at least 1-2 hours after the initiation of subcutaneous regular insulin and 30-60 minutes after initiation of subcutaneous rapid acting insulin analog. The overlap is recommended because sudden discontinuation of intravenous insulin (before onset of effect of subcutaneous insulin) may result in recurrence of hyperglycemia and/ or ketoacidosis. If the patient is not able to eat, it is preferred to continue the intravenous insulin infusion.

Prevention of DKA

DKA can be prevented by better access to medical care, proper patient education, and effective communication with a health care provider during an inter current illness. Paramount in this effort is improved education regarding sick day management, which includes the following (also refer to the sick day guidelines in the chapter on "Education"):

1. Early contact with the health care provider.

2. Emphasizing the importance of insulin during an illness.

3. Review of blood glucose goals and the use of supplemental short or rapid acting insulin.

4. Having medications available to suppress a fever and treat an infection.

5. Initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated. Taking plenty of fluids along with salt should be encouraged as it helps to restore intravascular volume.

6. Education of family members on sick day management and record keeping including assessing and documenting body temperature, blood glucose, and urine/ blood ketone testing, insulin administration, and monitoring of oral intake and weight.

7. The use of home glucose-ketone meters may allow early recognition of impending ketoacidosis, which may help to guide insulin therapy at home and, possibly, may prevent hospitalization for DKA.

8. The observation that stopping insulin for economic reasons is a common precipitant of DKA underscores the need for our health care delivery systems to address this problem, which is costly and clinically serious.

9. Emphatically counselling the family that insulin is the only effective treatment, and they should trynon-injectable alternative medications.

Complications of DKA

Cerebral edema

About 0.5-1% of DKA episodes in children may be complicated by cerebral edema. Clinical features include persistent headache, recurrent vomiting, irritability, drowsiness, incontinence inappropriate for age, focal neurological deficits and signs of raised intracranial tension (hypertension, bradycardia, and irregular respiration). The postulated risk factors for the

development of cerebral edema include overtly rapid fluid resuscitation with acute decline in serum osmolality, administration of bolus intravenous insulin or use of intravenous insulin in first hour of fluid resuscitation and administration of bicarbonate therapy[14]. Young children (<5 years of age) with severe acidosis and hypocapnia, elevated blood urea nitrogen and less than expected rise in serum sodium with declining plasma glucose are at highest risk of cerebral edema[14]. The treatment should be started immediately pending the results of neuroimaging studies and includes:

1. Head end elevation

2. Reviewing and adjusting the fluid administration rate so that excessive fluids are avoided

3. Intravenous mannitol (0.25 to 1 g/kg) over 20 minutes; the dose can be repeated in two hours, if there is no initial response

4. Hypertonic (3%) saline, at 2.5–5.0 ml/kg over 10–15 minutes may be used as an alternative to mannitol, especially in cases where there is no initial response to mannitol

5. Intubation and mechanical ventilation for airway protection and assisted ventilation

Infections

Apart from bacterial infections, rare fungal infections like rhinocerebral mucormycosis and pulmonary aspergilllosis are seen at an increased incidence in patients with DKA. A high index of suspicion coupled with appropriate investigations may help recognize and treat these potentially life threatening infections.

Acute kidney injury (AKI)

AKI with urine output < 0.5 ml/kg/hr is a poor prognostic marker and can predispose patients to cerebral edema and acute respiratory distress syndrome (ARDS).

Hyperchloremic acidosis

Hyperchloremic acidosis manifests as normal AG metabolic acidosis, usually at 8-12 hours after therapy, when ketosis has already resolved. It occurs as a result of administration of intravenous fluid containing excessive chloride (0.9% NS) and requires substitution to lesser chloride (0.45% NS) containing intravenous fluids.

Hypophosphatemia

Hypophosphatemia usually manifests after treatment initiation as a result of transcellular shift of phosphate from extracellular to intracellular compartment by insulin. Encouraging early oral intake (<24 hours), when possible, may help prevent this complication. Severe hypophosphatemia with serum phosphorous<1 mg/dl may manifest as muscle weakness and rhabdomyolysis, and should be treated regardless of the symptoms.

Deep venous thrombosis

DKA is considered to be a prothrombotic state, and therefore, to prevent venous thrombosis, central venous access should preferably be avoided. Heparin prophylaxis may be considered for children requiring central venous catheters placement and for those likely to remain immobile for more than 24–48 hours.

Other acute complications

These include hypoglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, aspiration pneumonia, acute gastric dilatation, acute pancreatitis, upper gastrointestinal bleeding, rhabdomyolysis, cortical venous thrombosis, basilar artery thrombosis and subarachnoid hemorrhage[28].

Section B-Hypoglycemia in T1DM

Definition and incidence of hypoglycemia

Hypoglycemia is the limiting factor in the glycemic management of patients with diabetes[29,30]. It causes recurrent morbidity in most people with T1DM, and is sometimes fatal. Hypoglycemia in a patient with diabetes is defined as all episodes of abnormally low plasma glucose concentration that exposes an individual to potential harm. Individuals with diabetes should become concerned about possibility of developing hypoglycemia at self-monitored plasma glucose concentration of 70 mg/dl or less[31]. Iatrogenic hypoglycemia is very common in patients with T1DM[32-34].

Physiological defenses against hypoglycemia and clinical manifestations of hypoglycemia

In normal individuals, the first defense against falling plasma glucose concentration is decrease in insulin secretion (at glycemic threshold of about 80-85 mg/dl). With further decline of plasma glucose, increased secretion of counter-regulatory hormones glucagon and epinephrine occurs (at glycemic threshold of about 60-65 mg/dl). Glucagon acts as the second line of defense, while epinephrine acts as third line of defense against hypoglycemia. Epinephrine defense becomes critical when glucagon is deficient. Cortisol and growth hormone are also released (at glycemic threshold of about 60-65 mg/ dl); however, they are not critical counter-regulatory hormones in the defense against hypoglycemia.
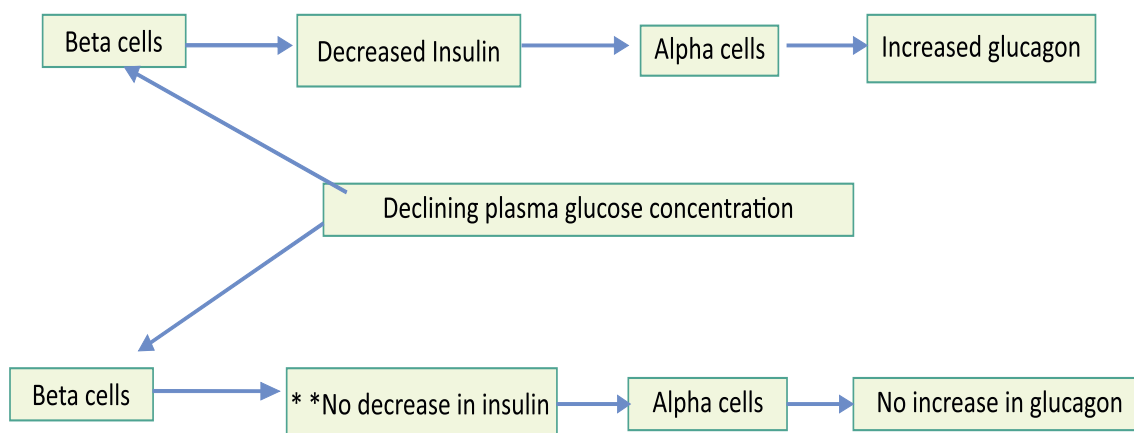
These defenses typically prevent an episode of symptomatic hypoglycemia; however, in case plasma glucose concentration continues to decline, neurogenic symptoms of hypoglycemia appear (at a glycemic threshold of about 50-55 mg/dl). These symptoms prompt behavioral defense against hypoglycemia (intake of oral carbohydrates). The symptoms are non-specific and glycemic threshold for appearance of the symptoms is rather dynamic. In patients with recurrent hypoglycemia, the glycemic threshold may shift to much lower concentration, while in those with poorly controlled diabetes, it may shift to much higher plasma glucose concentration[35]. The neurogenic symptoms are a result of sympathoadrenal discharge and include adrenergic symptoms (such as tremor, palpitations and anxiety/arousal) and cholinergic symptoms (such as hunger, sweating and paresthesias). The symptoms are typically stereotypical for a given individual. At further lower plasma glucose concentration (at a glycemic threshold of <50 mg/dl), neuroglycopenic symptoms due to brain glucose deprivation appear. These include cognitive impairment, behavioral changes, psychomotor abnormalities, seizures and finally, coma. A patient with neuroglycopenic symptoms may not be able to manage the episode of hypoglycemia by self, requiring assistance of another person to deal with it. In most instances, neurological recovery is complete following correction of hypoglycemia, however permanent neurological damage may occur in case of prolonged insult to the brain. Unpredictable playing/activity pattern and fussy eating behavior may put children at higher risk of developing hypoglycemia.

Additionally, they (especially young children) may be at a higher risk of developing severe hypoglycemia due to their inability to communicate the symptoms and show appropriate behavioral eating response.

Pathophysiology of iatrogenic hypoglycemia in T1DM

Therapeutic insulin excess coupled with impaired glucose counter regulation is the chief pathophysiology behind recurrent hypoglycemia in patients with T1DM. As plasma glucose levels fall in response to iatrogenic hyperinsulinemia, insulin levels fail to decline (loss of first line of defense). Additionally, glucagon levels fail to increase in response to falling glucose concentrations, despite presence of functional alpha cells (loss of second line of defense) (Figure 2).

Figure 2: Response to decline plasma glucose concentration in a normal person (top panel) and individual with type 1 diabetes mellitus (bottom panel). The bottom panel shows how the first and second lines of defense against hypoglycemia are lost in patients with type 1 diabetes mellitus.

Beta cells → Decreased Insulin → Alpha cells → Increased glucagon

Declining plasma glucose concentration

Beta cells → * *No decrease in insulin → Alpha cells → No increase in glucagon

* There exists a state of absolute endogenous insulin deficiency and relative exogenous insulin excess.

The epinephrine response, which becomes critical in such situations, is typically attenuated as well, especially in patients with long-standing disease and those with recurrent antecedent hypoglycemia. The lack of effective physiological defense mechanisms against hypoglycemia constitute the syndrome of defective glucose counterregulation, which is associated with 25-fold higher risk of severe iatrogenic hypoglycemia[36,37].

The attenuated epinephrine response is also a marker for impaired sympathoadrenal discharge (sympathetic neural and adrenomedullary response). This implies that neurogenic symptoms of hypoglycemia may be blunted, resulting in clinical syndrome of hypoglycemia unawareness, which is associated with 6-fold higher risk of severe hypoglycemia. The impaired glucose counterregulation and hypoglycemia unawareness set the tone for vicious cycle of recurrent hypoglycemia in such patients. The attenuated sympathoadrenal discharge in response to hypoglycemia is known as hypoglycemia associated autonomic failure (HAAF). Risk factors for HAAF include history of recent antecedent hypoglycemia, prior exercise and sleep, and aggressive glycemic therapy for control of hyperglycemia[35]. HAAF is a functional form of autonomic failure, which can be reversed by scrupulous avoidance of hypoglycemia for 2-3 weeks. The pathophysiology of iatrogenic hypoglycemia in patients with T1DM has been elucidated in figure 3.

**Figure 3: Pathogenesis of iatrogenic hypoglycemia in patients with type 1 diabetes mellitus.
HAAF: Hypoglycemia associated autonomic failure**
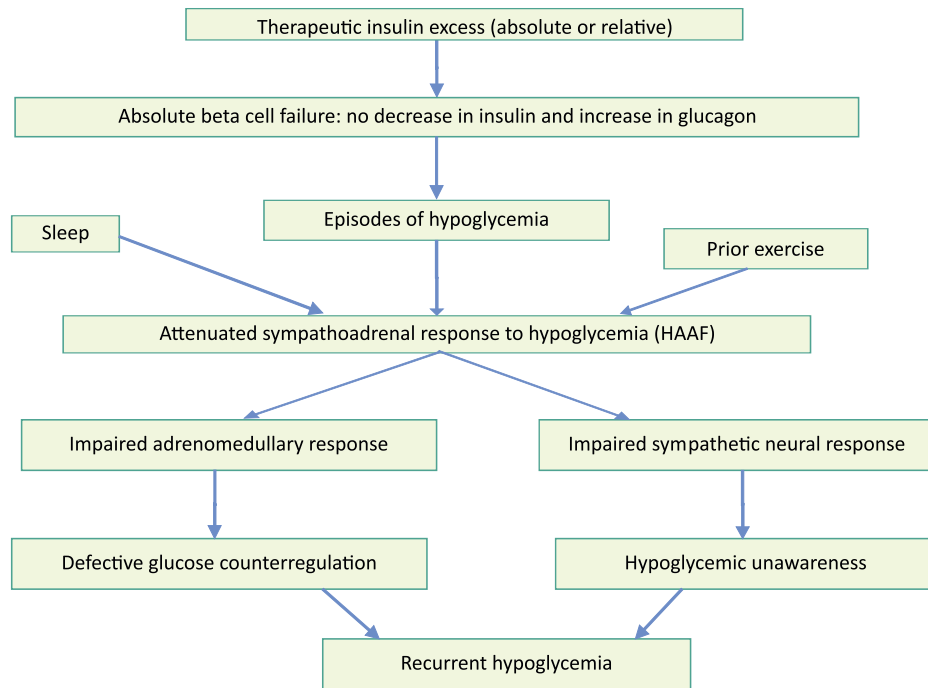
Risk Factors for hypoglycemia in T1DM

1. **Incorrect insulin therapy:** Syringe-vial mismatch, incorrect technique, incorrect timing, insulin stacking, higher insulin dose

2. **Decreased exogenous glucose delivery into blood:** Due to missed meals, delayed absorption or malabsorption

3. **Increased glucose utilization:** During or after exercise

4. **Impaired endogenous glucose production:** Due to alcohol ingestion, liver or renal disease

5. **Improved insulin sensitivity:** Late after exercise, in middle of the night or following improved fitness

6. **Decreased clearance of insulin:** Renal failure and uncontrolled hypothyroidism

7. **Others:** Concomitant adrenal insufficiency, use of high dose of insulin during the honeymoon phase of T1DM and infrequent self-monitoring of blood glucose (SMBG).

Prevention of iatrogenic hypoglycemia in T1DM

1. Patient education

Patients need to be educated about the action profile of different insulin preparations, importance of regular meal timings, avoidance of intramuscular administration and syringe-vial mismatch, symptoms of hypoglycemia, its recognition and appropriate management.

2. Frequent SMBG and CGMS

Frequent SMBG may help discover episodes of asymptomatic hypoglycemia, especially during the night. However, SMBG provides a snapshot of blood glucose values and not the longitudinal trend. CGMS provides an opportunity to capture the glucose data in a

longitudinal fashion as it records interstitial fluid glucose every 5-15 minutes. CGMS/ SMBG readings can be used to make meaningful decisions on adjustments in diet and insulin therapy to prevent future hypoglycemia episodes.

3. Insulin analogues

Use of relatively peakless long-acting insulin analogues (such as glargine, detemir or degludec) instead of intermediate acting insulin NPH (Neutral Protamine Hagedorn) may help reduce the incidence of nocturnal hypoglycemia in patients with T1DM[38-40]. Similarly, rapid acting insulin analogues (aspart, lispro, glulisine) may be preferred over regular insulin in patients having delayed pre-meal hypoglycemia with regular insulin. However, the extra cost of treatment associated with use of insulin analogues should be considered and substitution should only be done in cases where hypoglycemia persists despite best measures (such as ensuring a mid-meal snack).

4. Address the risk factors for HAAF

HAAF is associated with vicious cycle of recurrent hypoglycemia due to blunted sympathoadrenal flow. Temporary relaxation of glycemic control, and scrupulous avoidance of hypoglycemia for 2-3 weeks may help restore the awareness[41-42].

Management of hypoglycemia

Treatment is warranted for both symptomatic and asymptomatic episodes (detected by SMBG or CGMS). For most adults, oral intake of a concentrated and quickly absorbed simple carbohydrate source containing 15-20 g glucose (such as 3-4 teaspoon glucose powder dissolved in water or 4-5 glucose tablets) corrects hypoglycemia. In children, 0.3 g/kg body weight oral glucose is sufficient to correct hypoglycemia (approximately 5 g for a 15 kg child). Solution of simple sugar (sucrose) may be used in case glucose powder or tablet is not available. Glucose and sucrose are likely to be more efficacious than fructose in treating hypoglycemia[43]. Since the response to oral glucose is only transient, intake of oral glucose should be followed by a snack or a meal comprising of a mixed food source (proteins, fats etc.). The snack should be taken only after 15 minutes of intake of the simple carbohydrate to avoid interference with its absorption. Recheck the plasma glucose again in 15 minutes to affirm that glucose values have normalized and to decide if any further treatment is essential. In case repeat blood glucose is less than 70 mg/dl, above treatment should be repeated.

A small dose of subcutaneous glucagon has been used efficaciously to prevent approaching hypoglycemia or in the context of "sick day" management for a child with anorexia or with inadequate oral intake[44-45]. For patients with severe neuroglycopenic symptoms who may be unable to take glucose orally, parenteral administration of glucagon or dextrose is necessary. Glucagon can be administered either subcutaneously or intramuscularly and a close relative of the patient should be trained regarding the same. A 0.5 mg dose is used for body weight ≤20 kg, and a dose of 1 mg is administered when body weight is >20 kg. Glucagon may lead to nausea and vomiting within 45-60 minutes after injection and it is advisable to follow glucagon injection by oral consumption of concentrated carbohydrates, instantaneously upon recovering from the confused state. Since glucagon corrects hypoglycemia by stimulating glycogenolysis, in the rare scenario of hypoglycemia following alcohol binge in a patient with T1DM, glucagon will be ineffective. In scenarios permitting intravenous (IV) access and presence of a qualified medical personnel, dextrose

can be administered IV at a dose of 0.25 g/kg (maximum single dose 25 g). The intravenous bolus should be followed by a continuous IV dextrose infusion and when feasible, oral carbohydrate consumption.

It is recommended that every patient with T1DM should have a glucagon kit at home, at school/daycare, and during long journeys. Prescriptions of glucagon should be filled again before the date of expiration. Every patient with T1DM should wear a recognition band to ascertain proper intervention by emergency personnel, should such a situation arise.

Nocturnal hypoglycemia

Iatrogenic hypoglycemia often occurs at night, specifically during sleep, in patients with T1DM[46]. This is typically the longest inter-prandial interval and also the longest gap between two self monitored blood glucose measurements. Middle of night is also the time of maximum sensitivity to insulin[47]. The occurrence of hypoglycemia at night is particularly worrisome to children and adolescents with T1DM. This stems from the fear that nighttime hypoglycemia may not be treated in a timely fashion or that it may go entirely undetected and lead to irreparable brain damage or death. In addition, as discussed above, sympathoadrenal responses to hypoglycemia are reduced further during sleep[47,48] and probably because of their markedly reduced sympathoadrenal responses, patients with T1DM are substantially less likely to be awakened by hypoglycemia than non- diabetic individuals[48].

Therapeutic approaches to the prevention of nocturnal hypoglycemia in T1DM include the use of insulin analogs during the day in multiple daily injection (MDI) regimens, continuous subcutaneous insulin infusion (CSII) regimens[49,50] and a variety of bedtime treatments. Among the latter, bedtime snacks are the time- honored approach. Other measures intended to produce more sustained exogenous glucose delivery overnight include bedtime administration of the slowly digested complex carbohydrate (uncooked cornstarch)[51] and administration of an α-glucosidase inhibitor to delay the digestion of carbohydrates in the evening meal[52]. A possibility of midnight hypoglycemia causing high morning fasting blood glucose (Somogyi phenomenon) should always be considered before increasing the dose of intermediate or long acting insulin delivered at night.

Section C- Infections in T1DM

Introduction

Patients with diabetes are prone for a variety of infections which are also more likely to run a complicated course compared to the general population. In a prospective study from Denmark, patients with diabetes were found to have 1.5-3.0-fold higher risk for pneumonia, soft tissue infections and urinary tract infection (UTI) compared to the non-diabetic population. Among patients admitted with UTI, mortality at 28 days was 4-fold higher in those with diabetes. The authors also reported that each 1 mmol/L (18 mg/dl) increase in blood glucose increased the risk for pneumonia, soft tissue infection and UTI by 6-10% after adjustment for confounding factors[53].

Apart from infections common to the general population, certain infections are more specific to patients with diabetes including rhino-orbital-cerebral mucormycosis, malignant otitis externa, necrotizing fasciitis, fournier gangrene, emphysematous cholecystitis, emphysematous pyelonephritis, and diabetic foot infections[54]. Any infection in a patient

with T1DM may increase risk for DKA and hence sick day education to tackle such an event should be imparted to all patients (refer to sick day guidelines in the chapter on "Education").

Pathophysiology for increased susceptibility to infections in diabetes

Increased susceptibility to infections in patients with diabetes could be due to various mechanisms including impaired immune function, micro/ macroangiopathy, glucosuria and diabetic sensory and autonomic neuropathy (Figure 4)[54-56].

Figure 4 : Pathophysiology of infections in patients with type 1 diabetes mellitus
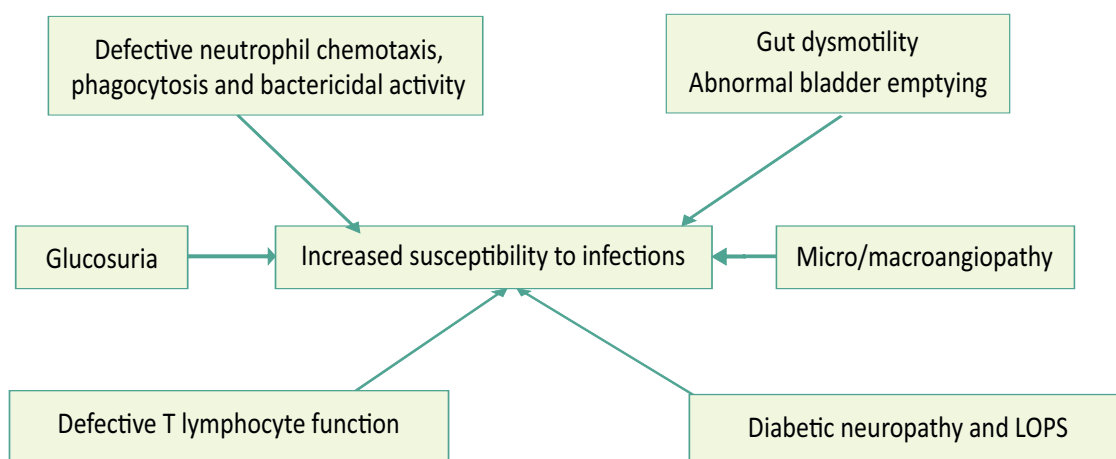
LOPS: Loss of protective sensation.

Impaired immune function

Hyperglycemia is known to affect chemotaxis, phagocytosis and bactericidal activity of neutrophils and macrophages. In addition, reduced T lymphocyte function and defect in humoral innate immunity (reduced complement factor C4 and impaired cytokine response to stimulation) may contribute to increased risk of infection in these patients.

Micro/macroangiopathy

Micro/macroangiopathy due to diabetes may lead to increased risk of skin ulceration and secondary infection.

Glucosuria

Glucosuria due to uncontrolled hyperglycemia is associated with increased risk of urinary tract infections.

Diabetic sensory and autonomic neuropathy

Loss of protective sensation (LOPS) due to neuropathy is associated with increased risk of foot ulceration and diabetic foot infection. In addition, impaired bladder emptying and gastrointestinal dysmotility due to diabetic autonomic neuropathy may predispose to urinary tract infection and gastrointestinal infection, respectively.

In the following sections, major infections encountered in patients with T1DM will be discussed.

Head and neck infections

Rhino-orbital-cerebral mucormycosis (ROCM)

This potentially fatal angioinvasive infection is caused by fungi of class Zygomycetes and the order Mucorales. The most common genera implicated in causation of mucormycosis are Rhizopus, Mucor and Rhizomucor. Rhizopus oryzae is the most common reported species among microbiologically proven cases[57].

ROCM commonly occurs in patients with uncontrolled diabetes mellitus and DKA is present in 30-70% of cases at the time of presentation. Low serum pH is known to inhibit binding of iron to transferrin, making free iron available for utilization by the ferrophilic fungi. Also, both hyperglycemia and acidosis inhibit chemotaxis, phagocytosis and bactericidal activity of neutrophils and macrophages, impairing host defenses against invasion by Zygomycetes[54,58].

Clinical features include facial swelling (especially periorbital region), redness, pain, decreased visual acuity, proptosis, headache, nasal stuffiness, rhinorrhea, ophthalmopelagia, facial numbness and presence of black eschar in nasal cavity or on the palate. A high index of suspicion should be kept for patients with uncontrolled diabetes presenting with any of the above clinical features. Diagnosis depends on demonstration of fungal elements in the tissue specimen. However, in appropriate clinical setting, it may be prudent to initiate therapy even in absence of fungal elements on initial tissue sampling. Characteristic histopathological feature of mucormycosis is the presence of broad aseptate hyphae which branch at right angles. Imaging studies like computerized tomography (CT) and magnetic resonance imaging (MRI) help in quantifying the extent of disease at initial presentation and on follow-up.

Prompt and aggressive surgical debridement along with institution of systemic antifungal therapy (amphotericin B) is the mainstay of treatment. It should be emphasized that medical treatment alone (in absence of surgical debridement) is likely to be ineffective. This is due to the limited drug delivery to the infected site as a result of extensive vascular thrombosis. Conventional amphotericin B is administered at dose of 0.5-1.5 mg/kg/day while liposomal amphotericin B is administered at dose of 3-5 mg/kg/day. The liposomal formulation has the advantage of being less nephrotoxic; however, it is more expensive than the conventional preparation. Patients on amphotericin B should be monitored for hypokalemia and hypomagnesemia besides renal dysfunction. The cumulative dose of amphotericin B administered may vary from case to case basis depending on the treatment response. Typically, a cumulative dose of 2.5-3.0 g has been described for the conventional formulation. The oral azole posaconazole may be used in patients not able to tolerate amphotericin or as a step-down therapy.

The current advances in diagnosis and management have significantly improved the prognosis associated with ROCM. However, despite best measures, mortality rates vary from 30-70% across various studies. Presence of cerebral involvement, hemiparesis, altered sensorium, bilateral sinus involvement, facial necrosis and delayed presentation are factors associated with poorer outcomes in patients with ROCM[59]. Among survivors of ROCM, residual defects such as blindness and cranial nerve palsies are common. In a review of 179 cases of paranasal sinus mucormycosis by Blitzer et al, residual defects were reported in 62/90 (70%) survivors, the most common being blindness (39/62, 63%) and cranial nerve palsies (11/62, 18%)[60].

Malignant otitis externa (MOE)

MOE is a potentially fatal necrotizing infection, which begins in external auditory canal and rapidly spreads to the underlying deep tissue. Pseudomonas aeruginosa is the most commonly implicated microorganism; however Staphylococcus aureus, Staphylococcus epidermidis, Proteus mirabilis, Klebsiella oxytoca, Aspergillus niger, Aspergillus fumigatus, and Candida species have also been associated with MOE[61]. The infection begins in external auditory canal (at junction of cartilage and bone), and rapidly spreads to the underlying temporal bone, leading to osteitis and eventually skull base osteomyelitis. A common inciting event is trivial trauma following irrigation for impacted wax or ear picking. Patients present with throbbing otalgia and purulent ear discharge. Lower motor neuron facial palsy is a complication seen early in the disease course, while other cranial nerves (IX,X,XI,XII) may get involved as the infection invades further into skull base. The presence of cranial nerve palsy portends a poor prognosis[62].

Otoscopic examination reveals presence of granulation tissue in external auditory canal at the junction of bone and cartilage with intact tympanic membrane.

CT and MRI help in defining the extent of disease in terms of soft tissue and bony involvement as well as intracranial extension[62]. Nuclear imaging modalities like Technetium 99m bone scintigraphy and Gallium (Ga-67) scan are helpful in monitoring the disease progression[63,64].

Antimicrobial therapy is the mainstay of therapy and should be initiated empirically once the pus sample has been sent for bacterial/fungal cultures. The initial antimicrobial therapy could be an antipseudomonal penicillin/cephalosporin (piperacillin-tazobactam, cefoperazone-sulbactam or ceftazidime) in combination with a fluroquinolone (ciprofloxacin)[65]. Ciprofloxacin has the advantage of oral administration and good bone penetration; however emergence of resistance against this agent is of concern[66]. The antibiotic regimen may be modified according to the culture results, once available. The total duration of antibiotic therapy is generally 4-6 weeks. Apart from antimicrobial therapy, achieving good glycemic control and regular aural toileting is important. Surgical intervention may be needed for drainage of abscesses, debridement of deep lesion and to obtain tissue diagnosis in cases not responding to systemic treatment (to exclude malignancy or granulomatous disease). With the advances in diagnosis and treatment coupled with early detection, mortality rate due to this dreaded infection has reduced from 50% to 20%[62]. It has therefore been suggested that it is more appropriate to use the term "necrotising otitis externa" or "skull base osteomyelitis" instead of "malignant otitis externa".

Skin and soft tissue infections (SSTIs)

Skin and soft tissue infections (SSTIs) include infection of skin, subcutaneous tissue, fascia, and muscle (Table IV). These may range from mild superficial infections to deep and rapidly spreading potentially fatal infections[67]. Gram positive cocci (Staphylococcus aureus and Streptococcus pyogenes) are the most common organisms implicated. However, in most cases of necrotizing fasciitis, etiology is polymicrobial (combination of gram positive cocci, gram negative bacilli and anaerobes).

Table IV: Classification of skin and soft tissue infection proposed by Infectious Disease Society of America (IDSA)

Class	Type of infection	Management
Class I	Superficial skin infections like impetigo, ecthyma	Oral (rarely topical) antibiotics +/- drainage
Class 2A	Purulent SSTIs like abscess, furuncle, carbuncle Erysipelas and cellulitis Traumatic wounds like post- operative/animal bites Systemically well, No SIRS	Oral/outpatient based parenteral antibiotics
Class 2B	Class 2A infections in a systemically unwell patient but no SIRS	Oral/outpatient based parenteral antibiotics; may need short course of admission
Class 3	Necrotising SSTI like necrotizing fasciitis/gas gangrene/pyomyositis	Urgent hospitalization

Abbreviation: SIRS-systemic inflammatory response syndrome

SSTIs-Skin and soft tissues infections

A furuncle is deep infection of hair follicle and surrounding tissue. Multiple furuncles may coalesce to form an inflammatory mass, termed carbuncle. This mass usually drains on to the skin surface with multiple pus points. The most common sites are the back, nape of the neck and buttocks. Staphylococcus aureus is the usual causative organism. Management involves prompt surgical debridement, administration of appropriate antibiotics and control of hyperglycemia.

Necrotising fasciitis (NF) is a rare invasive SSTI characterised by extensive local tissue destruction, microvascular thrombosis and systemic toxicity. The infection is generally polymicrobial and clinical features includes severe local pain and tenderness with associated swelling and erythema, crepitus, skin necrosis, bullae and features of systemic inflammatory response syndrome (SIRS). NF involving scrotal and perineal region is known as Fournier gangrene. It may begin in scrotal region and spread rapidly to involve penis, perineum, and anterior abdominal wall; however, testicles are spared due to separate blood supply.

NF is an acute surgical emergency and aggressive surgical debridement combined with parenteral antibiotics may be lifesaving. Like ROCM, prompt surgery holds the key since antibiotic penetration may be poor due to microvascular thrombosis[68]. Empirical antibiotic therapy should include a combination of clindamycin or metronidazole and a broad-spectrum penicillin plus beta-lactamase inhibitor (as piperacillin-tazobactam or ampicillin-sulbactam).

Insulin site infections

Injection site abscesses are a result of poor hygiene at injection site, repeated use of the same needle, repeated injections at same site, use of contaminated insulin and failure to change catheter at recommended interval in patients using continuous subcutaneous insulin infusion (CSII). Most common microorganisms implicated are Staphylococcus aureus and Streptococcus pyogenes; however, rarely atypical mycobacteria (as Mycobacterium chelonae and fortuitum) have been implicated in its causation[69,70]. Treatment involves incision and drainage of the abscess along with antimicrobial therapy guided by the results of pus culture.

Genitourinary infections

Genitourinary infections are the commonest infections among patients with diabetes. As already mentioned, not only are patients with diabetes at increased risk of recurrent genitourinary infections, they are also likely to have a more complicated course, compared to the general population. Factors predisposing to increased risk of genitourinary infections in these patients include presence of hyperglycemia, metabolic acidosis, cystopathy with significant post-void residual urine and obstruction due to calculi, papillary necrosis, fungal ball etc. Various genitourinary infections in patients with DM have been listed in Table V.

Table V: Genitourinary infections in patients with diabetes mellitus

Bacterial	Fungal
Cystitis Emphysematous cystitis Pyelitis Pyelonephritis Emphysematous pyelonephritis Perinephric abscess	Vulvovaginal candidiasis Invasive candidiasis Renal actinomycosis

Among the bacterial causes, E.coli accounts for the majority of UTIs followed by other Gram negative bacilli such as Proteus, Klebsiella, Acinetobacter and Pseudomonas. Enterococci, coagulase negative staphylococcus, beta-hemolytic streptococci and Staphylococcus aureus are other important microorganisms implicated. All UTIs in T1DM merit treatment and in recurrent cases, imaging should be obtained to exclude obstructive etiology.

Urinary tract candidiasis

Urinary tract candidiasis may be seen in patients on broad spectrum antibiotics and in those with prolonged indwelling catheter. Although often asymptomatic, it may present with cystitis, pyelonephritis, renal abscesses, and rarely formation of fungal ball. Candida albicans is the most common pathogen identified, followed by Candida glabrata. The infection can be acquired through genitourinary tract (ascending infection), from the gut or via hematogenous spread[71].

Asymptomatic candiduria in presence of indwelling catheter frequently resolves (20-40% cases) on removing or changing the catheter[72]. Stopping the antibiotics which are not necessary is also helpful. If candiduria fails to clear despite these measures, deep seated infection should be suspected and imaging of kidney and collecting system should be done. All symptomatic cases should be treated with oral fluconazole with or without flucytosine for 2 – 3 weeks. Fungal ball needs removal via cystoscope or ureteroscope or rarely, an open surgical intervention. Renal candidiasis should be treated with amphotericin B +/- flucytosine. Surgical intervention in the form of drainage or even nephrectomy may be rarely required.

Perinephric abscess

Perinephric abscess may be a complication of acute pyelonephritis and should be suspected in patients who fail to improve on conventional therapy. About 30-40% patients with perinephric abscess have diabetes[73,74]. Clinical features include flank pain, nausea, vomiting,

dysuria and polyuria. Most commonly implicated microorganisms include E.coli, Klebsiella and Proteus species. Samples for blood culture, urine culture and pus culture (obtained via USG or CT guided aspiration) should be collected, followed by institution of empirical antimicrobial therapy. Duration of antibiotics should be at least 2 to 3 weeks, and should be adjusted based upon improvement of clinical and laboratory parameters and resolution of abscess[75]. Percutaneous drainage of abscess should be done and any obstruction (as calculi) should be removed. Rarely, in advanced cases, nephrectomy may be required[76].

Renal papillary necrosis (RPN)

RPN, characterised by coagulative necrosis of renal medullary pyramids and papillae has been postulated to occur due to marginal changes in vascular supply leading to infarction of the renal papillae[77]. It should be suspected in patients with recurrent pyelonephritis or difficult to treat pyelonephritis, recurrent renal colic, gross hematuria and unexplained renal failure. Acute presentation is usually unilateral and is dominated by symptoms of fever, flank pain, renal colic and hematuria. A chronic presentation is, however, more common and is often bilateral. Intravenous urography (IVU) is the most sensitive investigation, but is rarely used due to associated renal dysfunction. Aggressive antibiotic treatment with relief of obstruction from sloughed papillae is the recommended treatment.

Emphysematous pyelonephritis (EPN) and emphysematous cystitis

Upto 90% of patients presenting with emphysematous urinary tract infections have diabetes. The presence of gas forming organisms, high level of blood glucose and impaired renal perfusion (contributing to gas accumulation) are the three prerequisites for emphysematous kidney disease[78]. Emphysematous pyelonephritis (EPN) is a severe, necrotizing form of multifocal bacterial infection with gas formation within the kidney parenchyma. Its presentation is usually similar to acute pyelonephritis with fever, flank pain, nausea and vomiting. Rarely, a palpable mass or crepitus may be appreciated. Acute presentation with sepsis, septic shock, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) is also reported, but DKA is surprisingly rare. The causative microorganisms include gram negative bacilli such as E.coli (most common), Klebsiella and Proteus[78]. Radiograph of kidney, ureter and bladder (KUB) region may show gas overlying the renal fossa while ultrasonography may reveal enlarged kidney with hyperechogenic foci within. CT abdomen is the imaging modality of choice to identify and stage the anatomical extent of abnormal gas accumulation. A radiological grading system based on CT findings proposed by Heung and Tseng is as follows[79]:

Grade 1   :   Gas confined to the collecting system
Grade 2   :   Gas in renal pelvis
Grade 3a :   Perinephric collection
Grade 3b :   Extension of gas beyond Gerota's fascia
Grade 4   :   Bilateral involvement or EPN in a single kidney

Grade 1 and grade 2 EPN can be managed conservatively with intravenous antibiotics (cefoperazone-sulbactam, piperacillin-tazobactam, meropenem, levofloxacin) with or without percutaneous drainage. Grade 3 EPN may be managed conservatively with intravenous antibiotics and percutaneous drainage, however, may require nephrectomy if poor prognostic factors (such as thrombocytopenia, DIC, shock, acute kidney injury) emerge while grade 4 EPN (especially with associated poor prognostic factors) often require nephrectomy[80].

Emphysematous pyelitis refers to the abnormal gas collection localized to the collecting system. It is most often a result of underlying obstruction. CT scan is the imaging modality of choice. Treatment requires broad spectrum intravenous antibiotics and percutaneous drainage. Emphysematous cystitis is less common than EPN, but portends a better prognosis. It presents with dysuria, abdominal discomfort and hematuria. Pneumaturia is a rare finding but is highly specific for this entity. Radiograph of KUB region reveals curvilinear or mottled areas of increased radiolucency in the region of bladder. CT is the imaging modality of choice as it defines the abnormal gas collection and its anatomic extent. Treatment involves administration of broad spectrum intravenous antibiotics.

Gastrointestinal infections

Gastrointestinal dysmotility in addition to immune dysfunction increases the predisposition to infection with several enteric pathogens in patients with diabetes. Emphysematous cholecystitis is a dreaded complication of acute cholecystitis, wherein, air fills the lumen and walls of gall bladder, leading to 30 times increased risk of perforation and 10 times increased risk of gangrene. The most common causative organisms include anaerobic gas forming bacteria, such as Clostridium perfringens and Clostridium welchii, followed by aerobes, such as Escherichia coli. Treatment requires an emergent cholecystectomy[81].

Respiratory tract infections

Pulmonary infections due to various microorganisms (such as pneumococcus, influenza) implicated in community acquired pneumonia (CAP) are associated with increased morbidity and mortality in patients with diabetes. Additionally, people with diabetes are also more prone to infections with organisms like Mycobacterium tuberculosis, Staphylococcus aureus, gram negative bacilli and fungi (such as Cryptococcus, Candida, Mucor).

Diabetes and Tuberculosis

Epidemiology

Diabetes and tuberculosis share a bidirectional relationship with each other and together they form a deadly syndemic. Patients with diabetes are not only at increased risk of tuberculosis but are also likely to have poorer outcomes with treatment. On the other hand, tuberculosis can lead to worsening of glycemic control giving rise to a vicious cycle of synergism[82].

Patients with diabetes are at 3.5-5.0-fold higher risk of developing tuberculosis, and the risk is especially high in patients with T1DM[83,84]. In a study involving 151 subjects with T1DM who were screened for pulmonary tuberculosis (PTB), prevalence of sputum culture positive PTB was found to be 10.6%[85].

Studies have shown that diabetes may influence the clinical features, radiological manifestations, sputum conversion rates, drug resistance patterns and treatment outcomes among patients with PTB. PTB might progress rapidly in diabetic patients, especially in patients with uncontrolled hyperglycemia and delayed diagnosis in such cases is associated with increased mortality. Multi-lobar disease, preferential involvement of lower lobe and multi-cavitary disease is also more common in patients with diabetes. Despite higher bacterial load, sputum negativity is common. Patients with diabetes show delayed mycobacterial clearance with treatment and are also at increased risk of relapse following the treatment[86,87]. Additionally, multidrug-resistant tuberculosis (MDR-TB) has been found to be more common in patients with diabetes[88].

Pathophysiology of the association between DM and tuberculosis

There is evidence of impaired cell-mediated immunity, micronutrient deficiency, pulmonary microangiopathy and renal insufficiency in patients with diabetes, all of which predispose to PTB. Stress due to a chronic infectious disease such as TB which causes considerable catabolism may increase insulin resistance and increase the demand for insulin secretion. When the increased demand cannot be met (due to a pre-existing low beta-cell mass), as is often the case in poor TB patients with associated malnutrition, the potential underlying risk of diabetes may be unmasked. Regardless of the direction of the association, the common diabetes–tuberculosis comorbidity presents clinical challenges: first, as a result of stress-induced hyperglycemia, and second, because rifampicin [one of the key drugs in any anti-tuberculosis treatment (ATT) regimen] may in itself have hyperglycemic effects[89,90].

Management of patients with tuberculosis and DM

Tuberculosis in patients with diabetes is associated with increased relapse rates. New cases of PTB with diabetes should be treated for 6 months (as per the standardized WHO regimen) Whether treatment in such cases should be extended to a total duration of 9 months needs an evidence-based justification. The recommended treatment for management of tuberculosis includes the standard four drug regimen- isoniazid along with pyridoxine, rifampicin, ethambutol and pyrazinamide. Whether patients with extensive cavitary disease should receive an additional drug (possibly a quinolone like moxifloxacin) to rapidly reduce sputum AFB load remains an unanswered question[82]. Tight glycemic control makes anti-tubercular drugs more effective and leads to better clinical, radiological and bacteriological resolution of the disease. Due to worsening of glycemic control with acute infection, insulin doses may need up-titration during the initial phase, requiring close follow-up with the treating physician.

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Chapter-6

Microvascular Complications-Retinopathy

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Introduction

Diabetic retinopathy (DR) is one of the most common microvascular complication of type 1 diabetes mellitus (T1DM) and a leading cause of blindness in adults[1]. It is a progressive disease which if untreated can lead to severe visual loss. With the advent of better insulin regimens and intensive management of diabetes, there is evidence for decrease in the occurrence of sight threatening proliferative DR (PDR)[2]. However, poor glycemic control continues to be a problem in many patients with T1DM, putting them at risk of complications. Significant improvement has been seen in the past couple of decades with regard to screening methods and treatment of DR. Patients with T1DM are also at a higher risk of developing other eye diseases such as cataract, glaucoma, retinal vein occlusion, and cranial nerve palsies. Besides, cataract surgery may run a complicated course and can be associated with worse visual outcomes in such patients. This chapter reviews epidemiological and clinical aspects of DR with emphasis on clinical practice guidelines for detection and management of sight threatening DR.

Epidemiology

There are limited studies on DR exclusively dealing with T1DM patients. One of the longest follow-up study is the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR). In this study, amongst 996 young subjects (<30 years) requiring insulin, the prevalence of DR varied from 17% in subjects with diabetes for less than 5 years to 97.5% in those with disease duration of 15 or more years. On the other hand, PDR varied from 1.2% in subjects with diabetes for less than 10 years to 67% in those with disease duration of 35 or more years[3]. A follow-up of the same cohort showed cumulative incidence of 59%, 89.3%, 95.9% and 97% at 4, 10, 14 and 25 years, respectively[4]. The risk of DR is higher in T1DM compared to adult-onsetT2DM. In a meta-analysis of 35 population-based studies in which fundus photographs were used to ascertain retinopathy, prevalence of any DR or PDR was higher in those with T1DM compared to adult-onset T2DM (77.3 vs. 25.2 % for any DR, 32.4 vs. 3.0% for PDR)[5].

The most significant paradigm change in T1DM treatment happened with the DCCT (Diabetes Control and Complications Trial) study. Intensive treatment and lower glycosylated haemoglobin (HbA1c) levels reduced the risk for DR by 76% and slowed the progression of existing DR by 54%. There were also marked risk reduction in development of PDR (47%), onset of macular edema (26%), and need for laser photocoagulation (56%). A follow-up of the same cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) showed lasting benefits of intensive control despite a subsequent

increase and equalization of HbA1c in both arms of treatment. Though intense glycemic control initially worsened DR, lasting benefits were evident in 1.5-3.0 years[6]. In the post-DCCT era, there is some evidence of decline in the prevalence of DR, as seen in an analysis of 1604 adolescents with T1DM stratified by four time periods between 1990-2009; retinopathy declined (53%, 38%, 23%, and 12%; p < 0.001) and use of multiple injection or insulin pump increased (17%, 54%, 75%, and 88%; P < 0.001) during this time period[7].

As opposed to adult-onset T2DM, the burden of DR is higher in patients with youth-onset T2DM compared to T1DM. Among a cohort of 1746 subjects with T1DM (mean disease duration: 7.9 years) and 272 subjects with youth-onset T2DM (mean disease duration: 7.9 years) who were a part of the SEARCH for Diabetes in Youth registry, 5.6% and 9.1%, respectively had DR. This observation suggests the aggressive nature of youth onset T2DM8. A higher burden of DR (and microvascular complications in general) in youth-onset T2DM may be governed by delayed presentation and poor glycemic control related to difficulties in accepting the diagnosis and low adherence to lifestyle measures and pharmacotherapy. Besides, a lower risk of developing ketoacidosis in the absence of adequate treatment increases the probability of exposure to sustained hyperglycemia in patients with youth-onset T2DM.

The literature on occurrence of DR in T1DM in India is limited and mainly available from hospital- based studies. These are summarized in Table I[9-14]. A variable burden of DR reported in these studies may be due to differences in diabetes duration and techniques of assessment employed in these studies. Most studies have utilized direct or indirect ophthalmoscopy for diagnosis. In a study by Rajalakshmi and colleagues which evaluated 150 subjects with T1DM using four-field digital retinal colour photography, the age and gender-adjusted prevalence of DR, DME and PDR was reported to be 62.5%, 10% and 7.3%, respectively[14].

Table I: Prevalence of diabetic retinopathy among subjects with T1DM in various Indian studies[9-14]

Author, Year	Method of examination	Sample size	Duration of diabetes (years)	Prevalence of DR
Ramachandran et al, 2000	Indirect ophthalmoscopy	617	Median: 4 years Range: 3-34 years	13.4%
Bhatia et al, 2004	Direct ophthalmoscopy	50	> 5 years	22.0%
Unnikrishnan et al, 2008	Direct ophthalmoscopy	535	Mean: 5.6 years	5.0%
Kumar et al, 2008	N/A	166	N/A	8.4%
Amutha et al, 2011	Direct and indirect ophthalmoscopy	224	> 5 years	35.3% 77.3% with > 15 years duration
Rajalakshmi et al, 2014	Four field digital retinal photography	150	Mean: 12.4 years	53.3%

Abbreviations: DR- Diabetic retinopathy; N/A- Not available; T1DM-Type 1 diabetes mellitus

Risk Factors

The potential risk factors for DR are summarized in Table II. Longer diabetes duration, poor glycemic control and suboptimal blood pressure control are associated with increased risk of DR in most studies. Total number of prepubertal years seem to add to the risk of DR[15], but glycemic control during puberty is a more important determinant. The increased risk for DR after the onset of puberty may be due to increased insulin-like growth factor-1 (IGF-1), growth hormone, sex steroids, and blood pressure and deterioration of glycemic control. There is a possible role of genetic susceptibility, which could explain variations in retinal response to hyperglycemia and hence the discordance between degree of glycemic control and severity of retinal disease in certain cases (no/mild retinopathy despite long duration of poor glycemic control and severe retinopathy in a short period despite relatively good glycemic control). In an Indian study, diabetes duration, increased waist circumference and microalbuminuria were significantly associated with DR[14].

Table II: Risk factors for diabetic retinopathy

Non-modifiable factors	Modifiable factors	Novel factors of possible role
Duration of diabetes	Hyperglycemia	Inflammation
Puberty	Hypertension	Genetic polymorphism
Pregnancy	Dyslipidemia	Adipose tissue hormones
Family history of retinopathy	Smoking Anemia	Oxidative stress
	Microalbuminuria	Vitamin D

Pathophysiology

In both T1 and T2DM, chronic hyperglycemia is the most important risk factor for the development of retinopathy. The exact mechanism by which hyperglycemia causes changes in retinal vasculature is not completely clear and several mechanisms have been proposed[16]. These include changes in the polyol pathway (accumulation of sorbitol and fructose), non-enzymatic protein glycation forming advanced glycation products, activation of protein kinase (PKC), hemodynamic changes, changes in renin-angiotensin-aldosterone system (RAAS), subclinical inflammation and leukostasis. These mechanisms lead to increased reactive oxygen species (ROS), and reduced clearance of free oxygen, causing oxidative stress.

Changes in cellular architecture including endothelial cell damage and proliferation, loss of pericytes and changes in blood retinal barrier occur due to above mentioned factors; this causes leakage and edema, including DME. Loss of pericytes correlates with microaneurysm formation. Another feature of DR is the thickening of capillary basement membrane similar to changes in glomerular membrane and increased deposition of extracellular matrix components. Together, these changes lead to capillary occlusion and ischemia.

Retinal ischemia is a potent stimulant for formation of various growth factors, most important of which is vascular endothelial growth factor (VEGF). Binding of these growth factors to their receptor triggers various pathways leading to endothelial damage, increased capillary permeability and promoting angiogenesis and neovascularization. The latter leads to PDR which increases the risk of intravitreal bleed and blindness.

Clinical features and classification

Symptoms

Most individuals with initial changes of DR are asymptomatic. The earliest change of DR is presence of microanuerysms, which we will describe in more detail in a later section. Therefore, screening at an early stage gives us a lead time before vision loss occurs. As DR progresses, some individuals may complain of blurring of vision. At this stage, swelling in the retina or DME is likely to be present. At a more severe stage, there may be presence of floaters / black moving spots in front of the eye, which are suggestive of bleeding inside the eye (vitreous haemorrhage). At a very advanced stage, there may be significant vision loss along with pain, which may be suggestive of increasing eye pressure due to advanced DR.

Signs

As mentioned earlier, the earliest sign is the presence of microanuerysms. These are seen as small deep-red dots between 25 and 100μm in diameter within the retina. These are essentially outpouchings from the retinal capillaries, caused due to pericyte loss. At this stage, the disease is classified as mild non-proliferative diabetic retinopathy (NPDR) (Figure 1).

Figure 1: On the left is the image of the fundus, showing mild NPDR; the right image is the same fundus picture, with the microanuerysms marked as blue circles
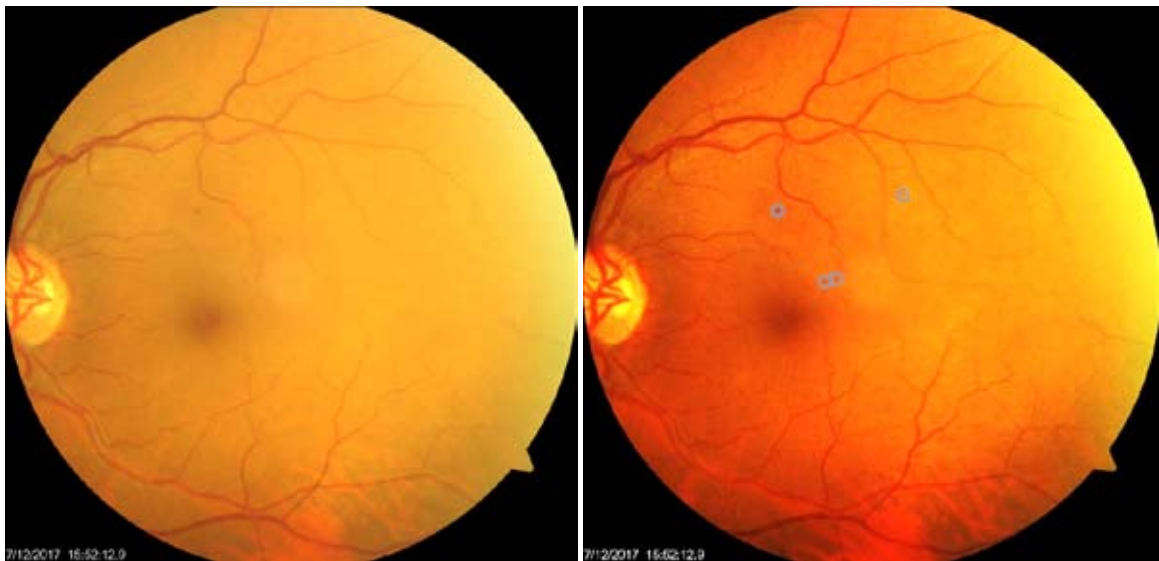
NPDR- NPDR- Non-proliferative diabetic retinopathy

As the disease progresses, presence of intra-retinal hemorrhages can be seen. These are of two types: flame shaped hemorrhages, which lie in more superficial retina (retinal nerve fibre layer) and dot-blot hemorrhages, which lie in deeper retinal layers. The type of retinal haemorrhage is not known to have a prognostic significance. Superficial retinal nerve fibre layer infarcts may be present, which are seen as yellow-white lesions with indistinct margins (cotton wool spots or soft exudates).

With further increasing severity, we see that the retinal veins have a sausage-like appearance, or beaded appearance, called venous beading. The retinal vessels may show

another sign, in which a fine abnormal vascular pattern may be seen within the retina (not elevated); this is called Intra-retinal microvascular abnormality (IRMA). In cases of extensive capillary occlusion, dot haemorrhages and IRMA may disappear and the retina may appear free of non-proliferative lesions. This entity, described as "featureless retina" is a sign of severe retinal hypoxia.

With increasing severity of DR and ischemia in the retina, there is an augmented release of VEGF inside the eye, leading to neovascularisation. These new vessels tend to grow on the surface of the retina, or into the vitreous. They may have a cartwheel, or sea-fan appearance. They are fragile, and cause pre-retinal haemorrhage seen as sub-hyaloid haemorrhage and vitreous haemorrhage. Neovascularization at the optic disc is considered as more severe and a sign of global ischemia. As this neovascularization becomes fibrotic and contracts, it leads to tractional retinal detachment.

With leakage from retinal capillaries, retinal edema develops, typically present at macula, and causing decrease in vision (DME). As the exudation from the capillaries also have lipids, their accumulation in retinal layers leads to formation of yellow waxy plaques, flecks or dots composed of lipoprotein and lipid filled macrophages (surrounding the leaking microvascular lesions in the retina). Such lesions are called hard exudates. When the macular edema involves or threatens to involve the center of the macula, it is called as clinically significant macular edema (CSME). CSME may exist with any severity of retinopathy, however, it is more common in the advanced forms, and deserves urgent attention of the ophthalmologist. CSME is defined as one of the following: a) retinal thickening at or within 500 μm of the center of the macula b) hard exudates at or within 500 μm of the center of the macula with adjacent retinal thickening c) zone or zones of retinal thickening one- disc area or large in size, any part of which is located within one-disc diameter of the center of the macula. The Early Treatment Diabetic Retinopathy Study (ETDRS) found that untreated CSME is associated with 30% risk of moderate vision loss over three years, and the risk can be reduced by 50% using focal laser photocoagulation. Evaluation for DME requires three dimensional assessment, best performed using a dilated slit lamp biomicroscopy and/or stereo fundus photography.

Classification:

The ETDRS study group has proposed a classification of DR which uses the Modified Airlie House classification to label fundus picture areas from 1 to 7[17]. As per the ETDRS classification, DR can be classified as follows:

- **MILD NPDR**

  At least one microaneurysm, AND criteria not met for more severe retinopathy.

- **MODERATE NPDR**

  Hemorrhages/microanuerysms ≥ standard photograph 2A AND/OR cotton-wool spots, venous beading, or IRMA definitely present; AND criteria not met for more severe retinopathy.

- **SEVERE NPDR**

  Cotton-wool spots, venous beading, and IRMA definitely present in at least two of photographic fields 4–7; OR two of the three preceding features present in at least two of fields 4–7 and hemorrhages/microanuerysms present in fields 4–7 ≥ standard

photograph 2A in at least one of them; OR IRMA present in each of fields 4–7 and ≥ standard photograph 8A in at least two of them; AND criteria not met for more severe retinopathy.

- **EARLY PDR**

  New vessels; AND criteria not met for high-risk PDR.

- **HIGH-RISK PDR**

New vessels on or within one disc diameter of the optic disc [neovascularization of the disc (NVD)] ≥ standard photograph 10A (approximately 1/4– 1/3 disc area) with or without vitreous or preretinal hemorrhage; OR vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ 1/2 disc area.

ETDRS classification is complex, requires comparison with standard photographs and is difficult to remember or apply in clinical setting; however, it is best suited for research studies. A simpler and clinically useful classification is the International Classification of Diabetic Retinopathy and Diabetic Macular Edema (the International Classification) (Table III)[18].

Differentiation from non-diabeteic retinopathy

Although a co-existing hyperglycemia is suggestive in almost all cases, differential diagnosis of DR would include:

1. Retinal vein occlusion: Typically, unilateral presentation; co-existing diabetes may be present

2. Ocular ischemic syndrome: Typically, unilateral presentation; a carotid doppler shows occlusion

3. Sickle cell retinopathy: Blood investigations are confirmatory of sickle cell disease

4. Radiation Retinopathy: History of radiation is present

Screening

Screening for DR fulfills all important pre-requisites for a screening program, i.e., the disease is an important public health problem, natural history of disease is well understood, long latent phase is present, acceptable and cost-effective tests for diagnosis are available, treatment is available and is known to improve outcomes, facilities for diagnosis and treatment are available and case finding is likely to be a continuous process and not just "once and for all" project.

Annual screening for DR in T1DM is recommended in individuals more than 10 years of age, with a disease duration of 5 years or more[19].

Screening can be done by various fundus examination techniques, which include (Figures 2 and 3):

a) Direct Ophthalmoscope

b) Indirect Ophthalmoscope

c) Slit Lamp Fundus Exam (Biomicroscopy)

d) Fundus cameras (mydriatic or non-mydriatic)

Table III: International Clinical Disease Severity for Diabetes Retinopathy

Proposed disease severity level	Findings on dilated ophthalmoscopy
DIABETIC RETINOPATHY (DR)	
No apparent retinopathy	No abnormalities.
Mild nonproliferative DR (NPDR)	Microaneurysms only.
Moderate NPDR	Microaneurysms with other signs such as dot and blot haemorrhages, hard exudates and cotton wool spots, but less than severe NPDR.
Severe NPDR	Any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants, definite venous beading in 2+ quadrants; prominent intraretinal microvascular abnormalities in 1+ quadrant AND no signs of PDR.
PDR	One or more of the following: neovascularization on the optic disc and/or elsewhere, and vitreous/preretinal haemorrhage.
DIABETIC MACULAR EDEMA (DME)	
DME apparently absent	No apparent retinal thickening or hard exudates in macula.
Non-central involving DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter.
Central involving DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter.

Abbreviations: PDR- Proliferative diabetic retinopathy

The sensitivity of screening by direct ophthalmoscopy may be lower, especially when performed by non-eye care professionals. The highest sensitivity is provided by mydriatic retinal imaging using more than two fields of view.
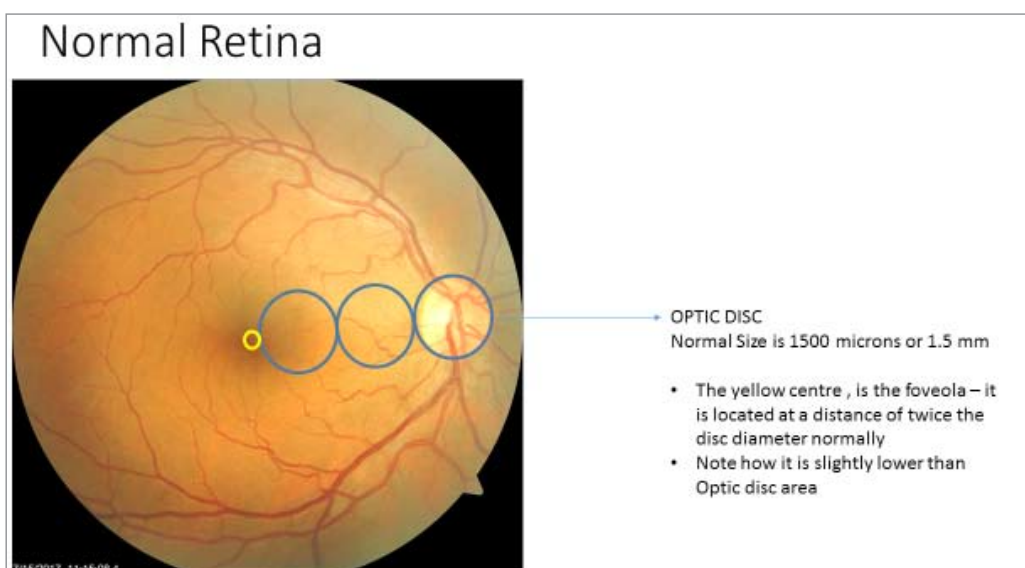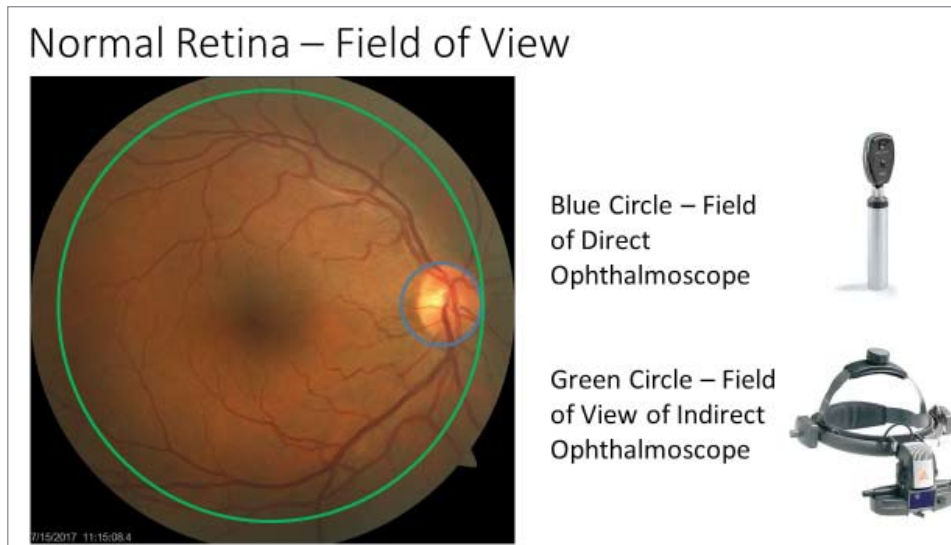
Figure 2: Image of normal retina, showing the optic disc in blue circle, and fovea in yellow circle

Figure 3: Image showing the field of view of the direct and indirect ophthalmoscopes. Further, by asking the patient to look in different directions, or with examiner changing the position, more areas of the fundus can be seen using the either technique

Investigations

A detailed investigative work-up for DR would include:

A. Fundus Photography

B. Fundus Fluorescein Angiography (FFA)

C. Optical Coherence Tomography (OCT)

D. B-Scan Ultrasonography

A. Fundus Photography

Fundus photography is a valuable tool which helps to document the status of DR, and monitor changes over a period of time. It is also useful to store data for subsequent clinical studies. A variety of portable, low cost fundus photography tools are now available. Ultrawide field fundus imaging is a relatively new retinal imaging technique that allows imaging of the peripheral retina[20].

B. Fundus Fluorescein Angiography (FFA)

An essential part of DR investigation is FFA which involves the injection of sodium fluorescein (3ml of 20% or 5ml of 10%) dye intravenously. Following injection of dye, images of the retina are taken using the FFA camera. The images are observed for presence of hyperfluorescent and hypofluorescent areas. Hyperfluorescense typically caused by leaking microanuerysms and neovascularization (Figure 4), while hypofluorescence results from areas of non-perfusion/ischemia to the retina. Another common cause of the latter is blocked fluorescence due to haemorrhage (pre-retinal/retinal). Ultra-wide field fluorescein angiography (UWFA) is a relatively new modality which allows visualization of peripheral retinal non-perfusion areas, as well as NVEs, thus aiding with targeted retinal photocoagulation[21]. Complications of FFA include painful extravasation of dye and allergic reactions which can range from mild to severe; resuscitation equipment should be available when FFA is done. The use of FFA is contraindicated in a patient with history of allergic

hypersensitivity to fluorescin. In the present day, the indications for use of FFA are gradually dwindling, with the advent of Optical Coherence Tomography (OCT).

Figure 4: Fundus Fluorescein Angiography (FFA) showing leaking microanuerysms at the posterior pole
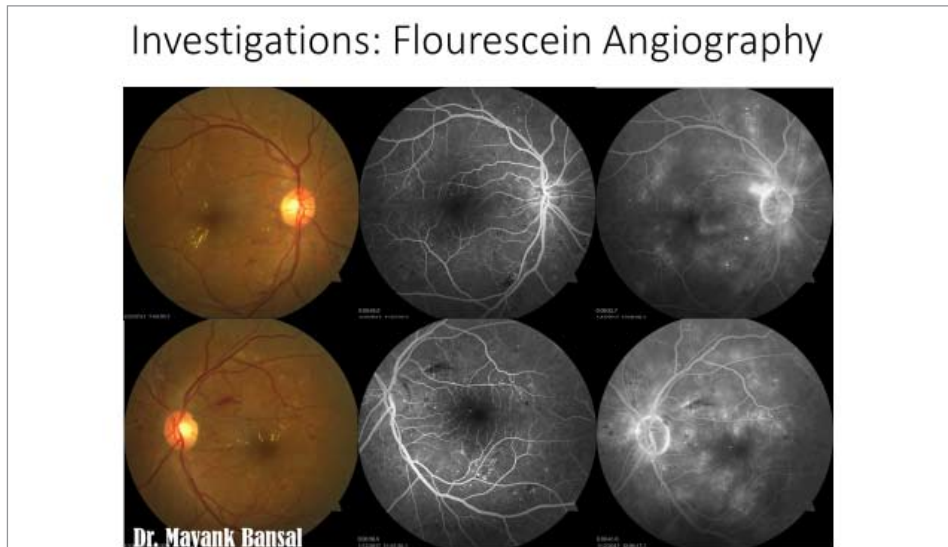
C. Optical Coherence Tomography (OCT)

This investigation uses a laser light source to image the layers of retina (Figures 5 and 6). The resolution provided is of the order of 5 to 30 microns (depending on the advancement of the system). The importance of OCT in evaluation of DR has been increasing. The clear advantage is that it is a non-invasive investigation which images the presence of DME, classifies it as center-involving or non-center involving and also quantifies its degree of severity. The cause of DME can be ascertained, and response to treatment can be followed up on an OCT (Figure 7)[22].

OCT Angiography (OCTA) is a recent advancement in ophthalmic imaging which allows visualization of retinal vasculature, without the use of any dye. Its role is being increasingly established in various retinal conditions[23,24]. However currently, it is not considered an important component of DR management.

Figure 5: Optical coherence tomography (OCT) of a normal eye showing the central foveal dip
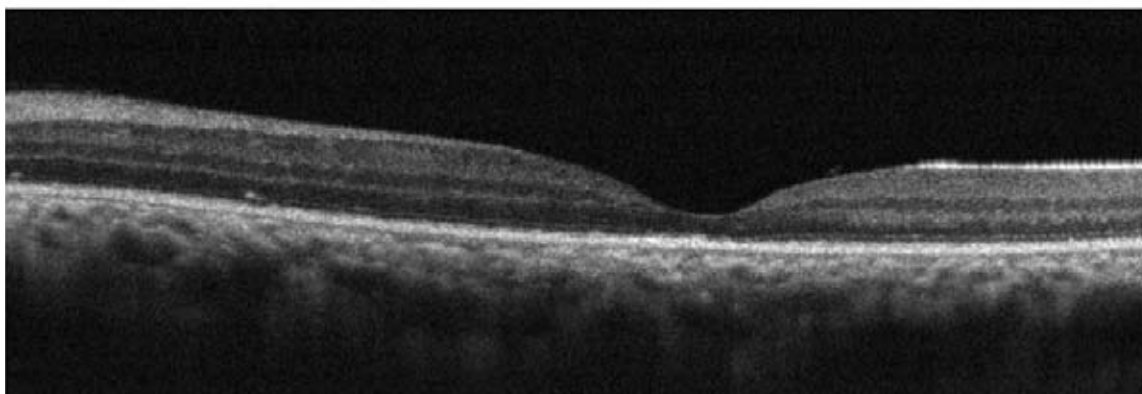
Figure 6: Optical coherence tomography (OCT) of a patient with diabetic macular edema (DME) showing loss of central foveal dip, with hypo-reflective fluid filled spaces at the macula. There is a co-existing hyper-reflective membrane at the surface of the retina, the epi-retinal membrane (ERM)
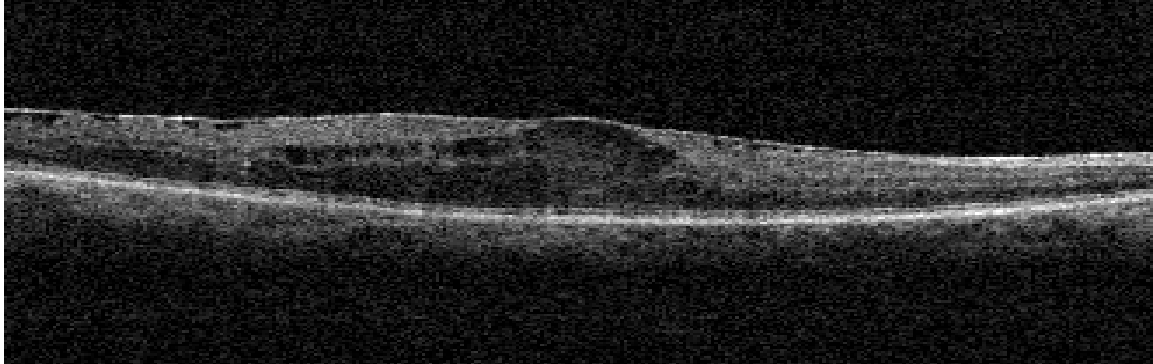
Figure 7: Optical coherence tomography (OCT) change analysis of a patient showing resolving macular edema following treatment with intra-vitreal injections.
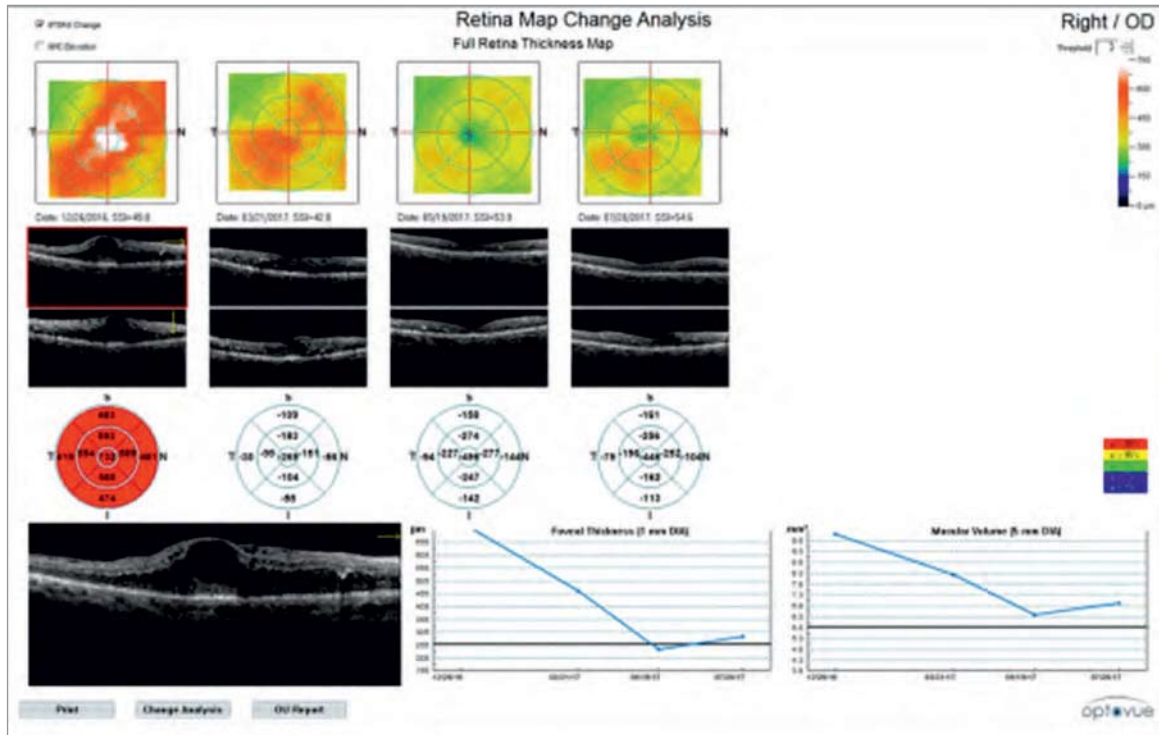
D. B-Scan Ultrasonography:

B-Scan Ultrasonography can be used for imaging of retina and serve as an important preoperative tool for surgical planning in patients with hazy media such as due to dense cataract or vitreous hemorrhage.

Overview of management, referral and follow up plan

Glycemic control remains paramount in management, as established by DCCT. There is strong evidence to suggest that controlling hyperglycemia is associated with reduction in the incidence as well as progression of DR. In DCCT, each 10 percent proportional decline in HbA1c (for instance, from 9.0 to 8.1%) was associated with a 39 percent reduction in the

risk of DR. Besides, the benefits of early glycemic control on microvascular complications including DR persist in the long-term even after deterioration in blood glucose control, as was shown in the DCCT follow-up study-EDIC (legacy effect or metabolic memory). There is some risk of early worsening of DR with glycemic control, especially in those who have higher baseline HbA1c; however serious vision loss is rare and evidence for long term benefits is quite clear. In addition, control of blood pressure, lipids, proteinuria and cessation of smoking is helpful.In T1DM, evidence for reduction in the incidence of DR with intensive blood pressure lowering is modest; however, considering other benefits such as reduction in risk of cardiovascular disease and nephropathy, optimal control of hypertension control should be actively pursued. There is no conclusive evidence to support the specific use of agents blocking renin angiotensin aldosterone system in patients with DR. Similarly, the use of lipid lowering medications has not been found to reduce the risk of DR; however, optimal lowering should be targeted for cardiovascular benefits.

Ophthalmologic management depends on severity of DR at the time of screening. Early treatment of PDR and DME is crucial because it can prevent vision loss and lead to stabilisation or improvement in visual acuity. The management plan for various stages of DR is as follows:

- For absent DR or mild NPDR, annual screening is adequate.
- For moderate NPDR and severe NPDR, follow-up is advisable at 6 months and 4 months-interval, respectively.
- For PDR, 3 monthly follow up is advised (this decision is also based on treatment response), while DME requires frequent monthly follow-up to look for progression and treatment response. Generally speaking, eyes with moderate NPDR or worse are more likely to have associated DME.

The reasons for vision loss in a patient with DR include CSME, PDR causing pre- retinal hemorrhage, or tractional retinal detachment, and neovascular glaucoma (resulting from neovascularization of iris causing blockage of aqueous humor outflow). While DME is a more common cause of vision loss and leads to loss of central vision, PDR can result in more severe visual impairment, such as loss of perception in both eyes. Once PDR with high risk characteristics is present (NVD $\geq$ 1/3 disc area, any NVD with vitreous or pre-retinal hemorrhage or NVE $\geq$ 1/2 disc area with vitreous or pre-retinal hemorrhage), laser treatment is required. The indications and side effects of various modalities of treatment for DR have been summarized in Table IV.

Laser

Following types of laser are used in management of a patient with DR:

Grid/focal laser photocoagulation: Grid/focal lasers are primarily used for treatment of DME. However, the indications for the use of these lasers are gradually diminishing with the availability of pharmacotherapy for DME. While effective in controlling DME, these lasers do cause collateral damage / burn to retinal tissue (Table IV).

Panretinal photocoagulation: Panretinal photocoagulation (PRP) is the gold standard in management of PDR with high risk characteristics. The role of laser photocoagulation in DR was established by the Diabetic Retinopathy Study[25]. PRP involves administration of 1200-

Table IV: Indications and side effects of various treatment modalities for diabetic retinopathy[34,35]

Treatment	Indications	Side effects/ Complications	Remarks
Laser PRP	PDR Severe NPDR, especially when close follow-up is not possible	Pain during treatment, constriction of peripheral visual field with delayed dark adaptation, transient loss of central vision due to macular edema, VH if neovascularisation present.	Non-invasive, completed in 1-2 visits. Retreatment can be done if incomplete regression of vessels.
Focal/grid laser photo-coagulation	DME	Paracentral scotomas and permanent central scotoma due to inadvertent laser burns close to or at fovea, expansion of laser scar, and choroidal neovascularisation. Transient decrease in central vision may occur.	Given as a one-off treatment which can be repeated, if needed. Use diminishing, being replaced by intravitreal VEGF and/or steroid injections. Preferred in pregnancy with DME.
Intravitreal VEGF	DME PDR	Invasive, risk of complications such as cataract, retinal tear and endophthalmitis. Worsening of traction, increased risk of intraocular inflammation.	Requires multiple visits, especially during the first year. Higher cost compared to laser. Most popular for DME. Also used in combination with laser PRP (one week or immediately before laser PRP) to reduce DME. Can be used as a primary treatment for PDR.
Intravitreal steroids	DME	Invasive, risk of complications such as cataract, glaucoma and infectious endophthalmitis.	Requires multiple visits. Useful for DME that does not respond to other treatment.
Vitrectomy	Non resolving VH Tractional RD involving or threatening macula Tractional rhegmatogenous detachment PDR which does not respond to aggressive laser PRP.	Recurrent VH, retinal tear or RD, vision loss, infectious endophthalmitis, cataract.	Better outcomes and safer procedure with the advancement in the surgical techniques and instrumentation for VR surgery.

Abbreviations: DME-Diabetic macular edema; NPDR- Non-proliferative diabetic retinopathy; PDR- Proliferative diabetic retinopathy; PRP- Pan retinal photocoagulation; RD-Retinal detachment; VH- Vitreous hemorrhage; VR- Vitreoretinal

1800 laser burns to the peripheral retinal tissue, destroying the outer photoreceptor and retinal pigment epithelium. The principle is to convert the hypoxic retina, which is releasing VEGF and other growth factors into anoxic retina by laser ablation. PRP is typically done in 2 to 3 sessions. The side effects of decreased peripheral field of vision and night vision must

be explained to the patient. PRP may exacerbate pre-existing macular edema and hence focal treatment of macular edema (clinically significant or not) should be considered in patients who may require PRP in future.

Vitrectomy

The Diabetic Retinopathy Vitrectomy Study (DRVS) was the initial study to lay down indications for vitrectomy in eyes with DR[26]. In general, vitrectomy is required when there is non-resolving vitreous haemorrhage (typically, vitreous haemorrhage present for more than 3 months), tractional retinal detachment involving or threatening macula, tractional rhegmatogenous detachment or PDR which does not respond to aggressive laser PRP. As technology evolves, results of vitrectomy are becoming increasingly predictable, and surgical results have improved. However, they depend on various patient-related factors, which include macular perfusion, and duration of macular detachment. Prior to any surgical procedure (i.e., vitrectomy, and intravitreal injections), patient's blood glucose must be adequately controlled to reduce chances of infection.

Other pharmacotherapy: Anti-VEGF, corticosteroids, systemic management

In the recent past, the Diabetic Retinopathy Clinical Research Network (DRCR.net) has extensively studied the role of pharmacotherapy and laser in management of DME[27], the results of which would be exhaustive for this chapter. It is important to mention here that there is good evidence available which suggest that DME with preserved visual acuity can be managed conservatively, and treatment can be considered in cases with progression of vision loss. Besides, treatment for DME should only be considered after exclusion of ischemic maculopathy, as inappropriate treatment can lead to further loss of vision. The characteristic feature of ischemic maculopathy is capillary dropout at fovea, with enlargement of foveal avascular zone. The treatment modalities for management of DME have been addressed below:

Intravitreal Anti-VEGF agents are used primarily for DME, although recently their use has also been reported in PDR. These include Ranibizumab, Aflibercept and Bevacizumab[28,29]. The use of these agents in DME has been found to provide better functional and structural outcomes compared to laser treatment.

Intraocular Corticosteroids have been used in the management of DME for a long period of time; their use should be especially considered in DME that does not respond to other treatment. The risk of cataract and increase in intra-ocular pressure must be explained to the patient when prescribing steroids[30]. Steroids are typically preferred in pseudophakic eyes, and eyes without a prior history of glaucoma. The various routes and formulations of corticosteroids are:

- Posterior sub-tenon injection of triamcinolone acetonide (PST): duration of action is 4 to 6 weeks
- Intra-vitreal injection of triamcinolone acetonide (IVTA): duration of action is 4 to 6 weeks
- Intra-vitreal dexamethasone implant (Ozurdex): Injected using a 23G system, the advantage of this implant is sustained action for upto 6 months
- Intra-vitreal fluocinolone acetonide implant (Illuvein): duration of action is upto 3 years.

Cataract surgery and diabetic retinopathy

Individuals with type 1 diabetes are likely to develop cataract at a younger age. It is important to remember that DR (especially severe NPDR, PDR or CSME) may worsen following cataract surgery. Ideally, stable and effective control of the retinopathy and maculopathy should be achieved for at least three months prior to cataract surgery. Post-operative inflammation should be minimised using topical non-steroidal anti-inflammatory drugs (NSAID) or steroids and intra-operative or early postoperative PRP, intravitreal VEGF inhibitors or intravitreal steroids should be considered in selected cases[31-33].

Pregnancy and diabetic retinopathy

Among women with pre-existing diabetes and DR (which was present before conception or was detected early in pregnancy), DR is known to progress faster compared to non-pregnant women. DME is also known to develop or progress during pregnancy. Besides, the progression of DR can continue in postpartum period up to a duration of 12 months. Accordingly, a close watch for DR should be kept in pregnant women with T1DM. Ideally, a dilated retinal examination should be carried out in preconception period for all women with T1DM planning pregnancy. If the same was not possible, a dilated retinal examination should be performed as early in pregnancy as possible; follow-up examinations should be performed at least once in each trimester (the frequency may vary according to severity of DR on initial examination and status of risk factors control). Dilated retinal examination should continue after delivery for patients with DR of any severity and for those with DME, initially at 1-2 months postpartum and subsequently at regular intervals for the next 10-12 months[34, 35].

Intravitreal injections of anti-VEGF agents and triamcinolone are contraindicated in pregnancy due to their teratogenic potential. For women with PDR, laser PRP should be considered within 4 weeks of the diagnosis. For women with severe NPDR, a close follow-up at 1-month interval should be considered; however, laser PRP should be offered for patients with single eye. For non-center involving DME, a close observation is warranted, while for center-involving DME, focal/grid laser photocoagulation should be considered[34,35]. A close collaboration between endocrinologist/diabetologist, ophthalmologist and obstetrician is needed to ensure optimal outcomes.

Conclusion

Screening and regular follow-up, along with systemic control, form the backbone of DR prevention. Patients are often unaware of retinal changes or ignorant of it until vision loss occurs. Retinal changes occur much before vision loss, therefore, providing us with a lead time; this highlights the role of retinal screening in prevention of DR. Once vision loss occurs, the retinopathy has already progressed, although various treatment options exist even at this stage. With improving technology, and availability of non-invasive investigations such as OCT, more accurate diagnosis and treatment of DR has been made possible. Laser PRP is the gold standard for treatment of PDR with high-risk characteristics, while intra-vitreal injections of VEGF and/or corticosteroids are preferred for treatment of DME. In advanced DR, surgical management maybe required, where advances in vitreo-retinal surgery have improved surgical outcomes.

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Chapter-7

Microvascular Complications-Nephropathy

Dr. Arunkumar Subbiah, Dr. Sanjay Kumar Agarwal

Introduction

Diabetic Kidney Disease (DKD) is the most common cause of chronic kidney disease (CKD) in India and worldwide. It is characterised by a combination of albuminuria, reduction of glomerular filtration rate (GFR), and hypertension with increased risk for cardiovascular diseases. A number of studies have revealed the presence of non-albuminuric diabetic nephropathy, which as the name suggests retains all other features of the disease apart from albuminuria. Although type 2 diabetes is the most common cause for diabetic nephropathy in terms of absolute numbers, nephropathy develops in around 25% - 40% of patients with type 1 Diabetes Mellitus (T1DM). End Stage Renal Disease (ESRD) remains the major cause of morbidity and premature mortality in patients with T1DM. Early diagnosis coupled with optimal glycemic control and blood pressure management has improved the prognosis of these patients in the last couple of decades. Herewith we present an overview of nephropathy in T1DM, its pathogenesis, risk factors, management options and outcome.

Epidemiology

Diabetic nephropathy is the single most common cause for CKD in India and worldwide[1]. Though type 2 diabetes mellitus is largely responsible for CKD burden, the incidence of type 1 diabetes mellitus (T1DM) causing CKD is increasing in India. The prognosis of patients with T1DM has improved significantly with better access to healthcare facilities, health education and therapeutic options[2]. This has increased the risk of nephropathy in T1DM patients due to their longer disease duration. Prior epidemiologic studies have shown that 20% – 30% of T1DM patients develop microalbuminuria at around 5 – 10 years after diagnosis[3]. Classically, ESRD is seen in 4% to 17% patients after 20 years of diagnosis of T1DM. In the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) cohort, after 25 years of diabetes, the incidence of ESRD was 2% and 1% respectively in the conventional and intensively treated groups[4].

Recent studies have shown that the risk of ESRD ranges between 2.5 – 7.8% at around 30 years of T1DM duration (Table I)[5]. In the study by Bhatia et al, out of 160 diabetic patients, 81% had T1DM and at a mean disease duration of 10.2±4.6 years, 18% developed nephropathy[6]. Ramachandran *et al* reported nephropathy in 7.1% patients with T1DM while in the study by Jevalikar et al 13.4% had nephropathy at a median duration of 10.5 years[2]. A study from North India on 512 T1DM reported hypertension in 11.7%, microalbuminuria in 10.3%, and gross albuminuria in 3% patients with median diabetes duration of 102 months[7]. Non-albuminuric phenotype of diabetic nephropathy has been

reported mainly in T2DM; in a Finnish study, this was present in 2% of T1DM patients[8]. Though this study demonstrated an increased risk for cardiovascular mortality, further studies would be needed to ascertain the exact risk posed by the non-albuminuric phenotype in T1DM.

Table I: Epidemiology of nephropathy in T1DM

| Ref.	Year	Author	No of cases	DOD (Yr)	Prevalence
4	2009	DCCT Trial	1602	25	▪ ESRD 2%
4	2009	EDIC Study	1602	25	▪ ESRD 1%
5	2010	Mollsten A et al.	11681	30	▪ ESRD 2.5 – 7.8%
6	2004	Bhatia V et al.	160	10.2	▪ Nephropathy 18%
2	2019	Ramachandran et al.	617	10.5	▪ Nephropathy 7.1%
2	2019	Jevalikar et al.	577	10.5	▪ Nephropathy 13.4%
7	2019	Sudhanshu S et al.	512	8.5	▪ Microalbuminuria 10.3% ▪ Overt proteinuria 3%
8	2015	Thorn LM et al.	3809	21.2	▪ Non-albuminuric nephropathy 2%

Abbreviations: T1DM-type 1 diabetes mellitus, Yr-year, DCCT- Diabetes Control and Complications Trial, DOD-Duration of disease; EDIC-Epidemiology of Diabetes Interventions and Complications

Pathogenesis

Hyperglycemia is the sine qua non for development of kidney disease in diabetes mellitus. In T1DM, this is the sole initiating factor for nephropathy while in T2DM, apart from hyperglycemia, risk for renal structural injury is often concomitantly contributed by ageing, effects of hypertension, obesity and dyslipidemia[9]. Hyperglycemia alters both blood flow and glomerular vascular permeability. The increase in renal blood flow and intra glomerular capillary pressure reduces nitric oxide synthesis in efferent vessels which in-turn increases its sensitivity to angiotensin II. Also, hyperglycemia stimulates mesangial matrix expansion and promotes apoptosis of mesangial cells. This causes a profibrotic milieu which in the early stages is potentially reversible. In addition to these rheologic effects, hyperglycemia induced mitochondrial superoxide production offsets the cellular redox balance resulting in oxidative stress. The resulting mitochondrial DNA damage initiates a vicious cycle of persistent reactive oxygen species (ROS) production. Furthermore, there is a concomitant increase in synthesis of advanced glycation end-products (AGEs). The AGEs interact with receptor for AGE (RAGE) to induce expression of TGF-β and other profibrotic cytokines thereby promoting tubulointerstitial fibrosis. The various pathways involved in development and progression of diabetic nephropathy are depicted in Figure 1.

Hyperglycemia, AGEs, ROS activate protein kinase C (PKC) which promotes glomerular basement membrane thickening. T1DM is associated with raised prorenin activity. Prorenin activates mitogen-activated protein kinase (MAPK) which is fibrogenic. Activation of inflammatory cytokines promotes matrix expansion in T1DM. Downregulation of expression of the transmembrane protein, nephrin is associated with improper filtration and albuminuria seen in T1DN. The role of toll-like receptors and ubiquitin proteasome system (UPS) in promoting progression of diabetic kidney lesions and renal fibrosis is being evaluated[10].

Figure 1: Pathophysiology of diabetic kidney disease. Central role of hyperglycemia and downstream effects leading to renal insufficiency.
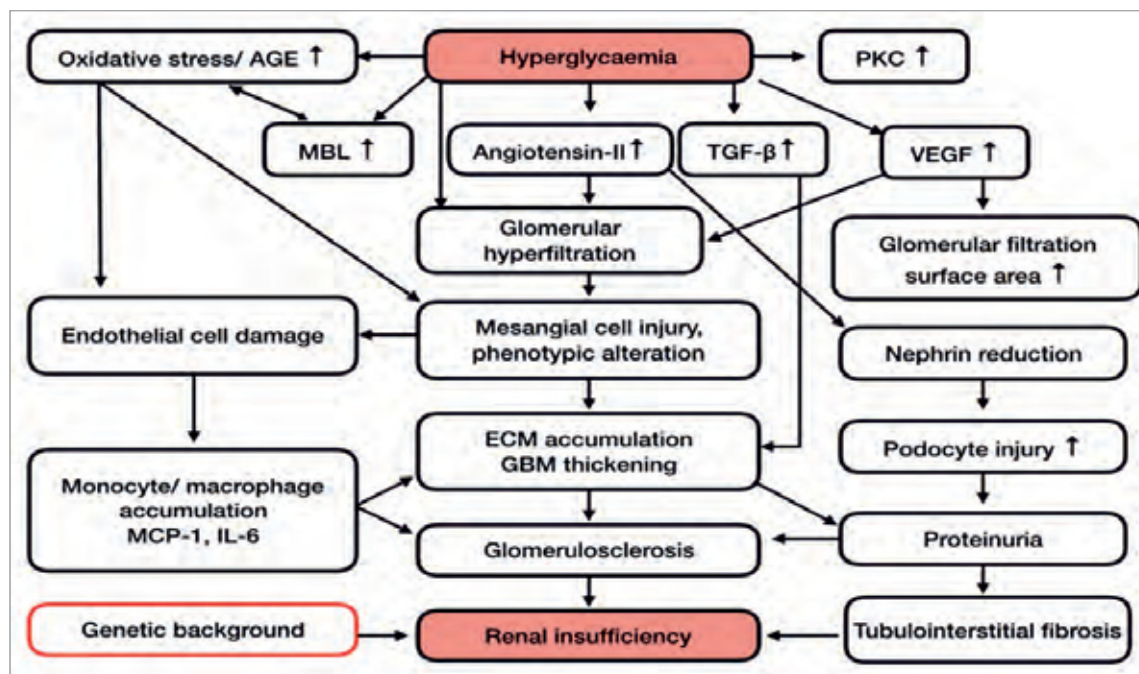
Abbreviations: AGE-advanced glycation end products; ECM-extracellular matrix; GBM,-glomerular basement membrane; MCP-monocyte chemoattractant protein; PKC- Protein Kinase C; TGF-β- transforming growth factor; VEGF- vascular endothelial growth factor, IL6-Interleukin 6. MBL - Mannose binding lectin

Risk Factors

Risk factors for nephropathy in T1DM can be grouped as modifiable and non- modifiable and can also be grouped as risk factors for initiation and progression of nephropathy.

A. Factors for initiation of nephropathy

- Genetic factors
- Hyperglycemia

B. Factors for progression of nephropathy

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Proteinuria

Recent data stress on the role of genetic variables in conferring susceptibility or protection from nephropathy in T1DN. The different time durations for development of DN in transplanted patients reaffirms the role of a genetic predisposition to kidney disease. Diabetic nephropathy is a complex genetic disease involving multiple genetic loci and not explained by any Mendelian inheritance model[11]. The importance of genetic background in T1DN was first shown by Seaquist et al who concluded that there was a four-fold increased risk of DN in patients whose siblings had T1DM and nephropathy. Familial clustering of cases suggests a genetic basis for the disease.

Susceptibility genes reported in DN of T1DM are:

1. FRMD3 gene
2. CARD gene
3. AFF3 gene
4. Intergenic SNP on chromosome 15q26 between the genes RGMA and MCTP2
5. Intronic SNP in the ERBB4 gene

The role of genetic factors in progression of DN is under study and may throw light on the approaches to contain and reverse DN. Recent studies highlight the importance of epigenetic modifications including DNA methylation and histone post translational modification (PTMs) in susceptibility to DN.

Poor glycemic control is an important predictor of both initiation as well as progression of diabetic kidney disease[12]. There is a "legacy effect" or "metabolic memory" wherein patients with initial poor glycemic control tend to develop progressive diabetic complications even after they have achieved better glycemic control in the later stages. This highlights the importance of early glycemic control in preventing microvascular and macrovascular complications of diabetes.

Glomerular volume and number are also believed to determine nephropathy risk. Lower the number of glomeruli, higher is the risk for progression of diabetic nephropathy. Patients with higher glomerular volumes develop DN later than those with lesser volumes. Other risk factors for progression of DN include an increased body mass index (BMI), smoking and oral contraceptive pill (OCP) use. Older age, female sex and longer duration of T1DM has been shown to be a risk factor for DN in non-albuminuric patients[8].

Clinical features and Staging

The natural history of diabetic kidney disease is a little different in T1DM and T2DM. The classic history of DN in T1DM is divided into five stages and was initially described by Mogensen[13]. Most patients with T2DM do not follow the classic pattern of DN progression from albuminuria to macroproteinuria to renal dysfunction, as seen in T1DM.

Stages of diabetic nephropathy (figure 2)

Stage 1: Hyperfiltration stage – The earliest preclinical stage associated with glomerular hypertrophy with resultant increase in GFR.

Stage 2: Silent stage – This is characterised by near normal GFR and also no overt clinical features. Characteristic pathological structural changes seen in renal glomeruli are basement membrane thickening and mesangial expansion. This occurs after 5 – 8 years of diabetes and can be associated with mild hypertension detected by ambulatory blood pressure monitoring (ABPM)[14].

Stage 3: Microalbuminuria (MA) stage or Incipient nephropathy – It is characterised by urinary albumin excretion in the range of 20 to 200 µg/min or 30 to 300 mg/24 h. The onset is usually 5 – 15 years after onset of T1DM and this is the earliest measurable marker of diabetic kidney disease. In the present classification this is referred to as 'moderately increased albuminuria'. Initially MA was considered to be a marker for progressive glomerular damage. This concept has lost favour with recent evidence showing that MA is often transient and reversible in a subset of patients with good glycemic and blood pressure control. In the DCCT/EDIC cohort of patients, after 10 years of onset of

MA, 40% reverted back to normoalbuminuria; 28% developed overt proteinuria while 4% progressed to ESRD[15]. In the Oxford Regional Prospective Study, 52% of patients exhibited 'intermittent' microalbuminuria. Therefore, as a marker of progressive diabetic nephropathy, MA should be persistent.

Stage 4: Macroalbuminuria stage or Overt nephropathy – This stage has urinary albumin excretion greater than 300 mg/24 h. In the present classification, this stage is referred to as 'severely increased albuminuria'. This stage is usually associated with development of hypertension and the GFR starts reducing from this stage.

Stage 5: Renal impairment – Progressive decrease in GFR occurs in 25 – 40% of T1DM resulting in worsening CKD and ESRD which is the final common endpoint of kidney disease progression.

Microalbuminuric T1DM patients have a median risk ratio of 21 for developing DN. Sequential progression of DN in T1DM does not always occur. It has now been observed that like in T2DM, patients can have renal dysfunction without albuminuria, the so called non-albuminuric phenotype. Also, in the second Joslin Kidney Study it was seen that even in the microalbuminuric stage, over one-third of patients had renal dysfunction. Apart from MA and glycemic control, the other risk factors for progression of DN include familial clustering, ethnicity, smoking, dyslipidemia and hypertension.
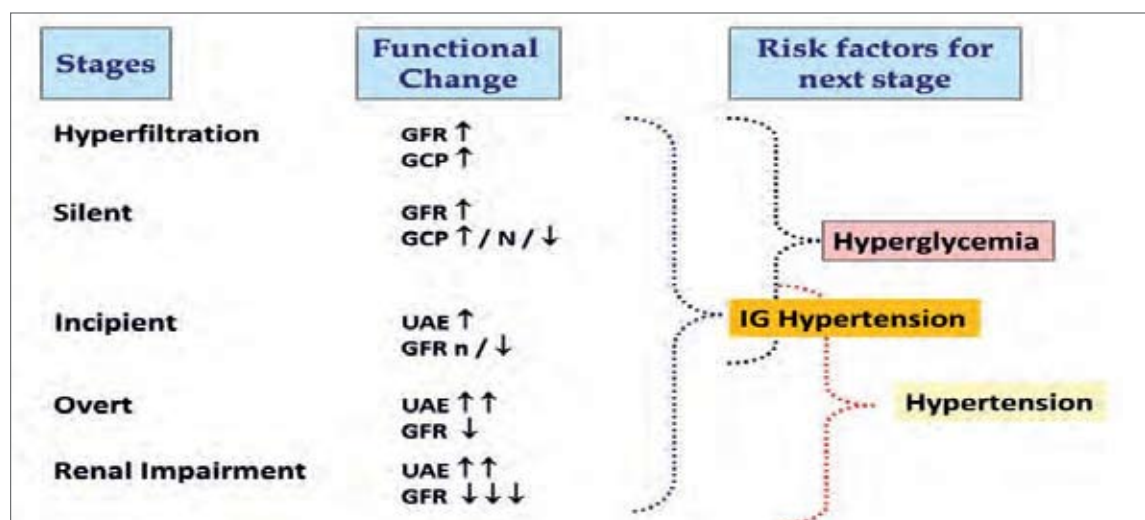
Figure 2: Salient features of stages of nephropathy in T1DM

Abbreviations: T1DM-Type 1 Diabetes Mellitus, GFR-glomerular filtration rate, GCP-glomerular capillary pressure, UAE-urinary albumin excretion, IG-intraglomerular, n and N-Normal

Diabetes affects the glomeruli, interstitium and the vascular component of the kidney. The classical pathological feature of diabetic nephropathy is diffuse or nodular glomerulosclerosis. This is however a late feature of DN. Early changes include mesangial expansion and glomerular basement membrane thickening, which are the most common lesions in DN. The histopathological classification of DN (both T1DM and T2DM) developed by Tervaert et al[16] is as follows:

Class I: Isolated glomerular basement membrane (GBM) thickening
Class II: Mesangial expansion (II a <25%; II b >25%)
Class III: Nodular mesangial matrix expansion with Kimmelstiel-Wilson lesion
Class IV: Advanced diabetic glomerulosclerosis (involving >50% glomeruli)

In addition, interstitial fibrosis and tubular atrophy (IFTA) is graded based on the extent of interstitial involvement:

Score 0 :   No IFTA
Score 1 :   < 25% IFTA
Score 2 :   25 – 50% IFTA
Score 3 :   > 50% IFTA

Glomerular and tubular basement membrane thickening with mesangial expansion is almost always present in DN. Kimmelstiel-Wilson lesion and Arteriolar Hyalinosis are often present in advanced disease while subendothelial hyaline "exudative" lesions and capsular drops, though rare, when present are characteristic of DN[17].

Podocytes maintain the integrity of the glomerular filtration barrier and are affected in diabetic kidney disease. Foot process effacement and decreased number of podocytes are seen in T1DM patients. Tubuloglomerular feedback results in hyperfiltration in diabetics; this tubular dysfunction contributes to albuminuria due to defects in lysosomal uptake and processing. Extensive studies are needed to understand the respective roles of tubuloglomeular feedback and podocytes in progression of diabetic kidney disease.

Differentiation from non-diabetic renal disease

Nondiabetic renal disease (NDRD) is rare in patients with T1 DM, unlike in type 2 diabetes, with a reported incidence of 2 – 3% among those with renal disease. The classical pointers for NDRD are presence of hematuria, rapidly deteriorating renal function, sudden onset of gross proteinuria, shorter duration of diabetes and absence of other microvascular complications (especially retinopathy)[18]. The presence of these features necessitates the requirement for kidney biopsy to establish the cause for kidney disease. Once the patient has had diabetes for over 30 years without any end organ involvement, it is very rare for the patient to develop diabetic nephropathy.

Diabetic patients can be afflicted with other renal diseases too. Patients with diabetes are at increased risk for atherosclerosis and consequently renal artery stenosis, which presents as difficult to control hypertension with episodes of flash pulmonary edema and progressive renal function. Papillary necrosis can occur in the setting of urinary tract infections or intake of nonsteroidal anti-inflammatory drugs. These patients present with hematuria, flank pain and fever. Diabetes results in a hyporeninaemic state with hypoaldosteronism and can present with hyperchloremic metabolic acidosis and hyperkalemia.

Screening and diagnosis

The diagnosis of diabetic nephropathy rests on the measurement of albuminuria and renal function. An annual assessment has to be done in all T1DM with disease duration of 5 years or more. The traditional model of diabetic kidney disease consists of three sequential stages – that of microalbuminuria followed by overt proteinuria, which is followed by progressive CKD culminating in ESRD. This was the basis for the therapeutic strategy of using renin angiotensin aldosterone system (RAAS) blockade to prevent progression of DN by controlling albuminuria.

Diabetic nephropathy is diagnosed by the presence of persistent albuminuria of > 300 mg/24 hours or an albumin-creatinine ratio (ACR) of > 300 mg/g in 2 out of

3 samples usually in the presence of diabetic retinopathy with no other obvious kidney disease. Microalbuminuria (30 – 300 mg/g) is the earliest detectable marker of DN. Screening for MA should be done yearly to detect renal involvement at an early stage. Early morning spot urine assessment is sensitive screening tool for MA. Due to issues with standardisation of tests and day-to-day variability, at least 2 spot samples in a period of 6 months are required to confirm the diagnosis of persistent MA. Alternatively, a 24-hour urine collection can be done for confirmation. The definition for albuminuria in diabetic kidney disease is provided in Table II[19].

Table II: Definition of albuminuria in diabetic kidney disease

Terminology	Definition
Normoalbuminuria	Urinary albumin < 20 µg/min or < 30 mg/24 h or ACR < 30 mg/g
Moderately increased albuminuria (Microalbuminuria)	Urinary albumin of 20 to 200 µg/min or 30 to 300 mg/24 h or ACR of 30 – 300 mg/g
Severely increased albuminuria (Macroalbuminuria)	Urinary albumin of > 200 µg/min or > 300 mg/24 h or ACR > 300 mg/g

Abbreviation: ACR- albumin creatinine ratio

Renal function assessment is done using serum creatinine based eGFR calculation. The most widely used formula is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae. Derangements in renal function usually accompanies worsening albuminuria in diabetic patients, the only exceptions being the non-albuminuric phenotype wherein renal dysfunction progresses without albuminuria.

The future for recognising patients at risk for DN and its progression depends on the "omics" platforms. Genomic studies are expected to throw light on susceptibility genes. Transcriptomics on renal biopsy specimen may aid in identifying progressors. The discovery of the role of JAK-STAT pathway and the probable role of its inhibitor in managing DN is a testimony for the future role of transcriptomics in DN. Metabolomic profiling of urine and serum samples have shown some promise in T2DM. Urinary proteomics of peptide profile in urine can identify cases at high risk for progression of kidney disease. The Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients with Normoalbuminuria (PRIORITY) is a study in progress to classify high risk patients based on proteomic analysis. The use of "omics" in DN will pave the way for personalized medicine in the future[19]. Neutrophil gelatinase associated lipocalin (NGAL), plasma growth differentiation factor 15, chitinase-3-like protein 1 are some new biomarkers being evaluated to identify early diabetic kidney disease before microalbuminuria sets in.

Overview of management, referral and follow up plan

The mainstay of management of DN focusses on glycemic control, antihypertensive therapy, lipid lowering drugs and dietary protein restriction. The aim of therapy is to prevent progression from normoalbuminuria to microalbuminuria (primary prevention), microalbuminuria to overt nephropathy and CKD (secondary prevention).

Primary prevention

Glycemic control is quintessential to prevent complications of diabetes be it type 1 or type 2. Any duration of strict blood glucose control preserves GFR, takes care of hyperfiltration

injury and hyperperfusion. Even 3 weeks of intensive therapy tends to improve the renal hemodynamics and consequently renal prognosis[20]. The DCCT study showed that MA reduced by 39% (95% CI, 0.21 to 0.52) and albuminuria reduced by 54% (95% CI, 0.19 to 0.74) in the intensive arm. On follow up in the EDIC study, the intensive arm had 50% reduced risk (95% CI, 0.18 to 0.69; P = 0.006) for worsening kidney disease[15]. Long term intensive blood glucose control has shown to reduce the odds for progressing from normoalbuminuria to microalbuminuria by 0.22 to 0.40[21].

Glomerular hypertension is a major factor for DKD and reducing the intraglomerular pressure is expected to be beneficial for the kidney. Among normotensive, normoalbuminuric TIDM patients, the Renin Angiotensin System Study (RASS) compared the efficacy of Angiotensin receptor blocker (ARB), ACE inhibitor and placebo over 5 years[22]. The trial failed to show any benefit for RAAS blockade with regard to nephropathy and albuminuria. However, there was a significant reduction in incidence of diabetic retinopathy. This was also shown in the DIRECT study wherein candesartan reduced the incidence (but not progression) of retinopathy with no beneficial effects on albuminuria incidence[23]. This is in contrast to T2DM where RAAS blockade has shown to reduce the incidence of microalbuminuria in multiple studies. One explanation could be that the trials in T2DM had hypertensive patients while the T1DM patients were normotensive. At present evidence base does not suggest the use of ACEi/ARB in normotensive normoalbuminuric diabetic patients.

Secondary prevention

Secondary prevention relies on the fact that multimodal intervention targeting risk factors for progression of DN will help revert the changes of DN. The most important element is optimal blood glucose control. Studies on patients with pancreatic transplantation revealed reversal of glomerulopathy with 5 years of normoglycemia. The time duration of normoglycemia or intensive glucose control to reverse the end organ damage in diabetes stays uncertain. There are no studies to show the direct effect of glycemic control on secondary prevention in T1DM.

Antihypertensive therapy with RAAS blockade has been shown to delay the progression of MA to overt nephropathy and CKD in T1DM patients. Though blood pressure targets are based on studies in type 2 diabetes, the general recommendation from American Diabetic Association (ADA) is to target a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg[24]. A lower target of <130/80 mmHg is suggested for those with high risk of cardiovascular disease. A recent meta-analysis in T1DM patients showed that RAAS blockade has a long-lasting effect on preventing progression to overt nephropathy with significant reduction in albuminuria. The risk of macroalbuminuria (from MA) was reduced significantly (OR 0.38; 95% CI, 0.25 to 0.57)[25]. The cost effectiveness of early screening and RAAS blockade has also been demonstrated by various studies.

Overt nephropathy

The primary aim of therapy in established diabetic nephropathy is to prevent progression of kidney disease to ESRD. Early initiation of therapy focussing on albuminuria reduction has long lasting beneficial effects on renal function. This was obvious in the study by Parving et al where early therapy improved both albuminuria and renal function in T1DM. The Captopril Collaborative Study Group demonstrated a remarkable reduction in risk of doubling of serum creatinine in T1DM patients treated with captopril (48%; 95% CI, 16 to

69%)[26]. Regression of DKD is seen in those on intensive antihypertensive therapy. There was an additional benefit for RAAS blockade in addition to the one obtained by routine antihypertensive therapy for blood pressure control.

The effects of RAAS blockade varies in patients due to interpatient variability of RAAS. This can be explained by the role of ACE gene polymorphism. Individuals with T1DM with homozygous II polymorphism have been shown to respond better to RAAS blockade. This was proven in the EUCLID study wherein patients with II genotype had 57% reduction with lisinopril as against 17% in the ID group and 19% in the DD group[27]. The DD genotype is associated with more rapid loss of renal function and warrants more aggressive RAAS blockade. Direct comparisons between ACEI and ARBs have shown that they offer similar short-term and long- term renoprotection. The optimal daily ARB dosage for maximum anti-proteinuric effect is 100 mg for losartan, 320 – 640 mg for valsartan, 80 mg for telmisartan, 128 mg for candesartan and 900 mg for irbesartan[28]. Though most patients achieve optimal response at standard dosage, some patients require supra-maximal dose for best results. Combined RAAS blockade is not advised as apart from minimal improvement in albuminuria control, none of the trials have exhibited substantial renoprotection or cardio protection.

The prognosis for diabetic nephropathy in T1DM has improved notably during the past three decades. Prior studies reveal a poor prognosis for patients with diabetic nephropathy with a median survival of 5 – 7 years and ESRD being the most important cause of death in 66% of patients. With the regular use of antihypertensive therapy in the 1970s, the mortality rate dropped to 18% at 10 years of diabetic nephropathy. The Collaborative Study Group showed that captopril reduced the risk for death or progression to ESRD by 61% (95% CI, 26 to 80%, P = 0.002)[26]. In one of the recent prospective study by Astrup et al, the median survival in DN was 21 years, a noteworthy improvement over the years[29].

Other treatment options

The therapeutic armamentarium in DN is limited. The effects of lipid lowering therapy on progression of DKD are variable and inconclusive. At present, statin therapy is recommended in diabetic patients with CKD stages 1-4 by the ADA and it can be continued in ESRD if the patient is already on therapy.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors block the SGLT2 transporter in the proximal renal tubule. This causes glucosuria, natriuresis and improves glycemic control in T2DM. The renoprotective and cardioprotective effects of SGLT2i in T2DM has been now proved beyond doubt. Hence, the question arises as to whether they can be used to prevent complications in T1DM. Some reports have suggested that SGLT2i use is safe in T1DM apart from the risk of diabetic ketoacidosis. Further long-term studies are required before they can be recommended for routine use in T1DM[30].

Dietary protein restriction (0.6 to 0.8 g/kg/day) reduces glomerular hyperfiltration and consequently albuminuria. In a prospective study of T1DM patients with progressive nephropathy it was seen that over 4 years, only 10% of patients on a low-protein diet progressed to ESRD as against 27% on a normal protein diet conferring a relative risk of 0.23 (95% CI, 0.07 to 0.72)[31].The present Kidney Disease Outcome and Quality Initiative (KDOQI) guidelines recommend a protein intake of 0.8 g/kg body weight/day for CKD patients of stages 1 to 4.

Vitamin D analogues have shown some promise in diabetic nephropathy in conjunction with RAAS blockade but further studies are required before any recommendation can be made. Soludexide, a glycosaminoglycan combination and Tranilast, an antifibrotic agent have been tried to prevent progression of DKD.

In patients who have progressed to ESRD, renal transplantation offers the best survival advantage and quality of life. Though people with diabetes in general have a poorer outcome than those without disease, the advantage of transplantation over dialysis is still significant in them. With the advent of better powerful immunosuppressants, combined kidney-pancreas transplantation is increasingly associated with better glycemic control, improved survival and better cardiovascular outcomes.

Conclusions

Diabetic nephropathy is a serious complication of T1DM associated with significant morbidity and mortality. Though the pathogenesis is multifactorial, hyperglycemia is the predominant inciting factor and early optimal glucose control ensures best prognosis. Screening and diagnosis depend on assessment of albuminuria and renal function which has to be done annually once the disease duration is five years or more. Non-albuminuric phenotype of DN needs to be thought of when isolated renal dysfunction is present. Though microalbuminuria has long been considered a reliable and the earliest marker of diabetic nephropathy, it can be temporary or transient and patients may have associated renal dysfunction even at diagnosis. Newer biomarkers and use of advanced "omics" technology may pave the way for earlier diagnosis and personalized management in the future. At present, management consists of adequate glucose control, optimal blood pressure management with RAAS blockade and close follow-up. The future research in DKD focusses on early screening and diagnosis with better preventive measures for protection from adverse renal and cardiovascular outcomes.

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Chapter-8

Microvascular Complications - Neuropathy

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Epidemiology

Neuropathy is a common microvascular complication in patients with type 1 diabetes mellitus (T1DM) which is associated with significant morbidity and mortality. It is the most important contributing factor for the development of foot ulcers and lower extremity amputations. The prevalence of neuropathy in T1DM varies from 7% to 57% in smaller studies, depending on the criteria used to define it. Data from Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/ EDIC) study suggest that at least 20% of patients with T1DM develop distal symmetric polyneuropathy (DSPN) by 20 years from the onset of diabetes[1]. Similar prevalence rates are also reported for cardiac autonomic neuropathy (CAN). In a systematic review and meta-analysis, the pooled prevalence of peripheral neuropathy was higher in subjects with T1DM in>16-yr age group compared to those in < 16-yr age group (59.1% vs. 9.5%) and in those with duration of diabetes >10 years compared to those with disease duration of <10 years (35.0% vs. 9.4%)[2]. In a long-term follow-up study involving 27 subjects with T1DM and mean diabetes duration of 40 years, small fiber and large fiber neuropathy were reported in 22 (81%) and 16 (59%) participants, respectively[3].

There is a paucity of data on the prevalence of microvascular complications in Indian patients with T1DM. In a multicenter study by Unnikrishnan and colleagues involving 535 subjects with T1DM with a mean diabetes duration of 5.6 years, the prevalence of neuropathy was reported to be 6%[4].

Pathogenesis

The factors contributing to development of neuropathy in individuals with diabetes are not completely understood. Multiple hypotheses have been proposed and it is believed that diabetic neuropathy (DN) is a multifactorial process. The most important factor in the pathogenesis of neuropathy in patients with T1DM is hyperglycemia whereas minor contributions are microvascular insufficiency and autoimmunity. The fact that hyperglycemia plays a pivotal role in pathogenesis of DN is evident from the results of DCCT trial, wherein benefits of intensive glycemic control persisted even >10 years after the study completion (metabolic memory). Hyperglycemia contributes to the development of DN by multiple mechanisms such as increased polyol pathway flux, AGE formation and PKC activation[5].

Increased polyol pathway flux

High concentration of intracellular glucose shunts the excess glucose into polyol pathway leading to increased production of sorbitol and fructose by the enzymes aldose reductase

and sorbitol dehydrogenase, respectively. Accumulation of these impermeable substances leads to osmotic stress and efflux of other osmolytes such as myoinositol, taurine and adenosine. The decrease in myoinositol reduces the formation of ATP and in turn, reduces the activity of $Na^+/K^+/ATPase$ leading to impaired axonal transport. Utilization of NADPH during aldose reductase-mediated conversion of glucose to sorbitol results in a shortage of NADPH required for regeneration of reduced glutathione (GSH), which in turn causes oxidative stress.

Increased advanced glycation end products

There is increased formation of advanced glycation end (AGE) products in intracellular and extracellular compartments. Increased intracellular AGE formation occurs due to nonenzymatic reaction of excess glucose with proteins and nucleotides which leads to impairment of neurotropic support and repair mechanisms. AGE also increases the glycation of mitochondrial proteins including enzymes of oxidative phosphorylation and alters their function leading to oxidative stress. Increased extracellular AGE formation causes activation of receptors for advanced glycation end products (RAGE) and stimulates an inflammatory response by activating nuclear factor kappa B (NF-kB).

Activation of Protein Kinase C pathway

Increased diacylglycerol formation leads to activation of protein kinase C (PKC) β and δ isoforms. The role of PKC pathway activation in the pathogenesis of DN is not clear. The limited data suggests that PKC activation may reduce nitric oxide (NO) production and increase endothelin-1 activity leading to reduced nerve blood flow; it may also reduce $Na^+/K^+/ATPase$ activity, resulting in decreased nerve conduction and nerve regeneration. The role of hexosamine pathway activation in the pathogenesis of DN is less explored.

Increased oxidative stress

Increased glycolysis and TCA cycle activity produces an over-abundance of NADH and FADH2 electron donors leading to a high proton gradient across the inner mitochondrial membrane, which disrupts oxidative phosphorylation and, in turn, markedly increases reactive oxygen species (ROS) production. This increased ROS production is in fact, the primary inducing process of each of the above described different mechanisms.

Autoimmunity

Although not definitive, there have been some evidences to suggest a role for autoimmunity in the pathogenesis of DN. Autoimmune neuropathies like chronic inflammatory demyelinating neuropathy (CIDP) and vasculitis are significantly more common in both T1DM and T2DM subjects and account for a large proportion of proximal neuropathies in these patients. In a retrospective health insurance administrative claims database study, the prevalence of CIDP in in a patient population with diabetes was found to be 9-fold higher compared to a patient population without diabetes (54 per 100,000 persons vs. 6 per 100,000 persons)[6]. Similarly, in a hospital-based study, Sharma et al reported that the odds of occurrence of CIDP were 11-fold higher in subjects with diabetes compared to those without diabetes[7]. While an occurrence of CIDP is reported to be equal in T1DM and type 2 diabetes mellitus (T2DM) by some investigators[7], others have reported it to be more frequent in T2DM[8].

Risk factors

Duration of diabetes and severity of hyperglycemia are the two most important risk factors for development of DN[9]. Features of insulin resistance such as dyslipidemia

(especially elevated triglycerides) and high blood pressure are additional risk factors. Smoking contributes significantly to the development of DN[10]. Besides, exposure to toxic substances like alcohol may enhance the development of DN. Patients with other microvascular complications such as microalbuminuria and retinopathy are at a higher risk of DN. Height may be an independent predictor since DN is a typical length dependent neuropathy. Recent evidences also favor a role of genetics in the development of DN.

Clinical features and staging

DN is defined as the presence of signs and/or symptoms of peripheral neuropathy in a patient with diabetes, after other causes of neuropathy have been excluded. The clinical presentation of DN is varied, depending on the type, duration and extent of neuropathy. Symptoms are often mild and frequently go unnoticed in the initial stages. It is mainly classified into diffuse neuropathy (>90%) and focal/multifocal neuropathy (<10%) (Table I). Focal/multifocal neuropathies are generally characterized by acute/subacute onset, focal deficits, presence of pain and spontaneous partial/complete recovery. These have been described more commonly in older patients with T2DM and may co-exist with the prototypical distal symmetrical polyneuropathy (DSPN) in a given patient.

Table I: Classification of diabetic neuropathy

I. Diffuse neuropathy (>90%) A. Distal symmetric polyneuropathy (DSPN) • Primarily small-fiber neuropathy • Primarily large-fiber neuropathy • Mixed small- and large-fiber neuropathy B. Autonomic neuropathy • Cardiovascular • Gastrointestinal • Urogenital • Sudomotor dysfunction • Hypoglycemia unawareness • Abnormal pupillary function	II. Focal or multifocal neuropathy (<10%) A. Mononeuropathy B. Isolated cranial or peripheral nerve neuropathy C. Mononeuritis multiplex D. Radiculopathy E. Lumbosacral polyradiculopathy (proximal motor amyotrophy) F. Thoracic radiculopathy

Diffuse neuropathy

Distal symmetric polyneuropathy

DSPN is the classical presentation of neuropathy in patients with diabetes. It can present as predominantly small fiber or large fiber neuropathy or more commonly as mixed small and large fiber neuropathy. DSPN is a typical length dependent polyneuropathy and hence, the initial symptoms and signs manifest in the feet and legs; as neuropathy progresses, the lower limb affection extends up to knees and hands are also affected.

Small fiber neuropathy

Small fiber neuropathy occurs due to involvement of unmyelinated C fibers and thinly myelinated Aδ fibers. Positive symptoms predominate and include burning, or lancinating pain (C fiber pain) often accompanied by hyperalgesia, dysesthesia and allodynia. As the disease progresses, numbness and hypoalgesia may occur. Hence, disappearance of pain should not always be interpreted as recovery of neuropathy and most often it reflects the progression of neuropathy, making the feet vulnerable to infection Loss of pinprick

sensation is a simple objective test for small fiber neuropathy. Abnormal thermal sensation is an additional manifestation of small fiber neuropathy.

Small fiber DSPN is also characterized by autonomic dysfunction in the feet with decreased sweating, dry skin, impaired blood flow and cold feet. Motor functions are usually preserved with intact motor strength and deep tendon reflexes. Since small fibers contribute less towards nerve conduction velocity (NCV), small fiber dysfunction may not be detected by routine nerve conduction studies. Sweat glands are innervated by unmyelinated sympathetic C fibers and abnormality of sweat gland innervation, that is, sudomotor dysfunction is an early and sensitive marker for small fiber neuropathy. Sudomotor dysfunction can be detected by: a) quantitative sudomotor axon reflex test (QSART) which measures postganglionic sympathetic cholinergic function. QSART involves iontophoresis of acetylcholine to produce local sweating which is quantified by a sudorometer, and b) electrochemical skin conduction test (Sudoscan) which is based upon the principle of reverse iontophoresis. This test involves application of low voltage current which attracts chloride ions from sweat gland, and an electrochemical reaction occurs between chloride ions in sweat and stainless steel based plate electrodes, on which patient's palm and sole (areas with highest sweat gland density) are placed. Reduced intra epidermal nerve fiber density (IENFD) on skin biopsies (3 mm punch) is also a good test for the early diagnosis of small fiber neuropathy. However, it is not recommended in routine practice. An alternative emerging non-invasive testfor the early diagnosis of small fiber neuropathy is corneal confocal microscopy (CCM).

Treatment induced neuropathy of diabetes (TIND) is a rare iatrogenic form of small fiber neuropathy which results from abrupt intensification of glycemic control in a patient with chronic hyperglycemia. This condition can occur subsequent to treatment with either insulin or oral glucose lowering drugs, and hence, the term "insulin neuritis" used previously for this condition is not preferred. TIND is associated with severe pain and is often accompanied by hyperalgesia and allodynia; fortunately this condition is rapidly reversible and remits in less than 6 months in most cases.

Large Fiber Neuropathies

In large fiber neuropathy, large myelinated, rapidly conducting Aα/β fibers (which serve sensory as well as motor function) are affected. Symptoms may be minimal and include numbness (sensation of walking on cotton, floors feeling "strange") and tingling without pain. Large fiber neuropathy is a disease of signs which include impairment of vibration perception (often the first objective evidence, 128-Hz tuning fork), light touch perception (reduced sensitivity to 10 g Semmes Weinstein monofilament) and joint position perception and presence of sensory ataxia. Initial motor system abnormalities include abnormal deep tendon reflexes (ankle reflex) and wasting of small intrinsic muscles of feet with hammertoe deformities. Large fiber neuropathy increases risk for falls, fractures, and development of Charcot neuroarthropathy.

Grading of DSPN severity

The severity of DSPN can be estimated by the staging system provided by Dyck[11]:

- Grade 0 = Normal nerve conduction (NC)
- Grade 1a = Abnormal NC without symptoms or signs
- Grade 1b = Abnormal NC plus signs of DSPN but no symptoms

- Grade 2a = Abnormal NC plus symptoms of DSPN with or without signs
- Grade 2b = Abnormal NC plus a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without DSPN symptoms.

Autonomic neuropathy

Identification and appropriate management of autonomic neuropathy is essential since it improves symptoms, reduces sequelae and improves quality of life. Clinical manifestations of diabetic autonomic neuropathy have been summarized in Table II.

Table II: Clinical manifestations of diabetic autonomic neuropathy

Organ system	Clinical manifestations
Cardiovascular	Resting tachycardia, orthostatic hypotension, exercise intolerance, heat intolerance, cardiac denervation with fixed heart rate, painless myocardial infarction, cardiac arrhythmia, intraoperative cardiovascular instability, increased risk of sudden cardiac death
Gastrointestinal	Esophageal dysmotility, gastroparesis, constipation, nocturnal diarrhea, fecal incontinence
Genitourinary	Erectile dysfunction, retrograde ejaculation, vaginal dryness, female sexual dysfunction, diabetic cystopathy, neurogenic bladder
Metabolic	Hypoglycemic unawareness
Pupillary	Argyll-Robertson pupil, impaired dark adaptation, difficulty driving in night
Sudomotor	Hypohidrosis involving the lower extremities, gustatory sweating

Cardiac autonomic neuropathy

Presence of CAN increases the risk of cardiovascular disease (CVD). In the early stages, CAN is usually asymptomatic and reduced heart variability during deep breathing may be the only abnormality. In advanced cases, resting tachycardia and orthostatic hypotension may be demonstrable. CAN is associated with increased mortality and sudden death (malignant arrhythmias). In patients with CAN, intensification of blood glucose and blood pressure control may increase the risk of a cardiovascular event.

Gastrointestinal autonomic neuropathy

Gastrointestinal autonomic neuropathies may affect any portion of gastrointestinal tract. Esophageal dysmotility, gastroparesis (gastropathy), enteropathy (diarrhea), colonic hypomotility (constipation) and fecal incontinence are among the major manifestations of gastrointestinal autonomic neuropathy. It is important to note that acute diabetic gastroparesis may occur in patients with severe hyperglycemia, and is reversible. Chronic gastroparesis is the result of autonomic neuropathy and may manifest with upper abdominal symptoms like postprandial fullness or glycaemic fluctuations.

Genitourinary autonomic neuropathy

The manifestations of genitourinary autonomic dysfunction include urinary incontinence and diabetic cystopathy (neurogenic bladder) which usually manifests as nocturia, frequent urination, urination urgency, and weak urinary stream. Genital dysfunction in men may manifest as erectile dysfunction and retrograde ejaculation, whereas female sexual dysfunction may manifest as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication.

Sudomotor dysfunction

It may manifest as hypohidrosis/anhidrosis of the lower part of the body where nerves are dying. This may lead to fissure and cracks over the skin, culminating into increased risk for foot ulceration. It may also manifest as hyperhidrosis of the upper body where nerves are still preserved. Gustatory sweating which manifests as increased sweating of the face especially during consumption of hot and spicy food could be another manifestation of sudomotor dysfunction in DN patients. Autonomic neuropathy also plays an important role in the pathophysiology of Charcot neuroarthropathy by causing an increase in peripheral blood flow through opening of arteriovenous shunts, thus resulting in increased bone resorption.

Focal and multifocal neuropathy

Cranial neuropathy

It manifests with acute isolated involvement of cranial nerve III, VI, VII, of which cranial nerve III is most commonly involved (diabetic ophthalmoplegia). Diabetic ophthalmoplegia presents with ptosis, diplopia and orbital pain. Peripheral pupillary fibers are often spared, as opposed to surgical causes of III nerve palsy. However, about 15% cases of diabetic ophthalmoplegia may have pupillary involvement and need exclusion of surgical causes like aneurysm and neoplasms.

Entrapment neuropathy

A number of peripheral nerves (such as median, ulnar, radial, lateral cutaneous nerve of thigh and peroneal nerve) are prone to pressure damage in patients with diabetes. Among these, median nerve is most commonly involved as it passes under the flexor retinaculum, leading to carpal tunnel syndrome.

Truncal radiculopathy

The common presentation is pain in dermatomal distribution in the region of chest/ abdomen and asymmetric bulge in abdomen due to weakness of abdominal muscles. The common differentials are herpes zoster and spinal nerve root compression. This condition shares striking similarities with diabetic amyotrophy in terms of significant pain, asymmetry, weight loss and morbidity.

Proximal motor neuropathy

This condition presents with severe pain in the region of thigh or lower back with associated weakness and wasting in proximal lower limbs. The involvement is asymmetric and even if bilateral, one limb is clearly affected to a greater degree. It is also called as diabetic amyotrophy or diabetic lumbosacral radiculoplexus neuropathy (DLRPN). The condition is associated with weight loss, depression and poor glycemic control, and improves over a period of months-years in most cases. Common differentials include chronic inflammatory demyelinating polyneuropathy (CIDP), monoclonal gammopathy of undetermined significance (MGUS) and inflammatory vasculitis.

Charcot neuroarthropathy

In subjects with long standing DN, the bones of the foot may undergo osteoporotic changes and this may lead to the deformity of the foot. When extreme, the destruction and deformity leads to a grossly deformed foot called Charcot foot. In its acute phase,

the foot is red and swollen with elevated local temperature. The differentials of acute Charcot foot include acute cellulitis, osteomyelitis, acute gout and deep venous thrombosis. Untreated, it leads to recurrent micro fractures, bone resorption and development of irregular deformed foot, which is at high risk for foot ulceration (chronic Charcot foot). Sensorimotor neuropathy, autonomic neuropathy and an intact peripheral circulation constitute the prerequisites for development of Charcot neuroarthropathy. Management of acute Charcot foot includes offloading with a total contact cast (TCC), followed by the use of a brace (such as Charcot restraint orthotic walker (CROW), patellar tendon-bearing brace) to protect the foot. Bisphosphonates have been tried in acute Charcot foot, however long term efficacy in preventing foot ulceration and deformity is not known. Reconstructive surgery may be required to correct the deformities of chronic Charcot foot.

Differentiation from non-diabetic neuropathy

Like general population, patients with T1DM are also at a risk of developingnon-diabetic neuropathies. Some non-diabetic neuropathies like pressure palsies and chronic inflammatory demyelinating polyneuropathy are more common in patients with T1DM and T2DM. In a study of T2DM subjects, around 10% of patients with neuropathy had a non-diabetic etiology. Identification of non-diabetic neuropathies often provides an opportunity for specific treatment measures. Hence, it is often recommended to make a diagnosis of DN only after the exclusion of nondiabetic neuropathies. However, an extensive laboratory evaluation for non-diabetic neuropathies in all patients with diabetes and neuropathy may not be cost-effective. In a patient with diabetes, a combination of typical symptoms and symmetrical distal sensory loss or typical signs in the absence of symptoms is highly suggestive of DSPN and may not require additional evaluation or referral to a neurologist. In contrast, patients presenting with some atypical features mentioned below are more likely to have non-diabetic neuropathies and hence, should be evaluated for the same.

a)   Onset of neuropathy at less than 5 years from the diagnosis of diabetes
b)   Pure or predominant motor neuropathy
c)   Asymmetrical neuropathy
d)   Rapid onset or progression of neuropathy
e)   Family history of non-diabetic neuropathy

Screening for diabetic neuropathy

Insensate feet are at a high risk for foot ulceration. Around 50% of T1DM patients with neuropathy may be asymptomatic. Hence, it is important to screen patients with T1DM at regular intervals for DN. It is surprising to know that DN is underdiagnosed not only by physicians but also by endocrinologists. Screening for DN should be initiated five years after the diagnosis of T1DM and repeated at least annually thereafter. Assessment should include a careful history and either temperature or pinprick sensation for small-fiber function and one or more of the following for large-fiber function: vibration sensation using a 128-Hz tuning fork, proprioception (joint position), light touch sensation using 10 g monofilament testing and ankle reflexes. The monofilament test uses 10g monofilament to assess light touch at the pressure points on the sole, and to detect large fiber neuropathy. The monofilament is placed at selected pressure points and just enough pressure is exerted for one second to buckle the filament. As per

the IDF recommendations, four sites should be tested-plantar surface of metatarsal head of first, third and fifth toe, and plantar surface of hallux. An abnormal response at any one site is diagnostic of Loss of Protective Sensation (LOPS). LOPS has been shown to be predict future foot ulcerations in various studies. Biothesiometry is a test that estimates the threshold of vibration in volts or microns using increasing levels of electrical stimulation. The threshold at which vibration is perceived is recorded, and if the patient can perceive vibration only above 15 V, the patient is said to have neuropathy. Nerve conduction studies should only be reserved for patients with atypical neuropathy. Special tests such as IENFD in skin biopsy, quantitative autonomic function testing and CCM should not be done routinely.

Cardiac autonomic neuropathy can be assessed by lack of heart rate variability on an ECG recording during 1-2 min deep breathing and demonstration of orthostatic hypotension (a fall in systolic or diastolic blood pressure by ≥ 20mm Hg or ≥ 10mm Hg, respectively, upon standing without an appropriate increase in heart rate). In a patient with erectile dysfunction, hypogonadism and thyroid dysfunction needs to be excluded (luteinizing hormone, total testosterone, prolactin, total T4 and thyroid stimulating hormone should be measured). The clinical tests and laboratory investigations to diagnose DN, and cardiac autonomic functions tests have been summarised in Table III and Table IV respectively.

Other investigations

Patients with suspected DN should be evaluated for glycemic control and other risk factors such as dyslipidemia. Common causes of non-diabetic neuropathies such as uremia, vitamin B12 deficiency, and hypothyroidism should be excluded. Although DN is a diagnosis of exclusion, it may not be cost-effective to extensively evaluate for other causes of non-diabetic neuropathies in all patients. An extended evaluation should be considered under the guidance of a neurologist in patients with atypical features as mentioned above.

Overview of management, referral and follow-up plan

Management involves achieving good and stable glycemic control, treatment of risk factors such as obesity, hypertension and dyslipidemia, and avoidance of smoking and alcohol use. Optimal glycemic control is the most effective therapy to reverse (in the initial stages) and prevent progression of neuropathy in T1DM. Maintaining glycated hemoglobin (HbA1C) level below 7% has been shown to reduce onset and progression of DN.

Despite a reasonable understanding of its pathophysiology, no pharmacological agent which can alter the natural history of neuropathic process has been found successful till date. We know that hyperglycemia leads to increased levels of markers of oxidative stress such as superoxide and peroxynitrite ions which lead to peripheral nerve damage. Besides, antioxidant defense mechanisms are also known to be impaired in patients with DN. Various therapies being tried/ under investigation for DN are aimed at reducing oxidative stress. These include aldose reductase inhibitors (epalrestat and zenarestat), antioxidants like α-lipoic acid, γ-linolenic acid and benfotiamine, and PKC inhibitor (ruboxistaurin)[12]. Of these agents, epalrestat, an aldose reductase inhibitor, which works by inhibiting glucose flux via polyol pathway, has shown some potential. In rat models with streptozotocin-induced diabetes and hyperglycemia induced peripheral neuropathy, epalrestat was found to reduce injuries to myelinated nerve fibers, non-myelinated nerve fibers and Schwann

Table III. Clinical test/invesigation to diagnose diabetic neuropathy

Clinical test/investigation	Remarks
Ankle jerk	Large fiber neuropathy
128 Hz tuning fork vibration test	Large fiber neuropathy
10 g monofilament test	Loss of protective sensation, if abnormal response at one out of four sites
Biothesiometry	VPT ≥ 15 V abnormal
Autonomic function tests	Abnormal cardiovascular AFT act as surrogate for autonomic dysfunction in other organ systems
Nerve conduction studies	May not be able to detect small fiber neuropathy. Indicated mainly in atypical cases to differentiate from non-diabetic causes.
QSART	Detects sudomotor dysfunction, an early and sensitive marker of small fiber neuropathy
Sudoscan	Detects sudomotor dysfunction, an early and sensitive marker of small fiber neuropathy
Skin biopsy for IENFD	Mainly a research tool for detecting small fiber neuropathy.
Corneal confocal microscopy	Mainly a research tool for detecting small fiber neuropathy.
Nerve biopsy	Indicated in selected atypical cases

Abbreviations: IENFD: Intraepithelial nerve fiber density, QSART: Quantitative sudomotor axon reflex test, VPT: Vibration perception threshold

Table IV: Cardiovascular autonomic function tests

Test	Interpretation
Resting heart rate	>100/minute is abnormal
Beat to beat heart rate variation	In resting and supine position with respiratory rate of 6/min, monitor heart rate by ECG. HRV >15/min is normal and <10/min is abnormal. RR interval ratio during expiration and inspiration (E:I) <1.2 is abnormal
Heart rate response to standing	Measure R-R interval at 15 and 30 s after standing. 30:15 ratio <1.05 is abnormal
Heart rate response to Valsalva maneuver	Ratio of longest to shortest R-R interval should be >1.2
Diastolic response to isometric exercise	Following isometric exercise of 5 min using hand held dynamometer, rise of >16 mm Hg in contralateral arm is normal
Systolic response to standing	After 2 min of standing, a fall of <10 mm Hg is normal, 10-30 mm Hg borderline and >30 mm Hg abnormal
QTc measurement	>440 ms is abnormal

Abbreviations : ECG: Electrocardiogram, HRV: Heart Rate Variability

cells of rat sciatic nerves[13]. In a study from India involving 2190 subjects (90%, T2DM and 10%, T1DM) with DN and mean diabetes duration of 11.3 years, epalrestat (50 mg three times a day) administration for 3-12 months was associated with significant improvement in spontaneous pain, numbness, coldness and hypoalgesia, peroneal motor nerve- conduction velocity, sural sensory nerve-conduction velocity and vibration sensitivity[14]. Epalrestat was generally well tolerated, and adverse effects were noted in 2.5% of study participants, most common being hepatic dysfunction, and nausea and vomiting. Benfotiamine is a

transketolase activator that is known to reduce tissue levels of AGE and has been shown to cause improvement in neuropathy symptom score in two small studies involving 40 (BEDIP) and 165 (BENDIP) subjects with DN[15,16].

Management of painful neuropathy

Almost 25% of the patients with DN may have painful neuropathy. Painful neuropathy often causes impairment of sleep and compromises the quality of life. Hence, it is essential to treat painful neuropathy. An appropriate and effective drug should be chosen based on efficacy and tolerability by the individual patient. Treatment should be continued for at least 2-4 weeks before concluding that the drug is not effective. Since none of the drugs provide complete pain relief, a reduction of pain by 30-50% may be considered as a marker of effectiveness. In a Cochrane review of 61 RCTs, for tricyclic antidepressants (TCAs), the number needed to treat (NNT) for moderate pain relief was 3.6, while number needed to harm (NNH, defined as an adverse event leading to study withdrawal) was 28[17]. An ideal drug for neuropathic pain should have NNT close to 1 and NNH>10.

Pregabalin and gabapentin bind to α2δ-1 and α2δ-2 subunits of voltage-activated calcium channels, causing inhibition of cellular calcium influx and attenuation of neurotransmission, leading to reduction of neuropathic pain[18]. Pregabalin is the most extensively studied drug and has demonstrated positive result in most studies. It is approved by FDA for management of neuropathic pain in patients with diabetes. Common side effects of pregabalin and gabapentin include sedation, dizziness, ataxia and fatigue; peripheral edema and headache are more common with pregabalin. Side effects are more pronounced in elderly population. Hence, initiation with small dose (75 mg/day for pregabalin and 300 mg/day gabapentin) and gradual titration to maximum doses (300-600 mg/day for pregabalin and 900-1800 mg/day for gabapentin), as needed may be safer. It is important to note that drugs like pregabalin are to be used in adults with T1DM, as their use is off-label in children.

TCAs are also effective in reducing neuropathic pain but their use is limited by side effects. These include anticholinergic side effects (such as dry mouth, constipation, ocular side effects and urinary hesitancy), orthostatic hypotension and sedation. Side effects may be more pronounced in elderly people and hence TCAs should be used cautiously in them. Serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine are the other proven drugs for management of neuropathic pain. These agents effectively reduce neuropathic pain, while being associated with fewer side effects. The use of opioid agents (tramadol and extended release tapentadol) in the management of painful neuropathy is limited to third line due to their limited safety profile (abuse potential) and efficacy. The doses and side effect profile of commonly used drugs for the management of painful DN have been summarizedin Table V[19,20].

Midodrine, a α1-receptor agonist may be beneficial in the management of patients with orthostatic hypotension. Erectile dysfunction in men may be treated with phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil (50-100 mg) or tadalafil (5-20 mg). These agents are contraindicated in patients taking nitrates. In advanced cases where PDE-5 inhibitors are ineffective, transurethral prostaglandin (alprostodil) [medicated urethral system of erections (MUSE)], intracavernosal injections of prostaglandin E1, papaverine and phentolamine, vacuum constriction devices (VCDs), and penile prosthesis may be required. Short-term metoclopramide therapy should be considered

Table V: Commonly used agents for management of neuropathic pain, their dosages and adverse effects

Agent	Starting dose	Maximum dose	Adverse effects	Remarks
Gabapentinoids Pregabalin Gabapentin	25-150 mg OD 100-300 mg OD	150-300 mg BD 600-1200 mg TDS	Sedation, dizziness, visual blurring, peripheral edema, weight gain.	Dose adjustment needed in renal failure
TCAs Amitriptyline Nortriptyline	10-25 mg/d 10-25 mg/d	100-150 mg/d 100-150 mg/d	Sedation, dry mouth, confusion, constipation, urinary retention, orthostatic hypotension, blurred vision, mydriasis, fatigue, weight gain, arrhythmia	Contraindicated in patients with glaucoma, symptomatic prostatic disease and cardiovascular disease. Use with caution in elderly population.
SNRIs Duloxetine Venlafaxine	30 mg/d 37.5 mg/d	60-120 mg/d 150-225 mg/d	Sedation, dizziness, dry mouth, nausea, constipation, dyspepsia, ataxia	Exercise caution in patients with renal or liver disease
Opioids Tramadol	50 mg/d	400 mg/d	Sedation, dizziness, light-headedness, nausea, vomiting, constipation Sedation, nausea, vomiting, constipation	May lower seizure threshold. Exercise caution in patients with seizure disorder Exercise caution in patients with seizure disorder, liver or renal dysfunction
Tapentadol (controlled release)	50 mg BD	500 mg/d		

Abbreviations: BD: Twice daily, OD: Once daily, SNRIs: Serotonin and Norepinephrine reuptake inhibitors, TCAs: Tricyclic antidepressants, TDS: Thrice daily

in the management of diabetic gastroparesis. Management of various aspects of diabetic autonomic dysfunction has been discussed briefly in Table VI [21,22].

Prevention of diabetic foot

Foot examination should be done at each visit in patients with DN and at least annually in those without DN. Identification of foot at risk is the most important step in the prevention of diabetic foot ulcer. Patients with at risk foot should be instructed to take the following precautions:

1. Inspect feet yourself (with the help of mirror to inspect soles) or with the help of someone (especially when your vision is compromised) daily.

2. Wash feet daily with a non-medicated soap; pat feet dry with soft absorbent cloth especially between toes.

3. Apply lubricants containing urea or salicylates to the feet sparing the inter- digital spaces.

4. Wear footwear both indoors and outdoors. Wear only proper fitting shoes (not too loose

Table VI: Management of diabetic autonomic dysfunction

Condition	Treatment	Remarks
Orthostatic hypotension	Postural maneuvers, compression stockings, avoid hot water bath. Fludrocortisone (0.5-2 mg OD), Midodrine (2.5-10 mg TDS). Octreotide (0.1-0.5 µg/kg/day) may be helpful in preventing postprandial hypotension. Clonidine and erythropoietin have also been tried.	Can be easily diagnosed in clinic. Fall of systolic blood pressure without increase in heart rate is characteristic of orthostatic hypotension related to autonomic dysfunction.
Gastroparesis	Diet: Low fat, small frequent meals. Metoclopromide (10 mg TDS), Domperidone (10 mg TDS), Erythromycin (250 mg TDS), Levosulpride (25 mg TDS) (use 30-60 minutes before each major meal)	Rule out obstruction, (upper GI endoscopy), hyperglycemia, psychogenic vomiting.
Diarrhea	Diet: Soluble fiber Antimotility agents: Loperamide 2 mg TDS-QID or SOS Gut antibiotics: Metronidazole (400 mg TDS), Rifaximin (400 mg TDS) Bile salt sequesterants: Cholestyramine (4-12 g/d). Clonidine (0.1 mg BD-TDS) and Octreotide (50 µg BD-TDS) may also help in some cases.	Rule out infective etiologies (HIV serology, stool routine microscopy and culture), thyrotoxicosis, exocrine pancreatic dysfunction (stool elastase, 24-h fecal fat estimation, abdominal ultrasonography), gluten sensitive enteropathy (tissue transglutaminase antibody), bacterial overgrowth (hydrogen breath test), lactose intolerance, intrinsic GI disorders (inflammatory bowel disease, abdominal tuberculosis). Consider gastroenterology consultation.
Erectile dysfunction	PDE-5 inhibitors: Sildenafil (50-100 mg), Taldalafil (5-20 mg) 1 h before sexual intercourse. Intracavernosal or transurethral PGE1 therapy, vaccum constriction device, penile prosthetic pump may be required in cases not responding to PDE-5 inhibitors.	Rule out psychogenic, medication related, vascular and hormonal causes. Avoid PDE-5 inhibitors in patients on nitrates. Patients should be advised to avoid oily, heavy meal on the night of medication intake.
Cystopathy	Timed voiding, double or triple voiding, behavioural interventions, manual pressure (Credes maneuver). Cholinergic agent: Bethanechol 10 mg QID	Urine routine and culture tests, ultrasonography of KUB region, urodynamic studies may be needed. Consider urology consultation.
	Alpha blocker: Doxazosin 1-2 mg BD. Most advanced cases with hypocontractile bladder will need training on self CIC.	
Hypoglycemic unawareness	Relax targets for glycemic control, avoid hypoglycaemia	Recurrent hypoglycaemia may be associated with functional autonomic insufficiency
Sudomotor dysfunction	Foot care education, use of emollients and skin lubricants, anticholinergic glycopyrrolate (topical/oral) may be used in gustatory sweating	May be diagnosed with Sudoscan or QSART

Abbreviations: BD: Twice daily, OD: Once daily, TDS: Thrice daily, QID: Four times a day, QSART: Quantitative sudomotor axon reflex test, CIC: Clean intermittent catheterization, GI: Gastrointestinal, PDE-5: Phosphodiesterase-5, KUB: Kidney, ureter and bladder, PGE1: Prostaglandin E1; HIV: Human immunodeficiency virus

or too tight) and physically examine the inside of a shoe before wearing it. Shoes should have a broad toe box and preferentially be bought in evening hours.

5. Wear clean, cotton socks, preferably white colored (for easy detection of blood stains) with seams facing outwards. Avoid wearing tight socks and change socks on a daily basis.

6. Cut the toenails very carefully straight across and not in a rounded fashion or not too short.

7. Check for the warmth of water with hands/elbow before rinsing the feet with hot water.

8. Don't self-treat calluses or corns

9. If you notice any blisters, cracks, sore, discoloration or any unusual mark on the feet or if the feet get accidentally cut or injured in any way, contact a podiatrist immediately.

Summary

- Diabetic neuropathy is a chronic microvascular complication of diabetes, which may significantly affect patient's quality of life

- Diabetic sensorimotor polyneuropathy, a symmetric length dependent neuropathy is the most common form of diabetic neuropathy.

- Focal/multifocal neuropathies are less common but need diligent neurological examination and aid of electrophysiological tests to distinguish from non- diabetic causes.

- Diabetic autonomic neuropathy is a great mimic, effecting almost every organ system in the body.

- Cardiovascular autonomic function tests may act as surrogate for autonomic dysfunction involving other organ systems.

- Management of diabetic neuropathy includes achievement of good glycemic control, treatment of risk factors, pain management and foot care education.

- Despite clear understanding of its pathophysiology, no pharmacological agent which can alter the natural history of neuropathic process has been found successful till date.

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Chapter-9

Macrovascular Complications

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Introduction

Patients with type 1 diabetes mellitus (T1DM) are at increased risk of morbidity and mortality from cardiovascular disease (CVD) compared to the non-diabetic population. This includes coronary artery disease (CAD), stroke and peripheral arterial disease (PAD), of which CAD is the most common. CVD remains a major cause of mortality in patients with T1DM and disease duration >20 years[1]. In patients with T1DM, cardiovascular (CV) events occur much earlier than in the general population. Most CV events occur more than two decades after the disease onset, implying a significant disease burden at a relatively young age (third and fourth decades of life)[2]. An early age at disease onset and a high CVD burden at a relatively young age has implications for potential loss of productive years of life and increased lifetime healthcare cost. There is also evidence to support increased severity of CVD in patients with T1DM; they are at a higher risk of having extensive disease (involving all the three major coronary arteries), distal vessel disease, and severe stenosis compared to subjects without diabetes[3].

The etiopathogenesis of CVD in T1DM is complex and mutifactorial, and will be discussed in detail in this chapter. With improving standards of care, and the resultant increase in the life expectancy of patients with T1DM, it is incumbent on the healthcare providers to appropriately understand and address the increasing burden of this long-term complication.

Epidemiology

In the Eurodiab IDDM Complications Study, > 3000 patients with T1DM (mean age 33 years and mean disease duration 15 years) were studied for CVD (defined by past history or presence of ECG abnormalities). The prevalence of CVD was reported to be 9% in males and 10% in females. The prevalence increased with age (6% in 15-29 years age group to 25% in 45-59 years age group) and duration of diabetes (6-9% in 1-7 years duration of DM to 13-15% in >15 years duration of DM)[4]. However, this study may have underestimated the actual CVD burden because patients with silent myocardial ischemia and inducible ischemia were not actively looked for. An important finding of this study (and confirmed by other studies) is that T1DM attenuates the protective effective of female sex (i.e., premenopausal age group) on CVD risk, which is usually seen in the general population [2,5]. As a result, relative risk compared to the general population is higher in females compared to males with T1DM. In the Allegheny County (PA) T1DM registry, the standardized mortality ratio (SMR) for total mortality (13.0 vs. 5.0) and CV mortality (24.7 vs. 8.8) was higher in females than males with T1DM[1].

Various prospective studies have also reported increased risk of CVD (CAD, stroke and PAD) in patients with T1DM, compared to the general population. UK General Practice Research Database (GPRD) comprised data from >7400 subjects with T1DM (mean age 33 years and mean disease duration 15 years) and >38000 subjects without DM, followed up for a mean duration of 4.7 years. The adjusted hazard ratio (HR) for CV events was reported to be 3.6 (95% CI, 2.9-4.5) in males and 7.6 (95% CI, 5.5-10.7) in females with type 1 DM. Besides, the CV event occurred 10- 15 years earlier in subjects with T1DM compared to the matched controls without diabetes. HR for CAD was reported to be 3.0 (95% CI, 2.2-4.1) in males and 7.6 (95% CI, 4.9-12.0) in females[6]. In the Nurses Health study, >100,000 women without diabetes and about 11,000 women with diabetes (both T1DM and T2 DM) were followed-up for a duration of 24 years. HR for fatal or non fatal stroke was reported to be 5.9 (95% CI, 4.2-8.2) in women with diabetes, compared to women without diabetes[7]. Patients with T1DM are also at higher risk of premature mortality after a stroke, compared to the general population. In the Finnish Diabetic Nephropathy study, 144 patients with T1DM who suffered a stroke were followed-up for a mean duration of 3.4 years[8]. Of these, 104 (72%) suffered a vascular composite end point (hard cardiovascular event or death from cardiovascular or diabetes- related cause), with an overall 1-year survival of 76% and 5-year survival of 58%. The presence of hemorrhagic stroke subtype and progression of diabetic kidney disease were predictors of worse outcome in the study cohort.

PAD, characterised by atherosclerotic occlusive disease of lower extremities, is a major risk factor for lower-extremity amputations. Its presence is also considered to be a surrogate marker for significant atherosclerotic burden in other vascular beds[9]. Like CAD and stroke, the risk of PAD and its adverse outcomes is significantly higher in patients with T1DM compared to the general population. However, due to its asymptomatic course, poor reporting of symptoms by the patient, attenuation of symptoms by the presence of neuropathy, and lack of a universal screening modality, PAD is often underreported in patients with diabetes[9]. In the Swedish Inpatient registry involving > 31,000 patients with T1DM followed for 12.5 years, HR for non-traumatic lower-extremity amputation (an outcome of PAD) compared to the general population was reported to be 85.5 (95% CI, 72.9-100.3)[10].

Risk factors and pathophysiology

1.   *Hyperglycemia*

Poor glycemic control has been associated with increased risk of microvascular and macrovascular complications in patients with T1DM. In the Diabetes Control and Complications Trial (DCCT), >1400 subjects with T1DM were randomized to receive intensive or conventional glycemic control and followed-up for a mean duration of 6.5 years. Although microvascular benefits emerged in the intensive arm at the end of trial, no significant macrovascular benefits were seen. This could be attributed to the overall small number of cardiovascular events in a relatively young population, followed-up for a short duration[11]. However, in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up of the DCCT cohort, significant differences for macrovascular events emerged in favour of intensively treated arm despite closure of the glycemic gap between the two groups (legacy effect). At 17 years follow-up (DCCT/EDIC combined), the overall risk of CVD events was reduced by 42% while the risk of

non-fatal myocardial infarction/stroke/cardiovascular death was reduced by 57% in the intensive arm compared to the conventional arm[12]. Also, the progression of carotid intima-media thickness (CIMT), a non-invasive marker of CVD was significantly lower in the intensive arm at six years after the end of DCCT[13]. The data from DCCT/EDIC therefore suggests that early intensive glycemic control may play a major role in reduction of future CV risk in T1DM patients.

Persistent hyperglycemia leads to increased generation of mitochondrial reactive oxygen species (ROS) and proinflammatory mediators through various pathways (Figure-1), resulting in endothelial dysfunction[14-16]. Healthy endothelium efficiently regulates vascular tone, thrombosis, leukocyte adhesion, platelet aggregation and inflammation. Hyperglycemia causes loss of vasodilatory, anti-inflammatory and anti-atherogenic properties of the healthy endothelium, leading to genesis of atherosclerotic CVD. In addition, uncontrolled diabetes is associated with other cardiovascular risk factors (such as dyslipidemia), as shown in the SEARCH for Diabetes in Youth study[17].

Acute hyperglycemia is also associated with poor post-stroke outcomes (both ischemic and hemorrhagic stroke)[18]. In patients with ischemic stroke, it increases cerebral lactate production and reduces the salvageable penumbral tissue, resulting in infarct expansion, while, in those with hemorrhagic stroke, it may cause expansion of hematoma and perihematomal edema. Optimal management of hyperglycemia is therefore extremely important in such patients.

2. Hypertension

Hypertension is a risk factor for microvascular as well as macrovascular complications in T1DM. The increased risk for CVD with hypertension occurs regardless of the presence of diabetic kidney disease (DKD)[2]. In the Coronary Artery Calcification in T1DM study (CACTI), involving 1416 subjects aged 19-56 years (652 T1DM subjects with mean age of 37 years and diabetes duration of 23 years, and 764 controls with mean age of 39 years) with no past history of coronary artery disease, hypertension was more common in subjects with T1DM than controls (43% versus 15%)[19]. Hypertension was better controlled in subjects with T1DM than controls, however, only 42% T1DM subjects met the target goal of <130/80 mmHg. In the SEARCH for Diabetes in Youth study involving >3600 patients with T1DM aged 3-17 years, hypertension was seen in about 6% of the study participants, predominantly affecting obese adolescents and those with poor glycemic control[20].

Hypertension in T1DM may occur as a result of DKD and obesity/insulin resistance. Poor glycemic control can also contribute to hypertension in the long-term. In the DCCT study, incident hypertension was not different in the two study arms, however during EDIC follow-up of the DCCT cohort, the risk of incident hypertension was found to be reduced by 24% (HR 0.76, 95% CI, 0.64-0.92) in the intensive arm compared to the standard treatment arm. In addition, higher glycated hemoglobin (HbA1c) at baseline or throughout follow-up was associated with increased risk of incident hypertension[21]. The landmark DCCT/EDIC study thus suggested that hyperglycemia may have a definitive role in the pathogenesis of hypertension; however, effects of intensive glycemic control on reduction of hypertension risk may appear in a delayed fashion (similar to the macrovascular complications).

3. Diabetic Kidney Disease (DKD)

DKD can manifest as microalbuminuria (albumin excretion rate (AER) 30-299 mg/ day), macroalbuminuria (AER ≥ 300 mg/day), and impaired glomerular filtration rate (GFR) (estimated GFR<60 ml/min/1.73m^2) with or without albuminuria. In various studies, DKD has been associated with graded increase in CV mortality from microalbuminuria to macroalbuminuria to end stage renal disease (ESRD)[2]. The presence of microalbuminuria is associated with about 4-fold higher risk of CVD and 2-fold higher risk for all cause and CV mortality[22-24]. Despite adjustment for potential confounders like dyslipidemia, hypertension and obesity (which accompany microalbuminuria), the risk of CV events remains significant, suggesting it to be an independent CVD risk factor. Microalbuminuria is, therefore, an early non-invasive marker for both DKD and CVD. In the EURODIAB study, the presence of macroalbuminuria was associated with a 9-fold higher risk of CV mortality[25]. Similarly, impaired GFR, regardless of albuminuria, is associated with increased CVD risk (with patients having ESRD at highest risk)[26,27].

Increased CV risk in patients with DKD could be a result of following factors: a) co-existence of other CV risk factors such as dyslipidemia, hypertension, obesity and insulin resistance, b) increased activity of renin-angiotensin-aldosterone system (RAAS), and volume retention due to DKD, c) anemia (common in patients with DKD, especially at low GFR) may contribute to left ventricular hypertrophy and dysfunction in the long-term.

4. Cardiac Autonomic Neuropathy (CAN)

CAN manifests as resting tachycardia, loss of heart rate variability, exercise intolerance, orthostatic hypotension and loss of nocturnal dip in blood pressure. Risk factors for CAN include poor glycemic control, hypertension, dyslipidemia and obesity[28]. CAN may be associated with silent myocardial ischemia and delayed presentation of CVD. In T1DM patients without CAD, CAN has also been related to impaired coronary flow reserve, which may predict future diastolic dysfunction[29]. In various studies, CAN has been shown to be an independent predictor of CV morbidity and mortality[30,31].

5. Dyslipidemia

As in general population, dyslipidemia is a risk factor for CVD in T1DM. While patients with normal body weight and well-controlled T1DM show lipid and lipoprotein concentrations similar to the general population, those with poor glycemic control/ obesity/insulin resistance tend to have an atherogenic lipid profile[32]. In the Search Diabetes for Youth study[17], among subjects with T1DM and poor glycemic control (HbA1c ≥9.5%), high concentration of total cholesterol (≥200 mg/dl), LDL-cholesterol (≥130 mg/dl) and triglycerides (≥200 mg/dl) were seen in 35%, 27% and 12%, respectively. The corresponding numbers in patients with youth onset T2DM and poor glycemic control were 65%, 43% and 40%, respectively. Diabetic dyslipidemia is defined by the presence of elevated triglycerides, low HDL-cholesterol and predominance of LDL particles in the small dense form. The small dense LDL particles are more atherogenic because of their affinity to the arterial wall and susceptibility for oxidation, leading to recruitment of leukocytes, formation of foam cells and development of the atherosclerotic plaque. In addition, upon glycation, the half life of LDL particle is increased, while that of HDL particle is reduced, further worsening the atherosclerotic process[33].

6.   *Obesity and insulin resistance*

The phenotype of patients with T1DM has evolved in the recent past, reflecting the increased rate of obesity in the general population. The adoption of unhealthy dietary practices and sedentary lifestyle coupled with improved glycemic control (less glucosuria) and at times, excessive eating for fear of hypoglycemia, may place these patients at increased risk of weight gain. In the DCCT/EDIC study, obesity prevalence increased from 1% at DCCT baseline to 31% at EDIC 12-year follow-up[34]. In particular, excessive visceral adiposity is associated with worsening insulin resistance, poor lipid control and increased CVD risk.

7.   *Smoking*

Smoking is associated with increased risk of vascular complications-both microvascular and macrovascular. It increases CVD risk through unfavorable alterations in glucose and lipid metabolism, and development of endothelial dysfunction[35]. There is definite evidence to suggest reduction in CVD risk (particularly peripheral arterial disease) with smoking cessation[36].

8.   *Age and duration of diabetes*

As discussed earlier, both increasing age and duration of diabetes are risk factors for CVD in T1DM population[4]. The pathophysiology of macrovascular complications in T1DM is illustrated in Figure-1.

Figure 1: Pathophysiology of macrovascular complications in patients with type 1 diabetes mellitus
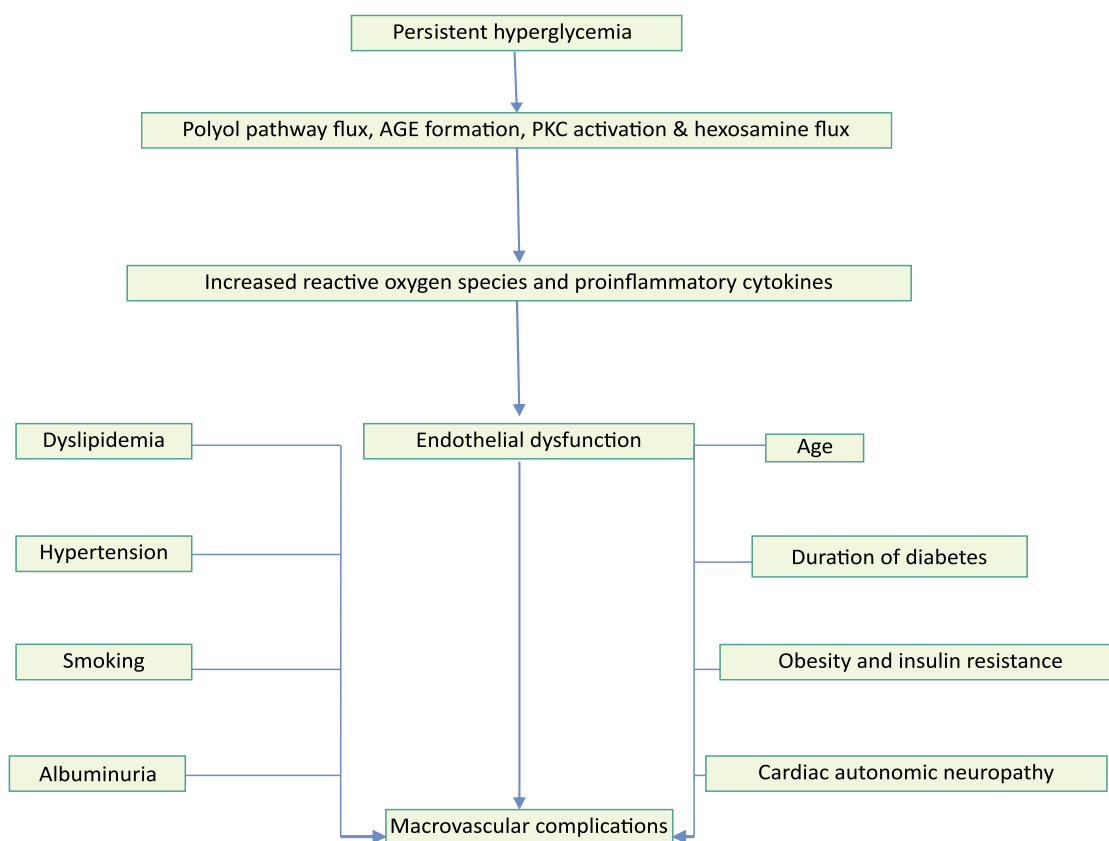
Abbreviations: AGE- Advanced glycosylation end products; PKC-Protein kinase C

Cardiovascular risk factors in children and adolescents with T1DM

Although frank CVD may be rare in children and adolescents with T1DM, it is not uncommon to encounter clustering of CV risk factors in this population, placing them at high risk for future events. According to population-based studies, 14- 45% of children with T1DM have two or more cardiovascular risk factors[37-39]. In a study involving 283 children (median age 12.8 years) with T1DM (median duration 5.3 years), about 40% were found to be overweight/ obese. The overweight/ obese children were more likely to have hypertension (23.9% vs. 5.7%), metabolic syndrome (25.7% vs. 6.3%) and transaminitis (15.6% vs. 4.5%), compared to those with normal body weight[40]. With the rising prevalence of childhood obesity, these numbers are likely to increase in the future, posing tremendous challenges to the existing healthcare system.

Diagnosis/screening

Blood pressure and weight should be measured at each visit. In children, hypertension is defined as systolic or diastolic blood pressure ≥95th centile for age, sex and height on three or more occasions[41,42]. As per Center for Disease Control and Prevention (CDC), in childhood and adolescence, overweight is defined as body mass index (BMI) between 85th-95th centile for age and sex, while BMI ≥95th centile is considered as obesity[43]. On the other hand, the World Health Organisation (WHO) defines overweight and obesity as BMI ≥1 and 2 standard deviation (SD) above the mean for age and sex[44]. Since these BMI cut- offs are arbitrary and not related to specific health risk, there is a secular trend for increasing weight in populations worldwide (percentile or SD score based cut-offs may apparently normalize "childhood obesity") and because the increased risks of childhood obesity are mediated through tracking of obesity and related behaviors to adulthood, the International Obesity Task Force (IOTF) recommends the usage of BMI cut-offs which corresponds to adult BMI of 25 kg/m^2 (childhood overweight) and 30 kg/m^2 (childhood obesity)[45]. Considering that at a given BMI, South Asians are at a higher risk for cardiometabolic disease, the recent Indian Academy of Pediatric guidelines recommend that BMI cut-offs 23 and 27 kg/ m^2 be used to define overweight and obesity, respectively in Indian children[46]. According to International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines, screening for dyslipidemia should be performed soon after diagnosis of T1DM (once blood glucose levels are stable) and if normal results are obtained, the evaluation should be repeated every 5 years[47]. Although a fasting lipid profile is ideal, a non-fasting lipid profile may be performed if the former is not feasible; if serum triglycerides or low-density lipoprotein cholesterol levels are elevated on a non-fasting study, a fasting lipid study may then be performed. Similarly, ISPAD recommends annual assessment of urinary albumin excretion in patients with T1DM beginning after the age of 11 years and 2-5 years of disease duration[47]. Routine screening for coronary heart disease beyond a resting electrocardiogram (ECG) is not recommended in patients with T1DM[2]. However, patients with symptoms of CVD or baseline resting ECG abnormalities (suggestive of ischemia) or those with clustering of multiple CV risk factors (intermediate or high risk on Framingham risk score or Reynolds risk score) should undergo a detailed assessment (Tables I and II). Of the various risk factors included in the Framingham risk score, age provides the most significant weightage. Both Framingham and Reynolds risk scores have been derived based on studies performed in older North American population[48-51], and their performance in young South Asian population with T1DM is not well understood[52].

Table I: Cardiovascular disease (CVD) assessment in patients with type 1 diabetes mellitus

Indications for detailed CVD assessment
Presence of symptoms of CVD
Baseline electrocardiogram suggestive of ischemia
Presence of multiple CV risk factors
Tools for CVD assessment
Exercise treadmill test (TMT) Dobutamine stress echocardiography
Dobutamine stress myocardial perfusion imaging (MPI)
Coronary artery calcification (CAC) by electron beam computerized tomography (EBCT)
Carotid intima media thickness (CIMT) Ankle-brachial pressure index (ABPI)
Endothelial dysfunction assessment by flow mediated dilation/brachial artery reactivity and Cardiac magnetic resonance imaging (MRI)

Table II: Components of cardiovascular disease risk prediction scores

Framingham risk score
Age
Sex
Total cholesterol
HDL-cholesterol
Smoking
Systolic blood pressure
Diabetes
Reynolds risk score
Age
Sex
Total cholesterol
HDL-cholesterol
Smoking
Systolic blood pressure
HbA1c, if person has diabetes
hs-CRP
History of MI in parents at age <60 years

Abbreviations: hs-CRP-High sensitivity C-reactive protein; MI-Myocardial infarction

Exercise treadmill test (TMT) remains the first line test for patients without peripheral neuropathy, foot deformity, previous amputation and baseline significant ST-T abnormalities, as it is cost-effective and easily available[2]. In patients who cannot undergo TMT due to above reasons, pharmacological stress testing (dobutamine stress echocardiography or dobutamine stress myocardial perfusion imaging (MPI)) may be performed. The use of pharmacological stress tests may, however, be limited by cost and availability.

Coronary artery calcification (CAC) is measured using electron beam computerized tomography (EBCT), and is an extremely helpful tool in quantifying the atherosclerotic plaque burden. CAC is scored as: 0-no plaque, 1-10-minimal, 11-100-mild, 101-400-moderate and >400-severe. CAC is seen at higher rates in patients with T1DM compared to the general

population and is more likely to progress in those with suboptimal glycemic control[53,54]. In the 10-year follow- up examination of Pittsburgh Epidemiology of Diabetes Complications Cohort, 302 adults with type 1 DM (mean age 38 years) underwent EBCT and clinical examination[55]. The prevalence of any CAC was reported to be 11% in participants with age <38 years and it increased to 88% in those with age 50-55 years. CAC was found to correlate with clinical CAD independent of other risk factors; however, the association was stronger in males compared to females. Also, a CAC score of >400 was found to be most efficient coronary calcium correlate of clinical CAD. In the CACTI study[19], CAC was seen in 39% males and 12% females with T1DM. Both men and women with CAC had higher age, BMI, waist circumference and waist-hip ratio, compared to those without CAC. CAC testing by EBCT has been suggested as an initial screening tool, followed by stress testing in those with CAC score >400[15].

Ultrasound guided CIMT measurement is another tool for CVD assessment. It has been proposed as a surrogate marker of early atherosclerosis; however, unlike CAC, the association between increased CIMT and subsequent CVD risk has not been studied in patients with T1DM. Hence, it is not recommended for routine clinical use. Ankle-brachial pressure index (ABPI) measured using hand- held Doppler device and sphygmomanometer is a standard tool for assessment of PAD. ABPI is ratio of systolic blood pressure of ankle (higher of the posterior tibial artery (PTA) or dorsal pedis artery (DPA) pressure on the given side) and arm (higher of the right or left brachial artery) and is interpreted as: normal (0.91- 1.3), mild ischemia (0.7-0.89), moderate ischemia (0.41-0.69) and severe or critical limb ischemia (<0.4). An ABPI value greater than 1.3 is also considered abnormal, suggestive of non-compressible vessels. Endothelial dysfunction can be assessed using flow mediated dilation/ brachial artery reactivity[56], and cardiac magnetic resonance imaging[57]; however, these are primarily research tools at present and not recommended for routine clinical use.

The utility of screening for asymptomatic CAD in diabetes was tested in two large randomised controlled trials (FACTOR-64 trial and The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study). In the FACTOR-64 trial, subjects with T1DM (n=108) and T2DM (n=791) with disease duration of at least 3-5 years and no CAD symptoms were randomized to screening with coronary computed tomography angiography (CCTA), followed by appropriate treatment or to standard care[58]. At a mean follow-up of 4 years, screening for asymptomatic CAD with CCTA failed to reduce the composite primary outcome of all-cause mortality, non fatal MI or unstable angina requiring hospitalization. Similarly, the DIAD study (included 1123 subjects with T2DM) found that the cumulative cardiac event rate over a follow-up of 4.8 years was not reduced by screening for asymptomatic CAD using myocardial perfusion imaging (MPI)[59]. Since these studies had few or no patients with T1DM, it may not be possible to provide a strong recommendation for or against screening for inducible ischemia in asymptomatic T1DM subjects; however, the limited evidence suggests that screening may not be required in asymptomatic individuals.

Prevention strategies

Macrovascular complications can be prevented if risk factors are addressed in a timely and appropriate manner. The role of glycemic control in etiopathogenesis of CVD has been proven beyond doubt by the landmark DCCT/EDIC trial. Optimal glycemic control (targeting HbA1c <7%), using multiple subcutaneous insulin injections (MSII) or insulin pump therapy (while minimizing iatrogenic hypoglycemia) should be attempted

in all individuals, especially those with short duration of diabetes and without other co-morbidities. Hypertension should be treated with angiotensin-converting enzyme inhibitor (ACE inhibitor)/angiotensin- receptor blocker (ARB) in combination with calcium channel blockers or thiazide diuretics, where needed. American Diabetes Association (ADA) recommends treatment to a target BP of < 140/90mm Hg, however, a target of < 130/80 mm Hg should be attempted in those where it can be achieved without additional treatment burden[2]. In patients with albuminuria, ACE inhibitor/ARB should be used regardless of hypertension in order to prevent further progression.

Diet and lifestyle modification along with optimization of glycemic control is recommended as the first line therapy for treating abnormal lipid levels. ISPAD clinical practice guidelines recommend dietary and lifestyle intervention for children and adolescents with T1DM and LDL-cholesterol >100 mg/dl; levels >130 mg/dl despite adequate dietary and lifestyle measures warrant institution of statin therapy in children aged 11 years or more[47]. Smoking cessation should be discussed actively and enrollment in smoking cessation program should be considered in selected cases. Finally, weight management is paramount and patients should be advised to engage in regular physical activity and consume a diet low in salt, saturated fat and simple sugars, and rich in fruits, green leafy vegetables, dairy products and fiber. A structured diet plan designed by a qualified dietician should be provided to each patient and body weight monitored periodically.

Patients with pre-existing CVD should receive lifelong statin (regardless of lipid levels), and antiplatelet agent (aspirin alone or aspirin plus clopidogrel combination for 12 months after acute coronary syndrome or percutaneous coronary intervention) as a secondary prevention strategy. Beta blockers should be added in those with previous myocardial infarction or left ventricular dysfunction.
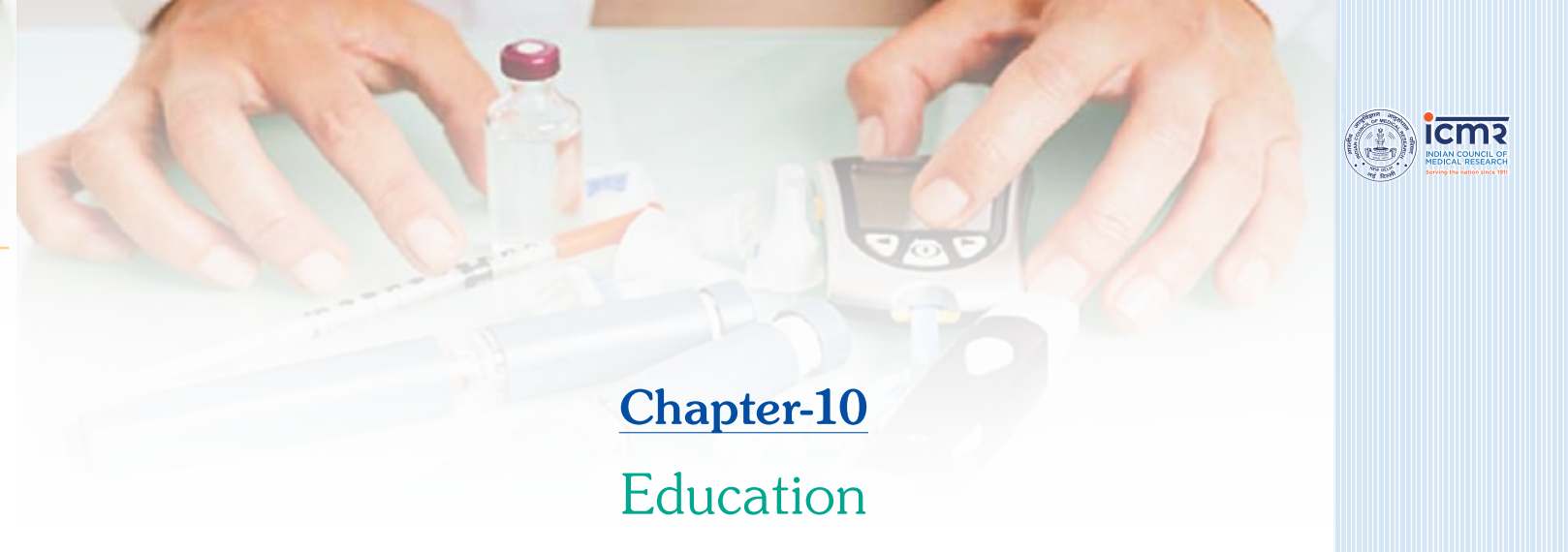
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Chapter-10

Education

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Introduction

Diabetes with onset in childhood or adolescence needs major lifestyle changes. These include several daily injections, frequent glucose monitoring either by painful finger prick testing or continuous glucose monitoring system (CGMS), periodic visits to a healthcare facility and annual screening for vascular complications. Besides, there remains a constant concern about low and high blood glucose and the background fear of chronic complications. Several skills have to be taught quickly, and then frequently reinforced, with the aim of empowering the child and family to effectively control their diabetes and life. It is therefore not surprising that diabetes education is the backbone of diabetes care, with the American Diabetes Association (ADA) emphasizing that "Medical treatment of diabetes without systematic self-management education can be regarded as substandard and unethical care".

A large proportion of children present initially with diabetic ketoacidosis (DKA), sometimes severe DKA. Once the child's clinical condition stabilizes, diabetes education has to start. With greater awareness of childhood diabetes, diagnosis is increasingly being made before florid DKA develops. For example, an otherwise well child presents with polyuria or new-onset bedwetting or vaginal/ penile infection, the urine exam shows glycosuria, so the blood glucose is tested and found high. In these and similar situations, management can be done on an outpatient basis.

Initiating education

The initial few days of handling the diagnosis and imparting the basics of education form the bedrock of later diabetes care. Once the diagnosis has been made, it is useful to have a checklist of aspects to be discussed immediately, in the near future, and much later during follow up (see checklist at the end of chapter). Encouraging acceptance of the illness and willingness to carry out an intensive daily regimen is the first step. The family should come for review at frequent intervals for the first few months, so that further aspects of care can be taught. The pace at which these aspects are covered will vary from patient to patient, and the nature of the diabetes care team.

Basic skills

Basic skills have to be taught as soon as the diagnosis is made. This includes self-testing and recording of blood glucose; handling insulin – understanding the action profile of basal and bolus insulins, injection technique, and insulin dose adjustment; and handling hypoglycemia. The initial days are also the most difficult for the family, as the diagnosis

causes shock, denial, despair, and fear. Parents are unwilling and unable to absorb the information given to them. It is therefore crucial that they start performing hands-on tasks of testing glucose and injecting insulin from the very beginning, this somewhat reduces the panic and restores a sense of control. It may be useful for the parents to practice injections on themselves using normal saline. This convinces them that present-day needles of insulin syringes are indeed almost painless, and bolsters the morale of the child when the parents' fear changes visibly into comfort. It also provides an opportunity to talk about the use of separate insulin syringe for each individual with diabetes and about the safe disposal of sharps.

During this period of turmoil, it may be necessary to teach things repeatedly, as stressed family members may not be able to concentrate. The family should be made to understand the need for good glycemic control, ensured by regular daily self-monitoring of blood glucose (SMBG), basal-bolus insulin regimen, and ongoing self-adjustments. Families from low socioeconomic strata may balk at the high costs of SMBG. They should be explained that management with regular SMBG and multiple dose insulin regimen gives not only much better quality of life but in the long term, is actually less expensive, as it saves the cost of emergency care and hospital admissions for acute complications, absenteeism, and later development of chronic complications and income loss.

Once the family has begun testing and injecting, as discussed above, other aspects need attention. These include insulin dose adjustments, dietary education including introduction to the concept of food exchanges and carbohydrate counting (where appropriate), and handling exercise, and lifestyle in general. History of the family's and child's pre-existing lifestyle is taken, and appropriate advice on required modifications is provided. It is crucial to emphasize from the beginning that some or all lifestyle modifications (LSM) should be made by all family members, for their own good as well as for the child's sake. The shock of the diagnosis can actually help, because the family is initially willing to make drastic changes. The principle that the child is not treated as an exception, since diabetes does not require a special diet –everybody eats healthy and is physically active –is a prerequisite for achieving good glycemic control. This will ensure stable mental health of the child and family members, avoid feelings of exclusion and inferiority, and reduce the burden of extra work that diabetes care entails. Teaching carbohydrate counting and carbohydrate exchanges is laborious but may increase flexibility and improve glycemic control. Occasional dietary indiscretions and eating "unhealthy" foods, especially on special occasions, should be condoned – the discussion should include ways to handle such situations.

Another guiding principle is to encourage the child to be as independent as possible, at age appropriate levels. Thus, children above the age of 5-7 years can be encouraged, under supervision, to test blood glucose and inject insulin on their own. Children should be involved in decision making, whether in deciding doses, play, or food - planning meal menus, helping buy and prepare food, including cooking for the older children. This enhances the feeling of control and confidence, and reduces helplessness and deprivation.

After stabilization

After diagnosis and stabilization over 2-5 days, the next important step is returning to school/college, work place, perhaps hostel. Education must be given to the key staff persons in these institutions: teachers, medical room staff, bus driver, few close friends, etc., explaining key points about diabetes care, and what to do in case of hypoglycemia, ketosis, or other

untoward situations. One or more handouts with clear guidelines, and contact details of the family and care team should be made available. It is a good idea to keep a diabetes identification card (detailing name, address and telephone number of parent/guardian, name of the treating doctor, name and dosage of insulin and other medications, and what should be done in case of hypoglycemia with unconsciousness) with the patient at all times. An emergency kit containing necessary items for management of hypoglycemia such as glucose powder/tablets/powdered sugar (simple carbohydrate source), some biscuits or other snack (complex carbohydrate source), glucagon injection (where possible), blood glucose meter, lancet and glucose strips should be available in patient's bag and school/college medical room at all times.

Safe disposal of sharps should be taught from the beginning. Later, aspects such as dealing with sick days, travel, festivals, should be carefully dealt with, and reinforced from time to time.

Psychosocial aspects

Diabetes is a self-managed condition which involves continuous care and frequent decision making - this can be overwhelming for the child and the caregivers. Given the disruptive and expensive nature of diabetes care, the importance of psychosocial care cannot be overstated. The family goes through challenges on a daily basis - from the time of diagnosis which brings shock, despair, denial, and fear, to day-to-day activities like going to school, playing, social gatherings etc. The initial stress, anxiety and depression give way to acceptance of the condition, and preparedness to carry out daily care activities. Different family members progress through these stages differently. The diabetes care team has to factor this in when dealing with the family and diabetes education.

Understandably, the prevalence of psychological disorders among children with type 1 diabetes (T1DM) and their caregivers is high, with relationships in the family also going through turmoil. In our experience, parents are often distressed by the need for coping with "the new normal" - learning the technical aspects of diabetes care; concern about the stigma of a chronic condition; fear of hypoglycemia, and its attendant complications, especially seizures; fear of future problems with career and matrimony; and conflicts amongst the caregivers. Many have clinical depression but are unwilling to seek professional help for a variety of reasons. Therefore, the presence of a psychologist with expertise in T1DM in the care team can greatly improve outcomes and reduce suffering. Where this is not possible, some training of other team members in dealing with these aspects is desirable. Formal psychiatric pharmacotherapy is needed in a subset of children or caregivers. When these issues are neglected for any reason, diabetes care and control deteriorate, setting up a vicious downward spiral.

From the beginning, restoring self-esteem and self-confidence is important. Cognitive behavioral therapy can help-techniques include learning coping skills, motivational interviewing, family conflict resolution, and stress management. It is useful initially for the diabetes care team to try to make sure responsibilities are divided, so that the entire burden (and often, blame) does not fall on one person, often the mother. As discussed earlier, lifestyle changes should be undertaken by the entire family.

A contentious question is disclosing the child's diabetes. People in contact with the child – immediate family, staff in school, sports and tuition classes, close playmates need

to know about diabetes and what to do in a crisis like hypoglycemia. However, informing everyone can attract a lot of unwanted attention and sympathy, so discretion is necessary. Body image issues may crop up in the growing child.

Parental supervision and help are needed during childhood and especially during the teenage years. Children and adolescents with T1DM may feel 'different' from their peers, and left out; they may be teased and bullied; or they may get too much sympathy from teachers and other adults. Parents must probe gently if they observe any unusual behavioral change in the child, discussing these issues in a non-threatening manner. Appropriate action (like informing the school, talking to parents of the other children) is needed to control the situation, and reassure the child that they have support. Adolescence needs increased but unobtrusive supervision and care, with increasing freedom and flexibility as needed. Over protectiveness and neglect are both damaging. Parents should be careful about their own mental health, that of the child, and equally, that of the siblings and significant others, to prevent resentments building up.

Red flags include disturbed sleep, disordered eating, lack of interest in social activities, poor interaction with friends/family, too much aggression, poor academic performance, complaints from school, and feelings of hopelessness and self-harm. The family should be encouraged to meet a professional psychologist/ counsellor if such problems persist. Sometimes pharmacotherapy may be needed. Self-help groups, peer support, altruism, and spirituality are other solutions.

The level of education imparted to the child and family varies, depending on the child's age, diabetes duration, and presence of risk factors; the ability and motivation of the family; local and cultural factors; and the resources available – financial, technological, and emotional - of the family and the diabetes care team. At every stage, goal setting and problem-solving should be emphasized. Content may change with time, as the child goes through life stages, and also as newer modalities become available. The timing and intensity of education will also change from time to time, as the care team has to factor in the psychological state of the family at that particular time, and deal with them accordingly. For example, since there is no clear-cut etiology of T1DM, it is common for family members to blame someone – spouse, another family member, physician, vaccination, etc. Disabusing them of fallacies such as this, or that diabetes can be transmitted to others, is an important task for the care team.

Awareness of the family dynamics is useful for the care team to optimally teach and are treat, e.g. who are the key decision makers in the family; who are reasonable, who not; who controls the finances; who is available to do the self-care tasks; who would be able to go to school for the initial days to teach.

Adolescence

Adolescence is particularly difficult to deal with, since the physiological poor control due to insulin resistance, is combined with the natural adolescent drives for independence, risk taking and rebellion. This can lead to creative ways to disrupt systems. They may refuse to test or take doses, falsify information, and experiment with diabetes care and risky behaviors. Parents have to be helped

to ensure they supervise without being oppressive, to discuss and share decision-making, and allow some leeway in daily routines. Smoking, alcohol and other addictions should

be discussed with and without the parents' presence, discouraged, and handled in a non-judgmental manner.

Modes of education, digital tools

Education can be done in a variety of settings – in the clinic, in school/other institutions, during picnics, camps and other events, and now increasingly, using social media and other electronic means. It can be one-on-one, or more effectively and inexpensively, in a group setting, which may be physical or virtual. Verbal communication should ideally be accompanied by reliable, age and culture, appropriate material which can be revised repeatedly at leisure (physical and virtual books, booklets, handouts, websites, apps, games, etc.). The internet is an easy way to access information, so patients should be guided where they can find reliable information. It can be imparted by the endocrinologist, diabetes educator, dietician, psychologist, parent-volunteers or older patients in self-help groups. Parent and peer education can be very valuable – again, more effective and inexpensive. However, it is very critical that the messages given by the diabetes care team and group members should be the same. Contradictions between team members can be confusing and distressing for the patient and family. Similarly, group sessions should be monitored by the diabetes care team, to ensure only correct information is available, and myths removed. Digital tools can be used by the team to reach out, and can be personalized or generalized; and one-way or two-way. They can be particularly useful at diagnosis, during sick days, or when changing providers (moving from pediatric to adult clinic, or moving place of residence).

Monitoring

The need for tracking glycemic control using glycosylated hemoglobin (HbA1c) every 3 months or time in range (TIR) if using CGMS should be emphasized from the beginning. In addition, clinical monitoring of growth, development, blood pressure, puberty, and the retina is useful. Tests for co-morbidities and complications are needed periodically – thyroid stimulating hormone (TSH), tissue transglutaminase antibodies (tTG-IgA), lipids, and hemoglobin in the blood, and albumin-creatinine ratio in the urine.

Co-morbidities, complications

Obesity should be avoided by effective dietary and lifestyle management. Regular monitoring enables early detection of problems like hypothyroidism, hypertension, celiac disease, dyslipidemia, or later, retinopathy or nephropathy. The diabetes care team should explain the need for such monitoring, and the benefits of early and adequate management.

Acute complications

A child or adolescent with well controlled diabetes should ideally have acute illnesses at a rate no higher than the normal population. When any illness does occur, management becomes more complicated. Therefore, the family must understand that good quality of life, and good glycemic control, is possible only with regular daily SMBG, multiple dose basal-bolus insulin regimen, and ongoing self-adjustments. This is particularly important for families from low socioeconomic strata, who balk at the high costs of care.

The major acute complications - DKA and hypoglycemia - are largely preventable. Clear instructions must be given to family members, and critical persons in institutions (school, college, workplace) about how to prevent these complications, and what to do if they occur.

They must also know whom to contact in an emergency. These teaching points need reinforcement at regular intervals.

Sick day guidelines

Sicknesses are often associated with high BG and an increased risk of ketoacidosis. In some conditions like gastroenteritis there is a risk of hypoglycemia. Hence, all patients need to be educated on handling sick days.

The key messages during an illness include:

(i)   Check BG frequently (at least 4 hourly, more frequently if needed)

(ii) Check ketones if BG are persistently high (>250 mg/dL) or child is having vomiting/ abdominal pain or rapid breathing.

(iii) Adjust insulin doses according to BG and ketone levels (Box 1 and Table I) giving correction doses for high BG especially with ketosis.

(iv) In case of low BG (more likely in gastroenteritis), BG can be maintained by regular intake of carbohydrates/sweet liquids or with mini dose glucagon (Box 2). Insulin doses can be reduced but should not be skipped altogether

(v)   Never miss insulin totally, since a common mistake is to miss insulin doses since the child is not eating

(vi) Ensure adequate hydration,

(vii) Treat the underlying illness.

The family should know when to bring the child to hospital. The indications are:

(i)   if he/ she is less than 5y of age

(ii) if he/she looks sick

(iii) if ketones are moderate-high or if the ketones are rising despite giving corrective insulin doses

(iv) if there is pain in abdomen, vomiting, severe diarrhea or poor oral intake,

(v)   especially if hypoglycemia is occurring.

(vi) if he/she is having symptoms of ketoacidosis such as rapid breathing, drowsiness or altered behaviour

(vii) if temperature is >101^0 F

Table I: Guidelines for extra dose of rapid/short acting insulin in sick days

KETONES		BLOOD GLUCOSE LEVEL (mg/dL)		
URINE	BLOOD (mmol/L)	180- 250	250- 400	>400
Negative	< 0.6	No extra insulin	5%	10%
Small	0.6 – 0.9	5%	5-10%	10%
Small to moderate	1 – 1.4	5-10%	10%	10%
Moderate to large	1.5- 2.9	5-10%	20%	20″%
Large	> 3	10%	20″%	20%

(Modified from ISPAD 2018 guidelines on sick day management)

Box-1: Guidelines for taking extra insulin for high BG/ketones in sick days

- Calculate total daily dose (TDD) of insulin by adding all the number of units that are given to the child (including long and short-acting insulin).
- Extra insulin to be taken as a percentage of TDD as shown in table I
- Extra dose is administered only as rapid/short acting insulin like regular, lispro, aspart/fast acting aspart or glulisine and can be repeated 3-4 hourly as needed.
- In case sugars running low, give extra carbohydrates/mini dose glucagon, consider reducing insulin dose by 10-20% but do not skip doses altogether. Basal insulin doses may need reduction by 20-50% depending on BG.

Abbreviation: BG: Blood Glucose, TDD: Total daily dose

Box 2: Mini-dose glucagon for prevention of hypoglycemia in sick days

- To be taken if BG low despite taking carbohydrates/not tolerating carbohydrates
- Take with U100 insulin syringe (black markings, orange cap)
- Dose:
  - < 2 years= 2 units
  - 3-15 years= 1 unit per age of the child (example 10 units for 10-year-old),
  - >15 years= 15 units
- Injected under the skin similar to insulin
- Do not take if moderate or large urine ketones/serum ketones> 1 mmol/L

Abbreviation: BG: Blood Glucose

Blood ketone meters are available in India (e.g. Freestyle Optium blood ketone test strips), and their use for monitoring should be encouraged, since they are more reliable than urine ketone monitoring. For children using CGMS, frequent monitoring of BG is not a problem, but they must be taught to be alert to the changes in BG patterns, and provide the correction doses of insulin. Pump users must be reminded that they can develop DKA quickly if there is pump malfunction, since there is no basal insulin. They must not neglect BG monitoring and keep extra supplies of regular or rapid insulin which can be used by syringe/vial or pen device in case the need arises. Families from low socioeconomic status who do limited BG monitoring should be encouraged to make sure frequent testing is done during sick days.

The sick child should be seen at the onset of illness by the endocrinologist, or pediatrician, for appropriate treatment of the underlying illness, and admitted if necessary, or reviewed as often as indicated. Infections may be more common and/ or more severe if the child's diabetes is poorly controlled. However, the tendency of many pediatricians and physicians to overtreat any child with diabetes, e.g. giving antibiotics when not indicated (as in a viral illness), is not justified.

Hypoglycemia

The other major acute complication is hypoglycemia. Severe hypoglycemia, marked by coma or convulsions, is very frightening, and fear of hypoglycemia can be an important barrier to good glycemic control. Therefore, prevention and management are essential survival skills to be taught to the patient and family at the time of diagnosis, and reinforced frequently.

Patients should be taught to avoid situations which can lead to hypoglycemia (Figure 1) - delaying or missing meals, and/ or exercising without adjusting insulin and calories, or overdose of insulin (accidental or deliberate). Frequent BG testing is important when starting a new exercise regimen or unexpected activity. Having at all times a diabetes I-card stating the symptoms of hypoglycemia and some form of plain sugar (glucose powder or tablets, sugar cubes, powdered sugar, sugar candy, gur, honey, juice) on one's person can be life-saving. This should be followed by a slowly absorbed snack like milk or peanuts. Family and staff who are familiar with the symptoms and signs of hypoglycemia, and know what to do, can usually prevent a severe episode. However, in case a crisis does occur, Injection Glucagon should be given, and the patient rushed to hospital for intravenous glucose infusion if needed. Glucagon must be kept at home or school/work - it is available in India. Glucagon can be administered via intramuscular or subcutaneous route. The dose is 0.5 mg for children <12 years and 1 mg for children and adults >12 years. Recently, the United States Food and Drug Administration (FDA) has approved nasal glucagon (3mg, Baqsimi) for treatment of severe hypoglycemia in patients aged ≥4 years. The approval was based on the results of two randomized trials, that showed non-inferiority of nasal glucagon to injectable glucagon for treatment of insulin-induced hypoglycemia. Patients can be asked to show I-card and hypoglycemia kit during clinic visits to drive home the point.

Figure 1: Common causes of hypoglycemia

Insulin
Incorrect type, high dose, injecting during or after meals, intramuscular injection, wrong sites, massage after injecting

Food
Inadequate or delayed meals, Missing meals or snacks , alcholol Unpredictable eating (toddler/adolescent) Eating disorder

Exercise
Unplanned exercise Inadequate insulin/food adjustment for exercise
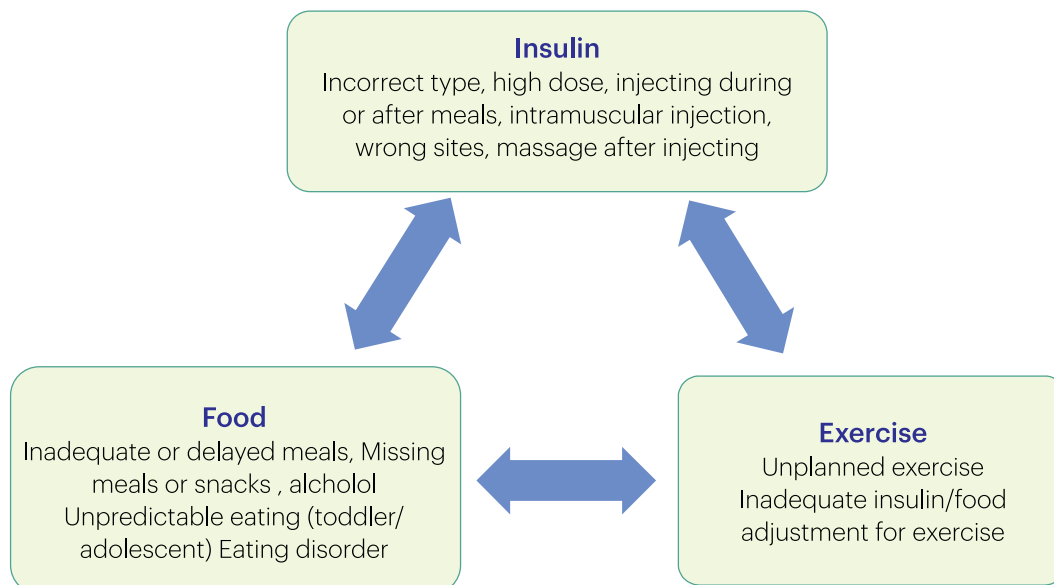
Symptoms (Table II) may be different at different ages or circumstances; for example, a change in behavior can be the only symptom of low glucose in toddlers. The occurrence of symptoms depends on the BG level, the rapidity of fall in BG, antecedent glycemic control and frequency of hypoglycemia. Therefore, as far as possible, BG should be checked for confirmation, especially with CGMS, which may show spurious lows. Special emphasis must be given to hypoglycemia occurring at night, as it is a very commonly missed phenomenon. In patients using CGMS, asymptomatic hypoglycemia and night hypoglycemia can be picked up easily. These situations pose a challenge to those on multiple daily tests, so the family should be taught how to distinguish persistent hyperglycemia

from rebound hyperglycemia. Intelligent CGMS users can analyze the glucose trends to prevent hypoglycemia episodes; the alarm feature is invaluable in toddlers and especially at night. Treatment of hypoglycemia is summarized in Figure-2 and has been discussed in the chapter of acute complications in detail. Table -III lists common treatment options for hypoglycemia treatment. It should be emphasized that hypoglycemia should not be used as occasion for treats and sweets. Use of milk or fat containing sweets like milk chocolates, ice cream, milk-based sweets and ghee/oil containing sweets is not appropriate for hypoglycemia treatment.

Table II: Symptoms of hypoglycemia

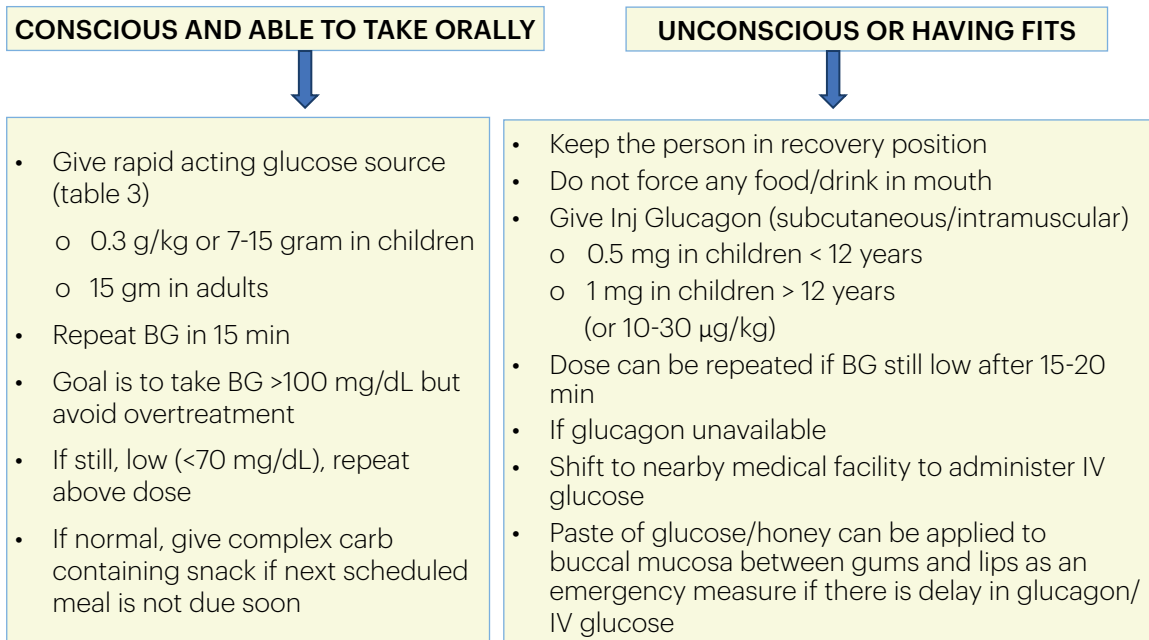| Symptoms due to body's response to low BG	Symptoms due to reduced glucose delivery to brain
Shakiness or tremors	Headache
Excess hunger	Confusion
Fast heartbeat	Behavioral change
Sweating	Slurred speech, blurred vision
Pale skin, cold extremities	Difficulty concentrating
Anxiety	Drowsiness
Feeling of weakness	Unsteady walking
	IF NOT TREATED SEVERE SYMPTOMS BELOW CAN BE SEEN
	Loss of consciousness
	Fits

Abbreviation: BG:Blood glucose

Table -III: Common sources of glucose used for hypoglycemia treatment

Source	Common brand names	Quantity	Carb content
Glucose tablets	Hypotab Glucovita bolts	1 tablet	4 g (hypotab), 2 g (glucovita)
Glucose powder, sugar & honey	Glucon-D	1 teaspoon	4 g
Hard candies	Poppins Mango bite	1 candy	3-4 g
Cold drink	Coca cola, pepsi etc	100 ml	11 g
Sweetened juices	Tetra pack juices – e.g. Real, Tropicana, Frooti	100 ml	14-15 g

Sports

Exercise has several benefits for diabetes control, and quality of health and life in general, and must always be encouraged for the child and family members. Hypoglycemia and to a lesser extent, hyperglycemia, interfere with games and sports; a severe hypoglycemic episode may cause the family to dissuade the individual with diabetes from all exercise. Therefore, it is important to check BG frequently – before and after, and for prolonged sports, during the activity, when first starting a play regimen, or during unexpected activity. If the activity is planned, insulin doses should be decreased in anticipation. For prolonged sports, a slowly absorbed snack like nuts and seeds, peanut chikki, coconut barfi or chocolate may be taken before starting. If hypoglycemia does occur, then of

Figure 2: Treatment of hypoglycemia (confirm hypoglycemia with glucometer whenever possible)

CONSCIOUS AND ABLE TO TAKE ORALLY	UNCONSCIOUS OR HAVING FITS
• Give rapid acting glucose source (table 3) o 0.3 g/kg or 7-15 gram in children o 15 gm in adults • Repeat BG in 15 min • Goal is to take BG >100 mg/dL but avoid overtreatment • If still, low (<70 mg/dL), repeat above dose • If normal, give complex carb containing snack if next scheduled meal is not due soon	• Keep the person in recovery position • Do not force any food/drink in mouth • Give Inj Glucagon (subcutaneous/intramuscular) o 0.5 mg in children < 12 years o 1 mg in children > 12 years (or 10-30 µg/kg) • Dose can be repeated if BG still low after 15-20 min • If glucagon unavailable • Shift to nearby medical facility to administer IV glucose • Paste of glucose/honey can be applied to buccal mucosa between gums and lips as an emergency measure if there is delay in glucagon/ IV glucose

course, simple sugars should be taken to correct it, as discussed above. BG responses differ in aerobic and anaerobic activity.

Preconception Care

All women of child-bearing age with T1DM should proactively receive counselling on methods of contraception, planning of pregnancy and the risks associated with an unplanned pregnancy. These include a higher risk of congenital malformations (commonly cardiac and neural tube defects), miscarriage, preterm labor, pre-eclampsia and fetal or neonatal deaths. Pregnancy may also aggravate complications of T1DM.

Contraception should be practised till the desired glycemic control is achieved, and folic acid supplementation started in the preconceptional period. Contraception could be hormonal or non-hormonal (barrier methods or intrauterine device)– the latter may be preferable in women with past or family history of thromboembolic diseases.

Preconception care should be aimed to achieve a HbA1c of < 7% (preferably as close to 6% as possible) without causing significant hypoglycemia. Recommended BG testing frequency is 6-7 times per day or with a CGMS; targets are fasting/ premeal readings of 80-110 mg/dl and 1-hour post-meal readings of 100-155 mg/dl. For this, physiological insulin dosing is needed - basal bolus regimen or continuous subcutaneous insulin infusion (CSII), i.e., insulin pump.

Preconception, all patients should be assessed for complications and co-morbid conditions, relevant changes made in treatment, and folic acid supplementation started (at least 400 µg/day). Issues like obesity, smoking, alcohol or drug consumption, and pre-existing complications like retinopathy (can worsen during pregnancy) should be dealt with before planning the pregnancy. Teratogenic or drugs with uproven safety during pregnancy such as statins, ACEI or ARB should be substituted by safer drugs (such as methyldopa, calcium

channel blockers or labetolol for control of hypertension) (also see chapter on "Special group- Pregnancy, Travel and Surgery").

Travel

Several aspects of diabetes care need attention during travel, and should be discussed well in advance. Eating, activity, and sleep patterns can be variable, even from day to day, so BG monitoring has to increase, and insulin doses adjusted accordingly. Insulin and glucagon need transport at 2-25°C, in a thermos or other insulated carrycase, never packed in check-in baggage. Depending on the duration of travel, all supplies - insulins, syringes, pen needles, BG strips, blood glucose meter, sensor and other disposables, candies to prevent hypoglycemia and some concentrated calorie sources like dry fruit – and 50% extra as spares - should be carried. On school trips, parents must ensure the accompanying teachers can handle routine care and emergencies, and have emergency contact details. Discarded sharps should be stored safely for later safe disposal (also see chapter on "Special group-Pregnancy, Travel and Surgery").

Driving

Indian law requires a minimum age of 16y for a learner's license, 18y for a regular license, and 20y for a commercial license. Indulgent parents who allow underage teens to drive should be vehemently discouraged. Frequent BG testing should be encouraged initially. The patient must make sure BG is not low, or trending low, before beginning to drive, as even mildly low sugars can interfere with cognition. Some non-perishable snacks (e.g. peanuts) and also simple sugar sources (candies) should be available in the vehicle for emergencies. Patients on CGMS should keep an eye on the BG trend, and avoid even mild hypoglycemia.

In addition, vision should be normal. Rapid BG changes can lead to some blurring of vision – driving should be avoided at such times. Of course, as with persons without diabetes, no alcohol or intoxicant should be consumed before or when driving.

Limited resources

The difficulties of managing T1DM are amplified in families with limited resources, including even food insecurity, and availability of insulin and glucose strips. Poverty and illiteracy often go hand in hand – they make the task of education more difficult, but also more rewarding, since diabetes care education can help overcome some of the barriers posed by these conditions. Every aspect of diabetes care should be viewed through the prism of cost-effectiveness and affordability, since parents may be too ashamed to tell the team they ration insulin, BG testing, etc. More expensive insulins and devices are not necessarily superior. Insulin in vials is less costly than in cartridges. Disposable pens are more expensive than reusable ones. Lancets and needles can be reused several times with proper care. Multiple dose insulin regimens can give good metabolic control; insulin pumps are not essential. By forming groups and buying supplies in bulk directly, families can reduce costs. Excellent outcomes can be obtained with careful attention to finding cost-effective solutions, peer support, charitable and subsidized options, and income generation.

Remote Areas

Health care providers with expertise in managing T1DM are few and far between in many developing countries, especially is smaller cities and villages. This frequently results in

poor management and therefore poor outcomes and needless suffering. In all developing countries, the deep penetration of mobile phones and the low cost of their use has begun to enable those living in remote areas to access experts and better care. In India, the recent decision of the Government to legalize telemedicine, and its extensive use during the COVID crisis, would enable better care to be possible for patients who could earlier not access experts. Use of digital tools is also helpful.

Another difficulty in remote areas is quality of insulin. Any breach of the cold chain would decrease the potency of insulin, leading to variability in glycemic control. This is a neglected area which needs urgent attention.

Fasting and Feasting in T1DM

Multiculturalism and practice of multiple religions means myriad of reasons for which Indians might consider undergoing fast. Hindus can consider nine days fast in Navratras, or day long fasts during Ekadashi or Purnimaevery month. Muslims observe Ramadan [where they refrain from eating and drinking from dawn to dusk, and consume calorie dense food at suhoor (before sunrise) and iftar (after sunset)] twice a year, Buddhists observe 12 hours fast for three lunar months during Vassa, Jains partake in 8-10 days of Paryushana, Christians keep fast during Lents, and Sikhs during Guru-Purnima. Most of these days of piety are followed by periods of celebration and feasting associated with consumption of high calorie food.

Since persons with diabetes are advised to consume food at regular intervals to maintain blood glucose levels within target ranges, these periods of fasting may lead to increased risk of hypoglycemia, whereas consumption of calorie rich food in post-fast period may lead to hyperglycemia, ketoacidosis or other metabolic abnormalities. Dehydration and electrolyte imbalance occurs due to abstinence from fluid intake, especially during summer festivals, while hyperglycemia worsens it by excessive fluid loss through urination. Dehydration increases the risk of thrombosis in persons with T1DM.To accommodate suhoor there is altered sleep pattern with decreased REM and increased NREM sleep, which decreases insulin sensitivity.

With these risks in mind, both religious and medical organizations allow for exemptions to these religious fast for persons with diabetes. ADA places persons with T1DM in very high-risk group, while the International Diabetes Federation Diabetes and Ramadan (IDF-DAR) guidelines places uncontrolled T1DM and well controlled T1DM in very high-risk group (category 1) and high-risk group (category 2), respectively with the recommendation that these patients must not and should not fast, respectively. These categories are advocated by Islamic Organization for Medical Sciences and the International Islamic Fiqh Academy, thereby exempting patients with type 1 diabetes from fasting without the guilt of not participating in their religious duties. However, many individuals still insist on partaking in these fasts due to the deeply religious connotations associated with them. In such a scenario, physicians should be aware of the risks and challenges associated with these fasts and counsel and educate the patients in ways to mitigate them. Following are the measures prescribed by IDF-DAR which can also be applied for other religious fasts:

1. Receive structured education
    a) All patients should consult their physician 6-8 weeks prior for proper risk stratification and quantification. Patients with T1DM and any of the following conditions should be strongly advised to avoid fasting:

      i.   History of recurrent hypoglycaemia

      ii.   Hypoglycaemia unawareness

      iii.   Poor diabetes control

      iv.   Brittle diabetes

      v.   Non-compliance with medical treatment

      vi.   Patients who are 'unwilling 'or 'unable' to monitor and manage their blood glucose levels

b) Self-Monitoring of Blood Glucose (SMBG): Misconception that pricking blood invalidates their fast needs to be allayed. Patients with T1DM should monitor their blood glucose:

      i.   Multiple times a day to understand the trend of the excursions and keep a Ramadan logbook of these records

      ii.   Post-*iftar* to detect hyperglycemia after heavy meal

      iii.   Whenever they experience symptoms of hypoglycaemia

c) Dietary advice: This needs to be individualised and includes having a well-balanced meal with 40-50% carbohydrates with low glycemic index, 20- 30% protein and <35% of fat, with daily calories divided equally between *iftar and suhoor* with 1-2 snacks in between, while including plenty of fruits and vegetables and avoiding caffeinated, sweetened drinks and deserts. These can be represented by the 'Ramadan Plate Method" for visualisation to patient. To aid with this, a mobile and web-based application known as Ramadan Nutrition Plan (RNP) has been designed to help physicians design individualised medical nutrition therapy (MNT) for patients with diabetes during Ramadan fasting. In order to ensure adequate spacing between the meals, the dinner should be taken as soon as possible at *iftar* and *suhoor* should be delayed as much as possible. The practice of staying up late at night to consume *suhoor* before eventually going to sleep should be discouraged.

d) Underscore the importance of breaking the fast immediately if any of these situations arises:

i.   Blood Glucose < 70mg/dL

ii.   Blood Glucose > 300mg/dL

iii. Symptoms of hypoglycaemia, hyperglycaemia, dehydration or acute illness occur

2. Pharmacological Management

    a.   Patients on Basal-Bolus Regimen have to make the following adjustments:

      i.   Long/intermediate-acting insulin

          1.   If taking once a day, then reduce it by 15-40% and take at *iftar*

          2.   if taking twice a day, then take the usual morning dose at *iftar*, and reduce the evening dose by 50% and take it at *suhoor*]

      ii.   Premeal insulin

          1.   Normal *iftar* dose,

          2.   Reduce *suhoor* dose by 25-50%

b. Patients on insulin pump

i. Basal rate is to be kept same as before, but reduce it by 20-40% in the last 3-4 hours of fasting and increase dose by 0-30% in the first 2 hours after *iftar*

ii. Bolus rate is to be decided by normal carbohydrate counting and insulin sensitivity principles

Target pre-iftar/pre-suhoor and post-iftar/post-suhoor BG is 90-130 mg/dl, and insulin is to be self-titrated in increments of 2 units till target BG is reached. Patients should be advised to follow up after the festivities are over to discuss the challenges they faced, and readjustment of medications.

Smoking, Alcohol and other substance abuse in T1DM

Adolescents tend to indulge in experimental behavior in a bid to develop an individual identity. The stress associated with a chronic illness like T1DM may further provoke indulgence in high-risk behavior in these individuals.

Smoking

Harmful effects of cigarette smoking are established across all age groups. However, adolescents with T1DM are predisposed to a larger magnitude of deleterious effect, be it impact on metabolic control or on micro- and macro- vascular complications. Smoking is associated with worse glycemic control in T1DM along with a tendency to have higher diastolic blood pressure and atherogenic lipid profile, leading to an increase in cardiovascular risk. Smoking also causes vascular damage, endothelial dysfunction and activation of coagulation pathway which in the background of vascular stiffness and poor cardiovascular profile, leads to an increased risk of cardiovascular events. Microvascular complications are also seen with increased frequency and an increased progression to micro albuminuria and nephropathy, worsening of retinopathy, and deterioration of neuropathy has been reported in smokers with T1DM. On account of these factors, the mortality has been reported to be higher in smokers in several T1DM cohorts.

There is good evidence to suggest that the deleterious effects induced by smoking are reversible upon its cessation. This makes for a compelling argument for the need of active intervention to curb smoking in patients with T1DM. As cigarette smoking in children with T1DM increases with age, it becomes essential to actively counsel children against the initiating of smoking from younger age, which puts physicians taking care of these patients at the forefront of combating smoking. ADA recommends smoking cessation counselling as a routine component of diabetes care. Multiple strategies, including the 5 A's plan of Ask, Advise, Assess, Assist, and Arrange have been proposed as an effective method to address smoking among adolescents with T1DM. Psychotherapy, nicotine patch and other nicotine cessation modalities may be tried in motivated patients. ADA recommends against the use of e-cigarettes.

Alcohol

Even though alcohol consumption is reported to be lower in individuals with T1DM compared to their peers, they are still at a higher risk of experiencing severe harm from it, as alcohol consumption is associated with worse glycemic control as well as higher rates of DKA and hypoglycemia. The metabolism of alcohol reverses the NADH/NAD-ratio (redox-shift) which inhibits gluconeogenesis. Besides, alcohol is also known

to inhibit glycogenolysis and enhance lactate and beta-hydroxybutyrate production. Lower release of glucose from the liver leads to hypoglycaemia and accumulation of beta-hydroxybutyrate causes ketosis. Further, the risk of hypoglycemia is compounded by reduced recognition of physiological warning signs (hypoglycemia unawareness) by patient along with mistaken identification of these signs by third party as those of intoxication. Chronic alcohol consumers also have reduced diabetes self-care behaviors, poor compliance with medications, and worse glycemic control and HbA1c levels.

Thus, patients with T1DM need to be adequately questioned and counselled regarding harms of both binge drinking as well as chronic consumption of alcohol. They should be educated regarding 'responsible drinking', which includes avoiding binge drinking, consuming carbohydrates while drinking alcohol, watching out for delayed hypoglycemia and preventing it by frequent monitoring or consumption of extra carbohydrate or decreasing the dose of insulin. Patients should never drink alone, and their peers should be informed about the diagnosis of diabetes and risk of hypoglycemia and DKA, and necessary steps that may be required if situation arises.

Other illicit drugs

Self-reported usage of street drugs is common in T1DM, with results varying from 10-77% depending upon survey method and countries involved. Risk of hypoglycemia and DKA remains high due to impaired self-care associated with intoxication, as well as having overall a poor glycemic control and HbA1c levels. Studies have indicated that past and current drug abuse is significantly associated with acute events leading to mortality in T1DM. Most of the individuals were unaware of the negative health consequences of these drugs on their disease or how to manage the complications. Thus, it becomes imperative for physicians taking care of these individuals to frequently ask them about usage of these drugs tacitly, and to counsel them for cessation and psychotherapy referral as required, for an overall positive health.

Summary

The diagnosis of T1DM means the start of a long and close relationship of the patient, family, and others, with the diabetes care team. The aim of a physically and emotionally healthy person and family can only be achieved by effective education, taking all aspects into consideration, at a pace which is appropriate for the age, socio-economic-cultural background, motivation, availability of technology and medical status of the child and caregivers. Outcomes can be very rewarding, as well managed children grow up to become confident, self- reliant "heroes".

Checklist of related topics

1. Diagnosis, symptoms, need for lifelong self-care with insulin
2. Pathophysiology, "cause" – no one's fault, not communicable, difference from T2D, other forms of diabetes, honeymoon phase (not cured)
3. Blood glucose (and ketone) testing, recording, discerning patters
4. Handling insulin: types, action profiles, transport, storing, devices, injecting, adjusting, sites
5. Hypoglycemia, I-cards, glucagon, Sick days, any illness/ surgery
6. Diet changes, carbohydrate counting, exercise, sports

7. Psychological responses, family dynamics, cognitive behavior therapy, coping mechanisms, avoiding burnout

8. Diabetes technology

9. Peer support, self-help groups

10. Special occasions: festivals, travel, diabetes camp, school camp/excursion

11. Detection and management of co-morbidities, complications

12. Careers, marriage, contraception, planning conception, driving,

13. Smoking, alcohol, drugs, other additions and risk taking behaviors

14. Financial issues

15. Transition to adult services

Suggested Reading

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Chapter-11

Special Groups: Pregnancy, Travel and Surgery

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Section A-Pregnancy

Introduction

Type 1 diabetes mellitus (T1DM) affects approximately 0.1-0.2% of all pregnancies and has a higher association with poor outcomes for both mother and her off spring[1]. The risk of perinatal death and stillbirth has been reported to be 4 to 6-fold higher in T1DM as compared to the general population[2]. Data (1996-2008) from England revealed a four and two times higher prevalence for fetal and infant death respectively, without any significant difference among women with pre- existing T1DM (n=1206) or type 2 diabetes mellitus (T2DM) (n=342). The study found that this adverse effect was largely moderated by glycemic control[3].The risk of congenital malformations (like neural tube defects, caudal regression, microcephaly or anencephaly, congenital heart disease) can be as high as 15% in offsprings of T1DM women with HbA1c above 14%[2,4-6]. The risk is also higher for miscarriage, intrauterine death, preterm birth, macrosomia and associated complications in women with poor periconceptional glycemic control.

In view of the strong link between poor glycemic control and adverse pregnancy outcomes, achieving euglycemia during preconception and pregnancy is important for improving pregnancy outcomes. The early recognition and care of associated complications like nephropathy, retinopathy, and comorbidities like hypertension is also essential for improving pregnancy outcomes.

Women in the reproductive age group should be aware of the importance of planned pregnancy, and education regarding it should begin during adolescence as part of routine diabetes care[5]. A woman who plans pregnancy would need about 6 months to achieve and maintain optimal glycemic control. The components of care from preconception (Table I) to postpartum phase are discussed below. This chapter aims to provide a description of components that can help in improving outcomes of pregnant women with T1DM.

Glycemic targets

Preconception

Near normoglycemia is the target when planning pregnancy. According to guidelines the goal of pre-pregnancy HbA1c should be < 7%[6-9]. Lower HbA1c (of < 6.5%) can be targeted if it can be achieved safely (especially avoiding the risk of severe or frequent hypoglycemic episodes)[6-9]. On the contrary, a woman with HbA1c > 10% should be strongly discouraged from getting pregnant till she achieves better control because of the high risk of adverse

Table I: Preconception care of women with diabetes

A.	Preconception counselling: Aim to inform woman to have optimal glycemic control before pregnancy.
B.	Optimization of insulin therapy preferably with multiple daily dose insulin or continuous subcutaneous insulin.
C.	HbA1c levels should be as close to normal as possible without undue hypoglycemia.
D.	Medications should be reviewed. Comorbidities and complications should be assessed and taken care of.
E.	Folic acid (5 mg) daily should be prescribed daily before conception to reduce the risk of neural tube defects.
F.	Measurement of serum TSH and thyroid peroxidase is recommended before conception.
G.	Discussion on contraception and providing the most appropriate method.

Abbreviations: TSH-Thyroid stimulating hormone, HbA1c-Glycated hemoglobin

pregnancy outcomes beyond this level[6]. A monthly measurement of HbA1c is suggested by UK NICE (National institute for Clinical excellence) guidelines in the pre-conception period[6]. Clear guidance on self-monitored capillary glucose targets is still required. Some suggest glycemic targets of 80-110 mg/dl for fasting and pre-meals and 100-155 mg/dl for 1-hr post-meals[10]. As per the UK NICE guidelines,the recommended target includes:

- A fasting plasma glucose (FPG) of 90–126 mg /dl on waking
- Plasma glucose of 72–126 mg /dl before meals at other times of the day.
- After meal plasma glucose level of 90–162 mg/dl.

Women may require monitoring of blood glucose around 6-8 times in a day to achieve these targets without hypoglycemia. To increase compliance on decided strategy the monitoring frequency needs to be individualized. This is based on shared decisions,and striking a balance between the need for achieving glycemic targets and available resources.

Insulin storage/technique, self-adjustment of insulin doses required at certain times, sick day rules, ketone testing and hypoglycemia care are important components of education for safety achieving glycemic targets. The woman herself or any family member should have necessary skills for the same.

The woman should undergo a review for drugs with potential teratogenic effect (like ACE inhibitors or angiotensin receptor blockers, statins) and evaluation for glycemic and blood pressure control, diabetes related complications and thyroid status (Table I). This is in addition to other investigations done as routine for all women in preconception period or special investigations required an individual basis.

During Pregnancy

The American Diabetes Association (ADA) has recommended targets for women with T1DM, similar to women with GDM, which are as follows[7]:
- FPG ≤ 95 mg/dl and
- Either one-hour postprandial ≤ 140 mg/dl or
- Two-hour postprandial ≤ 120 mg/dl.

The UK NICE recommends almost similar target levels for pregnant women except a slightly lower target (of < 115 mg/dl) for two hour postprandial glucose, if these can be achieved without causing problematic hypoglycemia.

Less stringent and individualized targets can be set in case efforts to achieve recommended targets result in significant hypoglycemia[7]. The HbA1c is used as an additional measure of glycemic control (a monthly measurement is suggested) and should not be a replacement of self-monitoring of blood glucose, due to physiological changes in pregnancy affecting its accuracy. The data suggest that HbA1c of < 6-6.5% is associated with lower rates of adverse fetal outcomes[7].

Fetal Growth monitoring

It is important to have an objective assessment of fetal growth in addition to close clinical monitoring of the pregnancy, since poor glycemic control is associated with accelerated fetal growth. Ideally a scan is done at 28 weeks and then 4 weekly to monitor growth. If this is not feasible in resource limited settings, at least one at 28 and another at 36 weeks is advisable. The presence of polyhydramnios and accelerated growth may be due to less than optimal glycemic control and needs to be factored in along with the blood glucose values.

Growth restriction can happen in women who have long standing type 1 diabetes and vasculopathy. Similarly, the tailing off of growth can also be a warning for impending preeclampsia. The risk of preeclampsia is higher in women with T1DM, and poor glycemic control increases it further.

In women with T1DM, there is higher risk of stillbirth. This is due to fetal hyperglycemia and hyperinsulinemia which induce fetal hypoxemia and maternal vasculopathy, causing poor utero placental circulation. This therefore, unlike pure placental dysfunction in IUGR or preeclampsia, does not lend itself to surveillance by fetal doppler examination. Indeed there are no good studies based on which one could make recommendations on the frequency or the best method of fetal surveillance. As of now, combination of a Non Stress test and amniotic fluid volume is monitored depending on local institutional protocols.

The NICE 2015 guidelines have elaborated in detail the antenatal management of women with diabetes during pregnancy and the same have been adapted here and presented in Table II. This table refers to physical activity and not antenatal management.

Insulin therapy

Multiple subcutaneous insulin injections (MSII) are standard of care to achieve glycemic control given higher efficacy and better safety than premix or split mix regimens[11]. According to NICE 2015 guidelines, insulin pump can be offered to women during pregnancy if glycemic control is difficult to achieve with MSII due to significant hypoglycemia. In view of increased potential of hypoglycemia in pregnancy, rapid acting analogs like aspart or lispro and long acting analogs like detemir are preferred over conventional insulins[11].

Insulin requirements may vary throughout pregnancy. It may increase in the first 9 weeks, thendecrease from 9-16 weeks, before further increasing until the 37th week[12]. With progression in pregnancy, the insulin requirements may increase by two to three times with a shift towards more prandial insulin requirement. The insulin requirements can be 40-50% higher for up to 1 week after the initiation of glucocorticoid treatment for premature fetal lung maturation.

Medical nutrition therapy

An individualized nutrition plan which is culturally sensitive and socio- economically viable and which provides adequate calories for fetal and maternal health, achieves glycemic goals without hypoglycemia, and helps in appropriate gestational weight gain should be made with the help of an expert dietician. The Dietary Reference Intakes (DRI) recommends a minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber[7]. A less carbohydrate-restricted approach may improve maternal adherence when combined with higher quality carbohydrates, lower fat, appropriate caloric intake, and ethnically acceptable foods[13]. Three major meals and three to four adequately spaced snacks help in avoiding hypoglycemia while preventing glycemic fluctuations, provided women also pay attention to timings, content and quality of meals/snacks.

Exercise

Exercise facilitates the glucose uptake, improves glucose clearance and sustains insulin sensitivity. Furthermore, exercise also regulates counter-regulatory hormones and decreases hepatic glucose output as evident in fasting blood glucose levels. Women without medical and obstetric contra indications (Table III) should be encouraged to doat least 30 min/day of physical activity[14]. Carbohydrates consumed (20 g of glucose) before, during, and after physical activity will help avoid hypoglycemia, especially if glucose is < 90 mg/dl[15].If starting glycemia is 90–124 mg/dl, one should ingest 10 g of glucose before starting aerobic exercise. If starting glycemia is 126–180 mg/dl aerobic exercise can be started without glucose ingestion[15].

During Labor

Women with T1DM should be managed with insulin infusion and intravenous dextrose (5%) running separately. Monitor glucose hourly and the level should be maintained intervals between 72 and 126 mg/dl[6]. During cesarean section blood glucose monitoring should be reduced to 30 minutes which should continue till the baby is born and mother is conscious. An anesthetic assessment should be done in third trimester for women with diabetes and comorbidities such as obesity or autonomic neuropathy[6].

Hypoglycemia

The aim to achieve near normoglycemia also increases risk of hypoglycemia. Severe hypoglycemia (hypoglycemia requiring help from another person to restore the blood glucose level) is 3 to 5 times more frequent in first half of pregnancy than before conception. It is mainly because of increased nausea and vomiting in the first trimester, thereafter the incidence is lower. Up to 45% of women with T1DM experience severe hypoglycemia during pregnancy. However, 60% of the severe hypoglycemic episodes are accounted for by only 10% of pregnant women with T1DM[16,17]. A history of severe hypoglycemia in the year preceding pregnancy and self-estimated impaired hypoglycemia awareness are significant risk factors for severe hypoglycemia. A simple question "Do you recognize symptoms when you have hypoglycemia?" can identify subjects with impaired awareness. The woman with impaired awareness has threefold increased risk of severe hypoglycemia compared to woman who has normal awareness[18]. A longer duration of diabetes, intensive insulin treatment resulting in lower HbA1c in early pregnancy, and fluctuating plasma glucose values (< 70 to > 180 mg/dl) contribute to a higher risk of severe hypoglycemia during pregnancy[16,17].

Limited evidence in humans suggests that hypoglycemia has no short or long- term adverse effect on the fetus[16]. However, consequences of severe hypoglycemia like convulsions, road traffic accidents, maternal death in extreme cases, are rare but dangerous complications of

Table II: Timetable of antenatal appointments − adapted and modified from UK NICE guidelines

Booking appointment Ideally by 10 weeks	• Review medicines for diabetes and its complications. • Patient should get blood pressure measurement, per speculum examination, hemogram, kidney function tests, liver function test, TSH, urine routine microscopy and culture. • Measure HbA1c levels in every trimester. • Confirm viability of pregnancy and gestational age at 7–9 weeks. Early viability scan is recommended since women with diabetes are at a higher risk of miscarriage. Dating is important to plan delivery and avoid prematurity. • Offer retinal assessment for women with pre-existing diabetes unless the woman has been assessed in the last 3 months. • Offer renal assessment for women with pre-existing diabetes if this has not been performed in the last 3 months. • Arrange contact with the joint diabetes and antenatal clinic every 1–2 weeks throughout pregnancy for all women with diabetes.
11-14 weeks	• Neural tube/nasal bone (NT/NB) scan with dual screen test for chromosomal anomalies.
18-20 weeks	• A detailed ultrasound needs to be performed between 18-20 weeks along with a fetal echocardiogram to rule out neural tube defects, cardiac and other structural abnormalities that are associated with diabetes. • Retinal assessment if diabetic retinopathy was present at their first antenatal clinic visit.
28-32 weeks	• Offer ultrasound monitoring of fetal growth and amniotic fluid volume • Need for antenatal steroids (ANS) to be evaluated • Women with uncontrolled sugars or high insulin requirement should be reconsidered for referral to higher centre with NICU facility • Daily fetal movement count should be explained • Retinal assessment of all women
36 weeks	• Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
	Provide information and advice about: • Timing, mode and management of birth • Analgesia and anesthesia • Changes to blood glucose-lowering therapy during and after birth • Care of the baby after birth • Initiation of breastfeeding and the effect of breastfeeding on blood • Contraception and follow-up.
37^{+0}-38^{+6} weeks	• Offer induction of labor, or caesarean section if indicated, otherwise await spontaneous labor. • Timing of delivery should be individualized Neonatal care: Neonate should be monitored for hypoglycemia, respiratory distress, hyperbilirubinimia.

Abbreviations: UK NICE guidelines: United Kingdom The National Institute for Health and Care Excellence guidelines, TSH: thyroid stimulating hormone, HbA1c: Glycated hemoglobin, NT/NB: Neural tube/nasal bone, NICU: Neonatal Intensive Care Unit, ANS: antenatal steroids

Table III Contraindications to physical activity during pregnancy

Contrain-dications	Medical	Obstetric
Absolute	• Hemodynamically significant heart disease • Restrictive lung disease	• Incompetent cervix • Multiple gestation at risk for premature labour • Persistent second or third trimester bleeding • Placenta previa after 26 weeks gestation • Premature labour during the current pregnancy • Ruptured membranes • Pre-ec lampsia , pregnancy induced hypertension
Relative	• Severe anemia • Unevaluated maternal cardiac arrhythmias • Chronic bronchitis • Uncontrolled diabetes • Extreme morbid obesity • Extreme underweight (BMI <12 kg/m²) • History of extremely sedentary lifestyle • Poorly controlled hypertension • Poorly controlled hyperthyroidism • Poorly controlled seizures • Orthopaedic limitations • Heavy smoker	• Intrauterine growth restriction in the current pregnancy

Abbreviation: BMI-Body mass index

severe hypoglycemia. Certain preventive measures as listed in Table IV can help in reducing the risk of hypoglycemia during pregnancy[16].

Table IV: Hypoglycemia prevention in T1DM during pregnancy

- Early identification of high-risk patients, particularly women with self-estimated impaired hypoglycemia awareness and / or history of severe hypoglycemia the year preceding pregnancy
- Reduction of insulin dose by approximately 10% at 8–16 weeks
- Cautious use of supplementary insulin in early pregnancy
- Use of rapid- and long-acting insulin analogues
- Avoid pre-bedtime plasma glucose values below 108mg/dl
- Perform frequent blood glucose monitoring including between 02:00 and 04:00 am
- Prescription of glucagon for administration at home by partner
- Use of continuous subcutaneous insulin infusion (insulin pump) therapy combined with real-time continuous glucose monitoring

Abbreviations: T1DM-Type 1 diabetes mellitus

CGMS and Insulin pump

Continuous glucose monitoring system (CGMS) provides detailed information regarding

glucose patterns that can be used for optimizing diet, lifestyle and insulin doses. It also can alert users to impending hypoglycemia or hyperglycemia allowing them to take earlier corrective action and therefore minimize out of rangeexcursions[19]. CONCEPTT was a multicenter, open-label trial where women with T1DM < 14-week gestation were randomized to capillary glucose monitoring with and without real-time CGM (used continuously from randomization until delivery). The study found that the numbers needed to treat with CGM to prevent one complication were six for both neonatal intensive care admission and large for gestational age, and eight for neonatal hypoglycemia. Sensor-integrated insulin delivery improves time in range compared to stand-alone pump therapy[21]. The first trial of sensor-integrated insulin delivery in pregnancy, which included 16 women with T1DM found that it improves time in target by 15% without increasing hypoglycemia as compared to sensor-augmented insulin delivery system[22].

Insulin pump therapy is an attractive option, given many unique challenges in pregnancy of T1DM women. Women with recurrent troublesome hypoglycemic episodes and those with hypoglycemia awareness can be good candidates for insulin therapy, preferably starting preconception. Good evidence is lacking in context for the use of currently available insulin pumps in T1DM during pregnancy[19].

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) must be excluded in all pregnant women with T1DM who become unwell, even if blood glucose values are not too high as seen in DKA (< 200 mg/dl) (euglycemic DKA can occur in pregnancy). The risk for DKA is enhanced in pregnancy due to increase in insulin resistance and enhanced lipolysis/ketosis associated with pregnancy. It is rarely life threatening for mother if it is recognized and treated promptly (Table V). However, fetal loss rates remain in the order of 10–25% for a single episode of DKA[23,24].

Other general measures to be taken care

Preconception evaluation and optimization of thyroid status

All pregnant women should be screened for thyroid disorders in preconception period using TSH, T4 and TPO, and should be managed and monitored as delineated in guidelines[11].

Folic acid supplementation

Folic acid supplementation with a daily dose of 5 mg should be started 3 months before planned conception, to reduce the risk of neural tube defects[11].

Cessation of smoking, alcohol and illicit drugs

Smoking, alcohol and illicit use of drugs is associated with adverse pregnancy outcomes. Women should be advised to stop their use in preconception period and thereafter. Referral to de-addiction clinic/expert may be done if required.

Associated metabolic diseases

Hypertension

There is two to four fold higher risk of hypertension in women with diabetes. Hypertension may be present in women with T1DM. Blood pressure (BP) <130/80 mm Hg) should be achieved before conception. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers should be discontinued prior to conception[11]. Women

Table V: Diabetic ketoacidosis (DKA) in Pregnancy - When to suspect DKA?

A high index of suspicion for DKA in diabetic pregnant women with nausea, vomiting, abdominal pain, fever, hyperventilation, hypotension, and change in mental status, in addition to symptoms related to hyperglycemia

Predisposing factors include

- Infection
- Omission of insulin doses
- Obstetrical use of β-sympathomimetic drugs and glucocorticoids.
- Protracted vomiting, starvation and dehydration
- Undiagnosed diabetes
- Insulin pump failure
- Poor glycemic control

Risks to mother

- Acute renal failure
- Adult respiratory distress syndrome
- Myocardial infarction
- Cerebral edema
- Death

Risks to fetus

- Preterm delivery
- Acidosis and hypoxia could result in fetal demise
- Adverse neurobehavioural outcomes and lower IQ

Educate

- All women with pre-existing diabetes who are planning pregnancy or already pregnant should be educated about DKA; prevention with self-monitoring of blood glucose (SMBG), medical nutrition therapy, and appropriate insulin therapy; and sick day management.
- The patient should be taught to perform urine ketone measurements at times of illness or when persistent glucose levels exceed 200 mg/dl and to promptly report positive values.

The management of DKA during pregnancy include

Multidisciplinary approach

- Intravenous fluid therapy
- Intravenous insulin therapy
- Electrolyte correction
- Evaluation of the need for bicarbonate administration
- Identification and treatment of any precipitating factors
- Monitoring of maternal and fetal responses

Fetal monitoring

- Continuous fetal heart rate monitoring and biophysical tests are used to assess fetal wellbeing in cases occurring after 24 weeks' gestation.
- Immediate delivery may not be necessary for ominous patterns, since correction of DKA often reverts the patterns to normal (usually after 4-8 hours).
- If fetal status does not improve or if the maternal condition continues to deteriorate despite aggressive therapy, delivery is warranted.

Abbreviations: DKA-Diabetic ketoacidosis, IQ-Intelligence quotient, SMBG- self monitoring of blood glucose

should be switched to safer alternatives like methyldopa, labetalol, or calcium channel blockers (nifedipine slow release).

In pregnancy, as per UK NICE guidelines (not specific to diabetes), treatment should be initiated if blood pressure is >150/100mm Hg for uncomplicated chronic hypertension/gestational hypertension/preeclampsia and at >140/90 mm Hg for target-organ damage secondary to chronic hypertension. Treatment goal is <160/110 mm Hg (but systolic ≥ 120 mmHg and diastolic ≥ 80 mm Hg, as uteroplacental and blood flow may get compromised below these levels) for chronic hypertension,<160/110 mm Hg for gestational hypertension and preeclampsia[25,26].

Dyslipidemia

In the case of women taking a statin, it has to stop if they are attempting to conceive. Use of fibrates and/or niacin is also not advisable. Bile acid-binding resins are safe alternatives in case hypercholesterolemia requires treatment[11].

Overweight/obesity

Pre-pregnancy overweight/obesity is an additional adverse factor, which adds to the insult for both the mother and her offspring. Therefore, optimization of weight before pregnancy is also desirable. Women having excess weight should preferably lose weight before pregnancy and those with BMI above 27 kg/m^2 should be strongly advised and encouraged to lose weight before conceiving[6].

Complications associated with Type 1 diabetes

The presence of active (requiring treatment for regression/stabilization) proliferative retinopathy, severe diabetic nephropathy with glomerular filtration rate reduced to < 30ml/min/1.73 m^2, severe autonomic neuropathy or severe coronary heart disease could pose serious increased risks during pregnancy and these complications should be evaluated in detail and necessary action taken[2].

Diabetic Retinopathy

Pregnancy increases the short-term risk of progression of diabetic retinopathy. In data compiled from 11 studies (till 2015) including 1026 T1DM pregnant women, the chances of progression to proliferative diabetic retinopathy (PDR) during pregnancy were only 0.5% if there was no diabetic retinopathy at baseline. However, the incidence was 10% if some degree of non- proliferative diabetic retinopathy (NPDR) was present at baseline[27]. Therefore, the presence of retinopathy especially moderate to severe NPDR is a risk factor for PDR in pregnancy. Longer duration of diabetes, poor blood glucose control, hypertension, and pre-eclampsia are other factors, which increase the risk of progression of retinopathy in pregnancy. In the DCCT trial, pregnancy was associated with 1.63- and 2.48-fold increased risk of developing short-term retinopathy in the intensive and conventional group, respectively[28]. The risk persisted for 1 year after delivery. It is recommended that all women with diabetes who are planning a pregnancy have a detailed ocular assessment (if it has not been done in the last 6 months). If retinopathy is documented, the patient should be apprised of the specific risks of worsening of diabetic retinopathy during pregnancy[11]. A baseline detailed eye examination should be done during the first (if not performed in the last 3 months) and in the third trimester for all. Patients with mild retinopathy should

be evaluated every trimester, and those with severe lesions should be evaluated monthly. Finally, strict follow-up should continue for 1 year after delivery[6-8,11,27].

If the degree of retinopathy warrants therapy, conception should be deferred until the retinopathy has been treated and found to have stabilized[11]. Laser photocoagulation for severe non-proliferative or proliferative retinopathy (PDR) prior to pregnancy reduces the risk of visual impairment in pregnancy. If not performed prior to pregnancy, it is still considered safe to receive during pregnancy. Data are lacking to guide treatment recommendations for diabetic macular edema (DME) during pregnancy[8]. It may often regress after pregnancy without specific therapy. However, an expert retina specialist should be involved for taking individualized decisions.

There is also insufficient evidence regarding safety of intravitreal anti-vascular endothelial growth factor injections (anti-VEGF) for DME or PDR during pregnancy. In case these are required, a negative pregnancy test should be ensured, contraception should be provided and conception should be delayed for 3 months after the last intravitreal injection. It should be avoided especially during first trimester due to potential risk of defective embryogenesis, and should be used cautiously if absolutely necessary in second and third trimester after discussion of the potential risks and benefits with the patient.

Diabetic Nephropathy

The risks of adverse pregnancy outcomes are higher for women with chronic kidney disease (CKD), and women should be screened for it prior to conception. In a recent systematic review and meta-analysis, pregnancy with CKD had nine fold greater odds of preeclampsia, four fold greater odds of premature delivery, eight fold greater odds for small for gestational age/low birth weight, two fold greater odds for cesarean section and failure of pregnancy[29]. Urine albumin to creatinine ratio, serum creatinine, and estimated GFR) should be measured prior to conception to assess the renal function[11].In the preconception period, estrogen-containing preparations usually are contraindicated in women with diabetic nephropathy because of an increased risk for thrombosis, cardiovascular disease, and the progression of albuminuria. Progesterone-only preparations, including oral contraceptives and implantable and intrauterine devices are preferred[30]. In general, pregnancy outcome is favorable in women with modest elevations in serum creatinine (below 1.4 mg/dl), proteinuria less than 1 g/24 h, and a normal blood pressure[31,32]. In contrast, serum creatinine above 2 mg/dl, severe hypertension, proteinuria in the nephrotic range ($\geq$ 3 g/24 h), and/or pre-existing cardiovascular disease are associated with a high risk of poor maternal and fetal outcomes[31].

Women who are taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker should discontinue the medication before conception[11]. However, in case of severe renal dysfunction, the patients should be informed about the possible loss of the renal protective properties if the medication is discontinued and the risk of teratogenesis if it is continued. In case ACE inhibitors or angiotensin-receptor blockers have been continued up to the time of conception, the medication should be withdrawn immediately upon confirmation of pregnancy[8,11,30].

Intensive glucose control and blood pressure control should be done. The risk of hypoglycemia is higher, therefore inulin analogues, CGMS and insulin pumps may be considered for such cases. Monitoring needs to be intensive and follow up should be frequent. Serum creatinine and albumin-creatinine ratios should be checked at least every 4 weeks till 32 weeks and

at least 2 weekly starting from 32 weeks gestation[30]. Thromboprophylaxis may have to be considered if there is high risk of thrombosis[30].

Autonomic Neuropathy

The most relevant manifestations of diabetic neuropathy during pregnancy are cardiovascular autonomic neuropathy (CAN), gastroparesis diabeticorum and hypoglycemia unawareness[33]. Airaksinen et al. studied 100 consecutive pregnancies complicated by T1DM and compared pregnancy outcomes between 23 and 77 gestations with and without autonomic neuropathy respectively. Patients with neuropathy had a significantly increased risk of adverse outcomes, from 23 to 52% (p<0.01)[34]. Impaired hypoglycemia awareness is a risk factor for severe hypoglycemia during pregnancy[16]. The Clarke Hypoglycemia Awareness Questionnaire can help in identifying women with hypoglycemia unawareness[18]. These can benefit from advanced technology such as sensor-augmented insulin pump, use of continuous glucose monitoring system, approved insulin analogues and frequent blood glucose monitoring. Pregnancy has not been a risk factor for the progression of diabetic neuropathy. Neuropathic changes of pregnancy when they are found are physiological, transient and resolve in a short time post-partum[35,36].

Cardiovascular disease

The frequency of myocardial infarction is 1 in 350 women with T1DM. Preconception optimization of risk factors such as blood glucose and blood pressure control, weight control for overweight/obese and cessation of smoking are important. Screening studies for CAD should be undertaken, women who are older and have longer duration of disease along with multiple cardiovascular risk factors[11]. Inpatients with CAD, good glycemic control is important. Hypoglycemia should be avoided since tachycardia secondary to catecholamine release increases myocardial demand. There is not enough evidence to make solid recommendations on the mode of delivery. Some suggestions are for instrumental delivery to avoid the Valsalva maneuver, (in case the patient is going for vaginal delivery) do continuous cardiac monitoring, and to treat labor pains aggressively with early epidural analgesia to decrease pain related stress and the subsequent cardiovascular response[33].

Psychological evaluation and social support

Depression, anxiety and stress are as such common in patients with T1DM[36].With the additional pressure of getting pregnant and challenges during pregnancy, these can increase. Health professionals should promote a positive transition to motherhood by proactively supporting women with T1DM in informed decision-making, by facilitating communication within the health care team and coordinating care for women with T1DM transitioning to motherhood[38]. Therefore, psychological assessment and referral to psychiatrist/psychologist if required should also be a part of preconception to postpartum care.

Postpartum care

The insulin requirement declines by 30-40% immediately after delivery, owing to lack of placental hormonal influence. Insulin requirements gradually increase over the next weeks, and usually return to pre-pregnancy levels in 2 to 4 months. The insulin-dose requirement is around 10% lower compared top reconception requirement in those who are breastfeeding[2]. Women should be advised to have a meal or snack before or during breastfeeding to decrease the risk of hypoglycemia[6].

Breastfeeding should be initiated within 30 minutes after birth and should be provided every 2 and 3 hours to avoid neonatal hypoglycemia, chances of which are maximum in the initial 24 hours after birth. Exclusive breastfeeding for 6 months and continuation till 2 years (with addition of complementary feeds after 6 months) should be encouraged. Medicines for the treatment of diabetes related complications and co-morbidities that were discontinued for safety reasons before or during pregnancy should be avoided during breastfeeding period also. The importance of good glycemic control to reduce future diabetes related complications and need for contraception to avoid unplanned pregnancies should be advocated. Lifestyle advice should be given after birth. Women should be monitored for diabetes related complications (especially diabetic retinopathy), thyroid status and mental status (depression) which may worsen in the first year after childbirth.

Summary

T1DM is associated with a higher risk of adverse pregnancy outcomes. In view of the strong link between poor glycemic control and adverse pregnancy outcomes, achieving normal or near normal glucose levels before and during pregnancy is important to optimize pregnancy outcomes. In addition, early recognition and care of associated complications like nephropathy, retinopathy and co-morbidities like hypertension is essential for improving pregnancy outcomes. Psychological assessment and referral to psychiatrist/psychologist if required should also be a part of preconception to postpartum care.

Section B- Travel

Introduction

Traveling either for work, leisure, or family functions/meetings is an essential component of life. Individuals with type 1 diabetes mellitus (T1DM) often face difficulties in multiple aspects while traveling. This document intends to present information, which is vital for a patient with T1DM while traveling.

Pre-travel advice and preparation

1. The patient should inform the physician in advance, preferably 4-6 weeks before the planned travel. Provide education and access patient's understanding regarding insulin storage, dose adjustment, hypoglycemia care, and sick day rules.

2. The physician should provide the patient with a legible prescription containing all details on medicines and blood testing materials like a glucose meter, lancet, and batteries. Some patients may require a specific travel letter.

3. The glycemic control should be adequate and appropriate change in insulin type/dose should be done, keeping in mind the travel schedule.

4. The patient should have medications and blood testing materials for the whole trip and should have reserve supplies for at least 2 to 4 weeks if unforeseen circumstances extend the travel.

5. Advise the patients to carry glucose meters (preferably two, if one malfunctions during travel) and an adequate number of batteries, glucose testing strips, ketone strips, logbooks, glucose tablets, and glucagon injection.

6. The patients on continuous glucose monitoring system (CGMS) and insulin pumps should carry all the supplies required for the devices' proper functioning. They

should also carry an insulin pen/syringes and cartridges/ vials in case the insulin pump malfunctions.

7. The patient should also be aware of the different strengths of insulin and different types of insulin syringes. Teach them regarding the appropriate insulin conversions. For example, if someone takes 20 units of regular insulin from a vial of 40 IU/ml but traveling abroad only can get a syringe with calibrations in terms of 100 IU/ml, they have to take insulin till the 50 units more of the 100 IU/ml syringe.

8. Instruct the patient to keep original labels of medicines and supplies as far as possible

9. A prescription of drugs for some common ailments like fever, emesis, diarrhea, and a first aid kit will help the patient.

10. Depending upon the region of travel, one may require specific vaccines.

11. Advise carrying comfortable shoes and socks to avoid straining the feet while on travel. The patients should avoid walking barefoot. Alternating between two pairs of shoes can decrease the risk of blisters and calluses. New shoes, if purchased, should be used for at least 2 to 3 weeks before travel.

12. Provide patients with a medical identification bracelet with information on the disease, use of insulin, and disclose any allergies.

13. Valid travel insurance should be ensured for international travel.

General information during travel

1. The patients should keep the medications and supplies in hand baggage and should keep this bag in their possession.

2. They should keep some supplies (which are not affected by temperature and pressure changes) in alternative baggage, which will help if the hand baggage is stolen or misplaced.

3. The patients should keep insulin between 4°C–30°C. In case the outside temperature is > 30 degrees Celsius, the insulin vial/cartridge should be kept in a plastic bag and tied from above. Instruct the patient to keep the plastic bag in a wide mouth bottle with ice cubes. The patients should carry their insulin with them at all times and not store it in a car glove compartment or backpack. Excessive sunlight may damage the insulin. The cold pack is a helpful alternative to refrigeration. During the stay at places where the refrigerator is not available, an earthen pitcher filled with water and kept at a cool place can be an alternative.

Specific instructions during air travel

Before boarding

1. The patient can inform the airline beforehand regarding their diabetes status, the medicines, and materials that they will carry with them. They should also be aware of the process of obtaining assistance like facilitated check-in or navigating through security checks and hypoglycemia care if needs arise.

2. Patients should pack their insulin and diabetes-related medications/equipment and the medical prescription in a separate bag, which will help them navigate security checks with ease. They should arrive well in advance, preferably three hours before scheduled departure giving them time to tackle any difficulty arising during check-in.

They should have ready measures to correct hypoglycemia if it happens. The measures to correct hypoglycemia should preferably be in solid form as there are restrictions to carry liquid beyond a specific limit at many airports. They should also be familiar with the regulations on check-in, including security checks (airport website or other means).

3. The insulin should be kept in hand baggage as it can get damaged due to extreme temperature and air pressure (during air travel) if kept in check-in baggage, though the ice packs can be kept in check-in baggage for later use after air travel.

4. In case the patient is using an insulin pump or CGMS, one should check with the manufacturer regarding their compatibility with traditional metal detectors and Advanced Imaging Technology (AIT) scanners. In case the devices are not compatible, one should inform regarding the problem and request the security officer alternative means of checking like a manual check-up.

5. The patients who have language problems should have cards or other means to communicate that they have diabetes, these are their medications, what to do if they have hypoglycemia. It will be helpful to teach simple phrases like "I have diabetes," "my sugar in the local language is going down," "and these are my medications," and "please give me some juice."

4. Patients with diabetes need to be aware of how different foods can affect their diabetes control. One should find out about the foods common to the local cuisine. Advise patients to actively monitor how their blood glucose is affected by new foods by checking blood glucose levels before and after each meal. Opting for vegetables and protein sources minimizes glucose fluctuations. Patients with celiac disease should specifically mention gluten-free diets while on air travel or should carry the appropriate food. Similarly, they should be vigilant regarding gluten-free food in situations other than air travel.

In-flight

5. During travel, it will be helpful to check blood glucose every 4 hours.

6. If patients inject insulin while in flight, one must be careful not to inject air into the insulin bottle. In the pressurized cabin, pressure differences can cause the plunger to "fight you," making it hard to measure insulin accurately.

7. Patients should always carry snacks and supplies to treat hypoglycemia. It is also safe to carry some food along even if traveling by air. It will also be helpful to make fellow passengers or crew members aware of their diabetes status so that they can help in the correction of hypoglycemia in case the need arises.

8. Also, be aware of the serving time of meals and snacks and put a request to serve as per personal schedule to avoid fluctuations in glucose due to perturbed schedule.

9. Do not keep sitting in one place, especially on long flights, and should keep exercising the feet and stand/walk intermittently.

10. Do not indulge in alcohol or caffeine-rich beverages.

After landing

11. The patient should check their blood glucose level as soon as possible after landing. Jet lag can make it hard to tell if one has very low or very high blood glucose.

Insulin adjustments during air travel

1. Diabetes management depends on a 24-hour medication schedule, and medication adjustments are needed only when the patient is traveling east or west, not north or south. Traveling east results in a short day, and requires a potential reduction in insulin. Traveling west increases the day length, possibly requiring an increase in insulin dose. The insulin adjustments are usually required if crossing more than five time zones and staying for more than three days abroad.

2. In general, the dose is reduced by 10% to reduce the risk of hypoglycemia during travel, especially if the glucose values are within the target range.

3. Dose adjustment while traveling east: Adjust the basal dose using the formula. Travel Dose = Normal Dose X [0.9- (Difference in time zones/Hours between basal doses)]

For example, a patient is on 30 units Glargine, which he takes at 8 pm. He is traveling from Dubai to Sydney. The flight is at 11 pm (Dubai time), and the flight distance is 13 hours. The arrival time will be noon Dubai and 6 pm Sydney time. Therefore calculate the travel dose as 30 X [0.9-(6/24)], which will be 19.5 units. He will inject 19 units at 8 pm, before flying and will resume his regular dose of 30 units at 8 pm Sydney time. If the patient is taking 18 units, Detemir at 8 am and 12 units at 8 pm. Then he will take both his scheduled doses before travel. He should keep Dubai time on the watch, and in-flight morning dose will get modified as 18 X (0.9-6/12), which will be 7.2 units. He will take seven units at 8 am as per Dubai time and will take a scheduled dose of 12 units at 8 pm Sydney time.

Example of dose adjustment while traveling west: a patient is on 30 units Glargine, which he takes at 8 pm. He is traveling from Sydney to Dubai. The flight is at 11 pm (Sydney time), and the flight distance is 13 hours. The arrival time will be 6 am in Dubai and noon Sydney time. Therefore, calculate the travel dose as 30 X [0.9- (-6/24)] = 34.5 units. So he can split his dose and take 50% of the dose at 8 pm before flying and can take 50% of the dose at 8 am as per Sydney time. This will provide coverage for over 12 hours. He can resume his normal dose of 30 units at 8 pm Dubai time. If the patient is taking 18 units, Detemir at 8 am and 12 units at 8 pm, he will take his scheduled dose of 8 pm before travel. He should keep departure time on the watch, and in-flight morning dose will get modified as 18 X [0.9- (6/12)], which will be 7.2 units. He will take seven units at 8 am as per Sydney time and will take a scheduled dose of 18 units at 8 am in Dubai.

The pump users need to change the time of the pump to match the arrival destination.

4. To avoid confusion, one should keep the same time during the flight and be aware of both zones' timings.

5. The meal and snack related doses should be adjusted based on carbohydrate or calorie content of the meal.

6. Insulin analogs offer more flexibility and lesser hypoglycemia: the person who travels frequnetly should prefer them.

7. Prefer basal-bolus regimen to premix insulin during travel and for the next 12 to 24 hours, giving more flexibility in insulin adjustments.

Section C- Surgery

Introduction

India has nearly 95,600 cases of T1DM below 14 years of age, and 15,900 cases

are diagnosed each year in this age group[39]. A recent study found an incidence of 4.9 cases/100,000/year in India, which is much lower than the incidence of 21.2 cases/100,000/year observed in the SEARCH registry of USA[40]. Management of these individuals often differs from those with type 2 diabetes mellitus [T2DM] due to increased hypoglycemia risk during fasting. They are at risk for ketosis on withholding insulin inappropriately. Due to increased life expectancy and the prevalence of T1DM, a number of these patients may require some surgical procedures in their lifetime.

The data suggest that patients with T1DM are at increased risk of complications (infections, poor wound healing, and prolonged hospital stay) after surgery[41,42]. Hyperglycemia results in impaired leukocyte function, increased inflammatory markers and reactive oxygen molecules, promotes platelet aggregation, and limits neovascularization and collagen synthesis, resulting in poor outcomes seen in T1DM[4]. There is further evidence that suggests that good glycemic control in surgical patients is associated with improved complications[43,44]. This chapter aims to review the perioperative management of T1DM patients planned for surgery, provide practical recommendations on glycemic targets, and therapeutic strategies for achieving it.

Definitions of different periods from admission to discharge for elective surgery under general anesthesia

The peri-operative period is the period from the time of admission to the pre-operative area until discharge from the post-anesthesia care unit (PACU). This period includes pre-operative, intra-operative, and post-operative segments. The pre-operative segment includes the time since admission to the pre-operative area until the patient's transfer to the operating suite. The intra-operative segment ends with the patient transfer to PACU and the post-operative segment with discharge from the PACU. The period before and after the peri-operative period is known as the pre-perioperative and post-perioperative phase, respectively. These definitions permit developing a systematic approach to assessing the quality of care throughout the spectrum of elective surgical procedures[45].

Glycemic targets

Optimization of glycemic control before surgery helps reduce both morbidity and mortality associated with surgical procedures in patients with diabetes. HbA1c should preferably be < 8-8.5% before elective surgery[45,46]. The Joint British Diabetes Society guidelines for adult patients' peri-operative management target a glucose range between 108–180 mg/dl but with acceptable values of 72–216 mg/dl[46]. As per the American Diabetes Association (ADA), the target glucose range for the peri-operative period should be 80–180 mg/dl[47]. It is safe to keep blood glucose between 140-180 mg/dl when the patient is under sedation[46-48]. The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines suggest a target of 90-180 mg/dl for children undergoing surgical procedures and 140-180 mg/dl in post-surgical ICU care[49].

Organization and planning of care

Pre-anesthetic assessment

Comprehensively assess the patients with diabetes well in advance, for associated co-morbidities and complications, and glycemic status. Assess the patient for ketones, electrolytes, and hydration status also. Urine ketones should be absent, and electrolytes should be normal before surgery. The ketone status should be checked whenever blood

glucose is > 250 mg/dl. Patients with autonomic neuropathy can have hypoglycemia unawareness, which can be another challenging problem in tight control. Prioritize the patients with diabetes for the operating list to avoid prolonged starvation time. Preferably, schedule patients with diabetes as the first case of the day[49] (Table VI).

Table VI: Points worth remembering in patients with Type 1 Diabetes Mellitus undergoing surgery

Parameter	Important message
Glycemic Targets	Aim for a glycemic target of 108–180 mg/dl in the perioperative period. It is safe to keep blood glucose between 140-180 mg/dl when the patient is under sedation.
Pre-anesthetic assessment and optimization	Comprehensively assess the patients with diabetes well in advance, for associated comorbidities and complications in addition to glycemic status.
Prioritization	Prioritize patients with diabetes for the operating list to avoid prolonged starvation time. Preferably, schedule the patient as the first case of the day.
Adjustment to insulin therapy during hospitalization	These patients can receive the usual insulin dose, the evening before surgery. If any, the morning dose of basal insulin analog can be reduced by 20% if the glucose readings are on the lower side on the morning of surgery. The dose of NPH should be reduced by 30-50% to prevent hypoglycemia. Stop the prandial insulin when the fasting state begins
When should an insulin infusion be started?	Start insulin infusion at least two hours before surgery. Prefer intravenous insulin for surgeries lasting more than two hours. The patients should be initiated on IV 5% dextrose/0.9% sodium chloride to reduce hypoglycemia. Use normal saline alone if blood glucose is >250 mg/dl.
The transition from intravenous insulin Infusion to subcutaneous insulin	The switch to subcutaneous insulin can be done in patients with stable infusion rate and blood glucose levels in the target range for at least 4 to 6 hours before the transition, oral intake has improved, and the patients are eating scheduled meals or are receiving stable enteral/ parenteral feeds.
Planning for Hospital Discharge	Educate the patient on self-monitoring, diet therapy, sick day guidelines, insulin injection technique, self-adjustment in insulin doses, medication instructions, and hypoglycemia management before discharge. Arrange for a follow-up visit to review glycemic control within a month, depending upon the glucose control.

Abbreviation: NPH-Neutral Protamine Hagedorn, IV-intravenous

Adjustment of insulin therapy during hospitalization, and a day before surgery

The insulin regimen and dosing in hospitalized patients with T1DM for surgery depend on several factors. This includes the type of outpatient insulin therapy, adherence to the prescribed regimen, glycemic control before admission, and nutritional status. In general, shift these patients to a basal-bolus regimen if they are on some other regimen, especially if they are not well-controlled. One should be vigilant, as the stress of surgery may result in severe hyperglycemia or ketoacidosis in patients with T1DM[50]. Frequent

blood glucose monitoring and appropriate escalation in insulin doses can help in avoiding these complications. These patients can receive the usual insulin dose, the evening before surgery.

Adjustment of insulin therapy during the day of surgery

If any, the morning dose of a basal insulin analog can be reduced by 20% if the glucose readings are on the lower side on the morning of surgery. The dose of NPH insulin should be reducedby 30-50% to prevent hypoglycemia. Stop prandial insulin when the fasting state begins[42,51]. Start insulin infusion at least two hours before surgery (Table VI). Prefer intravenous insulin infusion for surgeries lasting more than two hours[49]. The half-life of intravenous insulin is 4-6 minutes, which allows easy titration. The patients should be initiated on IV 5% dextrose/0.9% sodium chloride to reduce hypoglycemia. Use normal saline alone if blood glucose is > 250 mg/dl[46,49]. The aim for capillary blood glucose is between 108-180 mg/dl (acceptable range 72-216 mg/dl). Monitor the patient's blood glucose every 30- 60 minutes during the perioperative period, especially when the glucose levels are not in target or the patient is under sedation[46,49]. For afternoon surgeries, if breakfast is allowed, the usual dose of rapid-acting analog insulin or half the dose of short-acting regular insulin dose can be given. Give the usual patient dose of long-acting basal insulin, but if on NPH, reduce dose by 30%[49].

Transition from intravenous insulin infusion to subcutaneous insulin

The switch to subcutaneous insulin can be done in patients with a stable infusion rate and blood glucose (BG) levels in the target range for atleast 4 to 6 hours before the transition. Additional requirements for this transition include, improvement in oral intake, and the patients are eating scheduled meals or are receiving stable enteral/parenteral feeds[47].

When the regular insulin provides prandial coverage, total daily dosage (TDD) is divided equally into four portions, one for basal insulin injection and three prandial insulin injections. The TDD is 60-80% of the total dose requirement while on insulin infusion. On the other hand, while using insulin analog for prandial coverage, use 50% of TDD as basal insulin, and divide the rest 50% into three equal portions for each prandial injection. The intravenous infusion should never be discontinued abruptly because of the short half-life of intravenous insulin and a delay associated with subcutaneous insulin onset. The first dose of subcutaneous short or rapid-acting insulin should be administered 1-2 hours before the eventual discontinuation of intravenous infusion[52]. The insulin dose may be higher in the initial 24-48 hours due to surgical stress. The dose may also vary due to changing nutritional status and concomitant medications.

Planning for Hospital Discharge

Tailor the discharge plan as per the patient's recovery status, glycemic status at discharge time, and arrange follow-up visits with the diabetologist /endocrinologist within 1-4 weeks. The visit can be earlier if the glucose control is not good, else it can be at the end of one month[47]. The patient should also be educated on self-monitoring, diet therapy, sick day guidelines, insulin injection technique, self-adjustment in insulin doses, medication instructions, and hypoglycemia management. Try to ensure an adequate medical supply with the social workers' help for patients with financial constraints[51].

Organization and planning of care for surgeries on a daycare basis (Minor surgeries)

In general, minor surgery is a procedure that lasts less than 2 hours, and the patient will be able to eat within 2-4 hours[49]. Give basal insulin as usual. Give a subcutaneous rapid-acting analog for BG ≥ 180 mg/dl. Give a usual prandial dose of rapid-acting insulin, or 50% of regular insulin before surgery in those allowed to take a usual meal. After surgery, if the patient has resumed a regular diet, the patient's home schedule of insulin is initiated[51]. Due to the faster onset of action (between 5–15 min) and a rapid peak in 1–1.5 hours, prefer rapid-acting insulin analogs in daycare surgeries.

Organization and planning of care for emergency surgeries

Check the blood glucose (BG), blood beta-hydroxybutyrate (if available) or urinary ketone concentration, and serum electrolytes before surgery. Check the blood gases if ketone or BG levels are high. Delay the surgery till correction is done for diabetic ketoacidosis, circulating volume, and electrolyte deficits[49,53].

Insulin management during Enteral/Parenteral Feedings in T1DM

Intravenous insulin is the preferred approach for patients with T1DM receiving enteral or parenteral feedings[50]. The alternative approach uses a subcutaneous basal-bolus insulin regimen for those receiving intermittent feeds similar to major meals and minor snacks. Calculate the initial doses on the concepts mentioned previously for a transition from intravenous insulin to subcutaneous insulin, with long/intermediate-acting insulin comprising 50% of total daily dose (TDD) if given with rapid-acting analogs and 25% of the TDD if given along regular insulin. Give correctional doses as per the level of glucose and the urgency of correction[47,52,54]. Do the preliminary dose escalation using the assumption that 1 unit of regular human insulin or rapid-acting insulin given subcutaneously before each meal will be required per 10–15 g carbohydrate[47].

Hypoglycemia

Avoid hypoglycemia (defined BG ≤ 70 mg/dl) in the hospital setting. However, when hypoglycemia occurs, review the patient's overall treatment regimen to avoid future hypoglycemic episodes. Hypoglycemia triggers may include reduced dietary intake or unexpected interruption of oral or other nutrition modes, inappropriate timing/dose of insulin with meals[47].

In the perioperative period, if patient's BG is < 80 mg/dl, start a dextrose-containing intravenous solution (dextrose 5% or 10%) at 100–150 ml/h or 50–75 ml/h, respectively. If patient BG is < 70 mg/dl, administer 25 ml dextrose 50% solution IV and start IV dextrose 5% in water[48,49]. Increase BG monitoring to every 15 min until BG levels are above 100 mg/dl on two consecutive measurements. In patients who are alert and can eat/drink, treat hypoglycemia with 15–30 g carbohydrate administration (glucose)[47-50].

Summary

Prefer surgery in T1DM at centers with appropriate expertise and facilities to care for these individuals. Management of these individuals often differs from those with T2DM, due to increased risk of hypoglycemia during fasting and high risk for ketosis due to

withholding insulin inappropriately. The patients planned for elective surgery should be evaluated well in advance. Aim for the capillary BG between 108-180 mg/dl (acceptable range 72-216 mg/dl). Prefer intravenous insulin for surgeries lasting more than two hours. The switch to subcutaneous insulin can be done in patients with stable infusion rate and BG levels in the target range for at least 4 to 6 hours before the transition. Additionally, before making this switch ensure that oral intake has improved, and the patients are eating scheduled meals or are receiving stable enteral/parenteral feeds. Check the BG, blood beta-hydroxybutyrate (if available) or urinary ketone concentration, and serum electrolytes before emergency surgery. Delay the surgery till the correction of diabetic ketoacidosis, circulating volume, and electrolyte deficits. Avoid hypoglycemia (defined as BG < 70 mg/dl) in the hospital setting. However, when hypoglycemia occurs, review the patient's overall treatment regimen to avoid future hypoglycemic episodes. Educate the patient on self-monitoring, diet therapy, sick day guidelines, insulin injection technique, self-adjustment in insulin doses, medication instructions, and hypoglycemia management before discharge. Arrange for a follow-up visit within a month to review glycemic control within a month.

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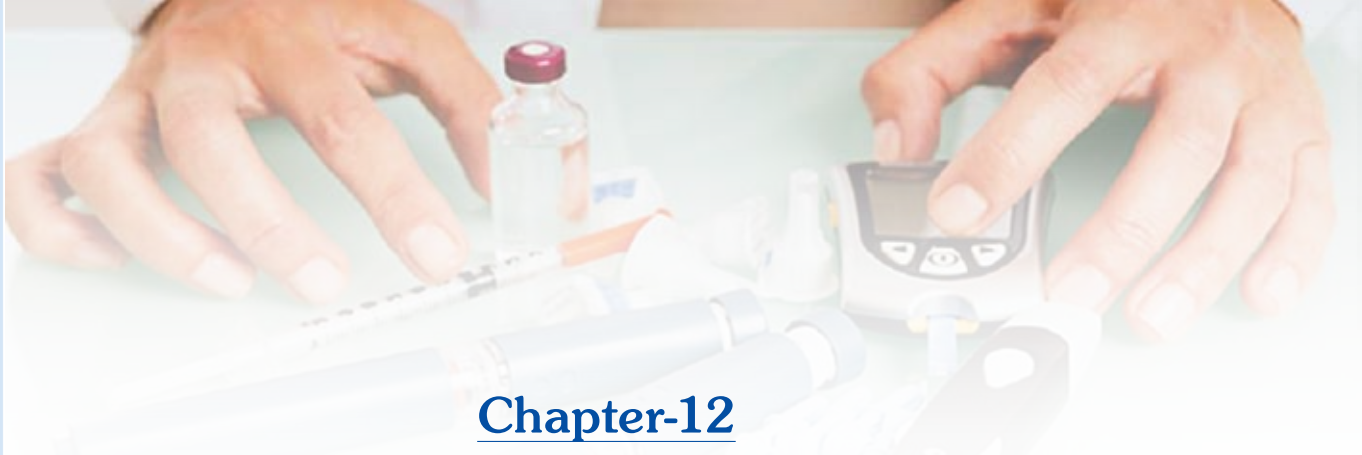
Chapter-12

Summary and Conclusions

Dr. V. Mohan and Dr Nikhil Tandon

The burden due to diabetes in the young is increasing rapidly. In India, diabetes in the young presents a fascinating array of different types of diabetes of which type 1 diabetes would be the commonest in children and adolescents. One should, however, also keep in mind that type 2 diabetes is also now becoming more common in children. Moreover, type 1 diabetes can occasionally be wrongly diagnosed in a patient with Maturity Onset Diabetes of the Young (MODY) or Fibro Calculous Pancreatic Diabetes (FCPD) or other forms of diabetes which present at a younger age.

Today, more and more children are being diagnosed with type 1 diabetes in our country. This may be because the actual prevalence of the disorder is going up in India. It may also reflect better awareness and therefore, improved diagnosis of type 1 diabetes. Finally, it could be that children are surviving more due to early diagnosis and better treatment.

Management options for children with type 1 diabetes have greatly improved in the last 3 – 4 decades. In the 1960s and 70s, urine glucose monitoring was the norm and glucometers had not arrived. Even when they did, they were expensive, painful, extremely cumbersome and mostly inaccurate. Today, we have blood glucose monitors which are extremely precise, and are less painful. Cost of strips however, still remains a challenge.

With the arrival of Continuous Glucose Monitoring (CGM), a paradigm shift in the monitoring and control of type 1 diabetes has occurred all over the world although again, cost considerations remain an issue in India. Thanks to better management, diabetic ketoacidosis is becoming less common, although in rural areas, and in peripheral centres, it still remains a big problem. Going forward, all efforts must be made to prevent or further reduce the incidence of diabetic ketoacidosis.

This document is a compilation of different chapters on type 1 diabetes dealing right from the epidemiology and diagnosis and differential diagnosis of type 1 diabetes to lifestyle, diet and exercise, insulin, monitoring, acute complications, microvascular complications including retinopathy, diabetic kidney disease and nerve diseases, macro vascular complications, education, problem of T1D in special groups like pregnancy, travel and driving. Thus, it covers practically the whole gamut of type 1 diabetes. It also incorporates most of the published Indian references on the subject.

A galaxy of authors and expert reviewers have contributed to make these guidelines a valuable addition to any library. Moreover, it will be useful for students, physicians, diabetologists and endocrinologists and practically to anyone else who would be interested in learning more about type 1 diabetes. It is hoped that these guidelines would ultimately translate into improved care of the child, adolescent or young adult with type 1 diabetes, thereby helping them to live a long and healthy life despite their disorder.

There are still formidable challenges in providing equitable treatment to everyone with type 1 diabetes in the world and India is no exception to this. It is hoped that with improved diabetes control, the dreaded complications of diabetes like blindness, kidney failure, amputations, heart attacks and stroke, not to mention diabetic ketoacidosis, impotence and painful neuropathy can all be reduced, if not totally eliminated.

Appendix

Table I: 15 g carbohydrate exchanges for the common Indian foods

Breads and cereals	Starchy vegetables	Snack foods	Fruits and juices	Biscuits and Sweets
Bread (white, wheat): 1 slice	Aloo Gobi: 1 cup	Papad: 2	Apple/Banana/ Orange/pear/ pomegranate: 1 small	Parle G/Good day / nutrichoice/ oreo/ cream crackers/oat meal cookies/digestive high fiber: 3
Roti (Bajra, Makai, Jowar, Multi-grain), paratha plain/ thepla/aloo paratha: ¾ (6")	Mashed potato/sweet potatoes/ yams: ½ cup	6 Panipuri/4 Dahipuri Sevpuri: 2 ½	Black-blueberries/ pineapple: ¾ cup	
	Baked Beans/Cassava: ⅓ cup	Bhelpuri: ½ cup		Good day (butter)/Dark fantasy/Bourbon: 2
Chapati: 1 (6")	Potato, Boiled or Baked: 1 small	Vegetable Cutlet: 1 medium	Cherries: 12	
Kulcha/Tandoori roti/ Paneer Paratha: ½	Green peas: ½ cup	Handavo/ Kachori: 1 (3/4" square)	Melon: 1 slice (300g)	Marie gold/Hide and seek: 4 Monaco biscuits/ vanilla wafers: 5
			Plums: 2 small	
Naan: ¼ (8" * 2")	Plantain: 1/3 cup	Veg Samosa: ¾ (1 samosa= 2 ½ carbohydrates)	Watermelon: 1¼ cup	50-50 Maska Chaska: 7
Puris: 2 (5" d)	Corn on the Cob: 1 (6")	Bread pakora: 2/3	Papaya: 1 cup	Britannia 5 grain: 1
Cornbread: 1 (3" * 4")	Sweet corn: ½ cup	Pakoda, Spinach: 3 pcs.	Apricots: 4 medium (fresh)	Animal Crackers: 8
Croissant/pav: 1 small	Pumpkin: 1 cup	Potato chips: 9-13 (¾ oz)	Fresh Figs: 2 medium	Rusk: 2
1 Dosa of approx. 10" diameter uttapam: ½ small vegetable or 1 smalluttapam, 4"	Vegetable Korma: ½ cup	Banana chips: 20	Grapefruit: ½	Gulab Jamun/besanladdoo/rasmalai/pudding: 1 small
Rice/ravaidli: 1 small rice idli or 2 smallravaidli		French Fries: 12	Seetaphal/ Chikoo/peach: 1 medium	
Vada: 1 ½	Pulses/Dals/ Beans	Namkeen: ½ cup		Honey/Jam/sugar/ jaggery: 1tbsp

Breads and cereals	Starchy vegetables	Snack foods	Fruits and juices	Biscuits and Sweets
Pancake: 1 (4" * ¼")	Cooked Bengal gram/ Black eyed peas/Black gram/Green gram/ horse gram/red gram/Rajma/ peas/ split peas/ moth beans: ½ cup	Dhokla: 2	Grapes: 17 small	Kulfi/Ice cream/seviyan kheer: ½ cup
Chocos/corn-flakes: ½ cup		Khandvi:12 medium	Guava: 1 large	
Cooked noodles: ½ cup		Momos: 2	Jackfruit/mango pieces: ½ cup	Puranpoli: 1/2
English Muffin/ Hot Dog bun: ½		Granola or Snack Bar: 1	Jambu/Jamun: 6	Rasgulla: 1 medium
Muffin: 1 small	Cooked lentils, Brown/ Green/Yellow: ½ cup	Dates (fresh): 6, Dry dates: 3	Kiwi: 1 small	Sooji Halwa: ¼ cup
Muesli/oats: 1/3 cup		Raisins: 35	Papaya cubes/ Raspberries: 1 cup	Cupcake edge shaved off: 1
Cooked White rice/Brown rice/Quinoa/ Bajra/Barley/ Bisibele bath/ / upma: ⅓ cup	Lima Beans: ⅔ cup	Groundnuts: 30	Passion Fruit: ½ medium	Cake: 1 (2" square)
	Rasam/thin mixed dal: 1 cup	Cashewnuts: 45	Pineapple: 3 slices (1/2 cup)	Cookie: 2 small
	Sambar: ½ cup	Walnuts: 65	Strawberries: 7 medium	Carrot Halwa: 1/3 cup
Cooked Poha/ Pasta/Ragi/ jowar/ dalia/ sprouted wheat/ oat meal/ sabudanakichdi/ kichdi/ Matkiusal: ½ cup	Roasted chana: ½ cup	Pistachios: 88	Cubed watermelon: 1¼ cup	Donut: 1 medium
	Sprouted moong:1cup	Almonds: 110	Apple/orange/ pineapple/guava / grape fruit Juice: ½ cup	Brownie/Rasmalai: 1 small
	Khadi: 2/3 cup			
		Nonvegetarian foods	Grape/ mango/ prune juice: ⅓ cup	Milk and Milk products
Pizza: 1 slice (6")	Nonstarchy vegetables	Chicken wrap: ½	Soft Drink/ Soda: ¾ cup	Low-fat or fat-free milk/plain yogurt/ Masala chai with 1% milk: 1 cup
Veg wrap: 1/2	Cooked Vegetables: 1½ cup	Dhansak/Haleem: ½ up	Energy Drink/fruit drink/lemonade: ½ cup	
25 g/3 tbsp atta (whole wheat)	Raw Vegetables: 3 cups	Mutton biryani/chicken biryani/egg biryani: ½ cup		
25 g/ 3 tbsp maida	Vegetable Juice: 1½ cup			

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