

DIABETES TYPE 1

BY

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DEFINITION

- ❑ Metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both.

OLD CLASSIFICATION (1985)

- Type 1, Insulin-dependent (IDDM)
- Type 2, Non Insulin-dependent (NIDDM)
 - obese
 - non-obese
 - MODY (between 18 to 25 years)
- IGT
- Gestational Diabetes Mellitus

New Classification (WHO)

- Is based on etiology not on type of treatment or age of the patient.
- Type I (Beta cell destruction-absolute insulin deficiency)
 - Immune mediated
 - Idiopathic
- Type II
 - predominant insulin resistant with relative insulin deficiency
 - predominant secretory defect with insulin resistance

Other specific Types

- Genetic defect of beta cell function
 - MODY (maturity onset diabetes of the young) syndromes
 - mitochondrial mutations
- Infections
 - Congenital rubella
 - CMV
- Disease of pancreas
 - Pancreatitis
 - Trauma/pancreatectomy
 - Neoplasia
 - Cystic fibrosis

Other specific Types

- Endocrinopathies
 - Acromegaly
 - Cushing's Syndrome
 - Pheochromocytoma
- Drug or chemical induced
 - Nicotinic acid
 - Glucocorticoids
 - Thiazides
- Genetic disorder with diabetes
 - Down syndrome
 - Turner syndrome
 - Klinefelter syndrome
 - Prader willi syndrome
- Gestational Diabetes Mellitus
- Neonatal Diabetes Mellitus

Type 1 Diabetes Mellitus

Formerly called insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes

T1DM is characterized by low or absent levels of endogenously produced insulin

EPIDEMIOLOGY

- Most common endocrine disorder of childhood and adolescence.
- The onset occurs predominantly in childhood, with 2 peak one 5-7 yr, and another at puberty but it may present at any age.
- In india an average prevalence of Type I diabetes is 10 per 100000 population.

Risk of development of Type 1 DM

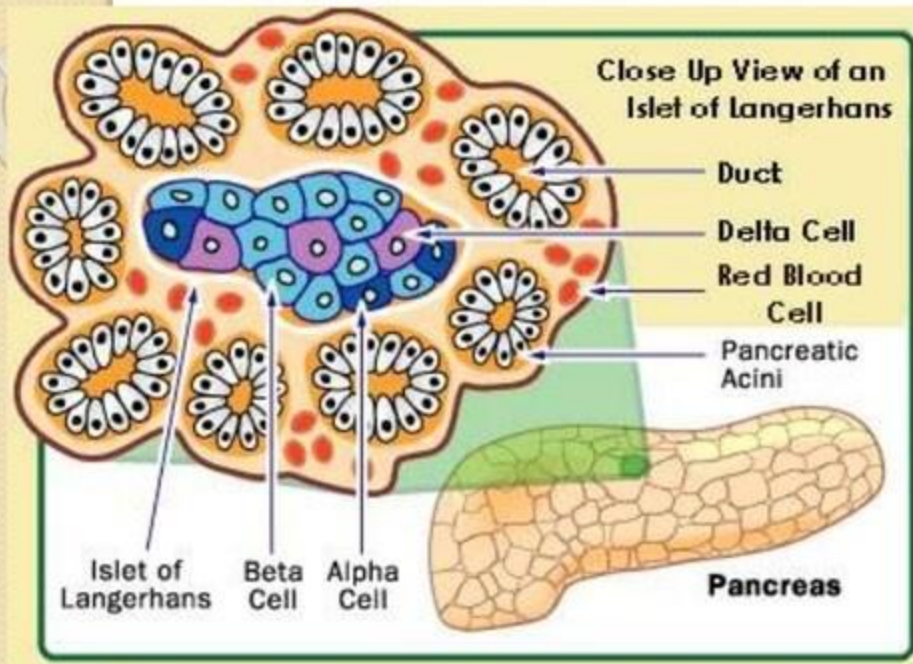
- If mother has Type 1 DM risk in child is 2%.
- If father is affected risk is 7%.
- In a sibling of the index case is estimated as 6%.
- Risk is 6-10% in dizygotic twins & 30-65% in monozygotic twins

Pathogenesis & Natural history

The natural history includes distinct stages

- 1) Initiation of autoimmunity
- 2) Preclinical autoimmunity with progressive loss of β -cell function
- 3) Onset of clinical disease
- 4) Transient remission("Honeymoon period")
- 5) Established disease
- 6) Development of complications

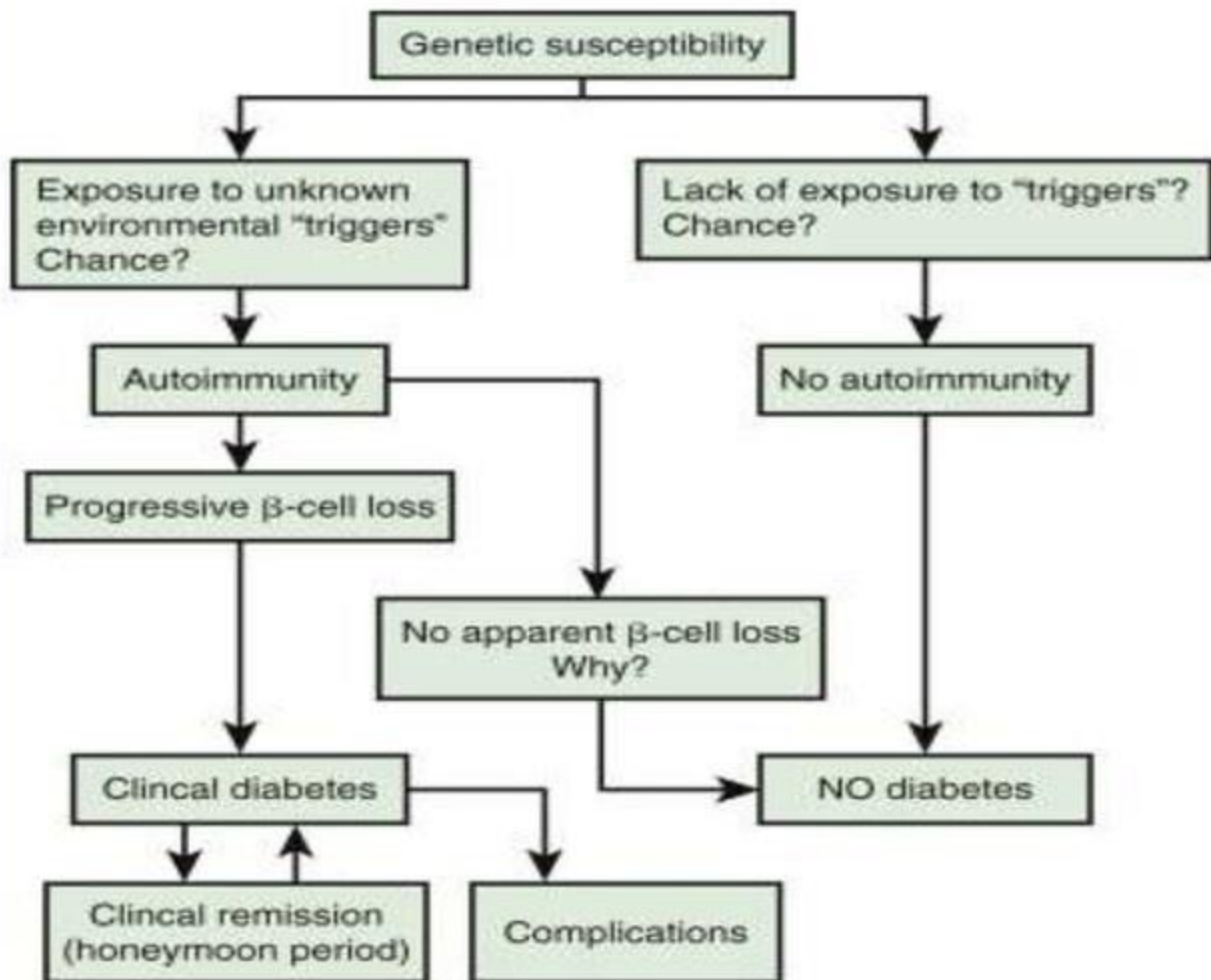
The Pancreas



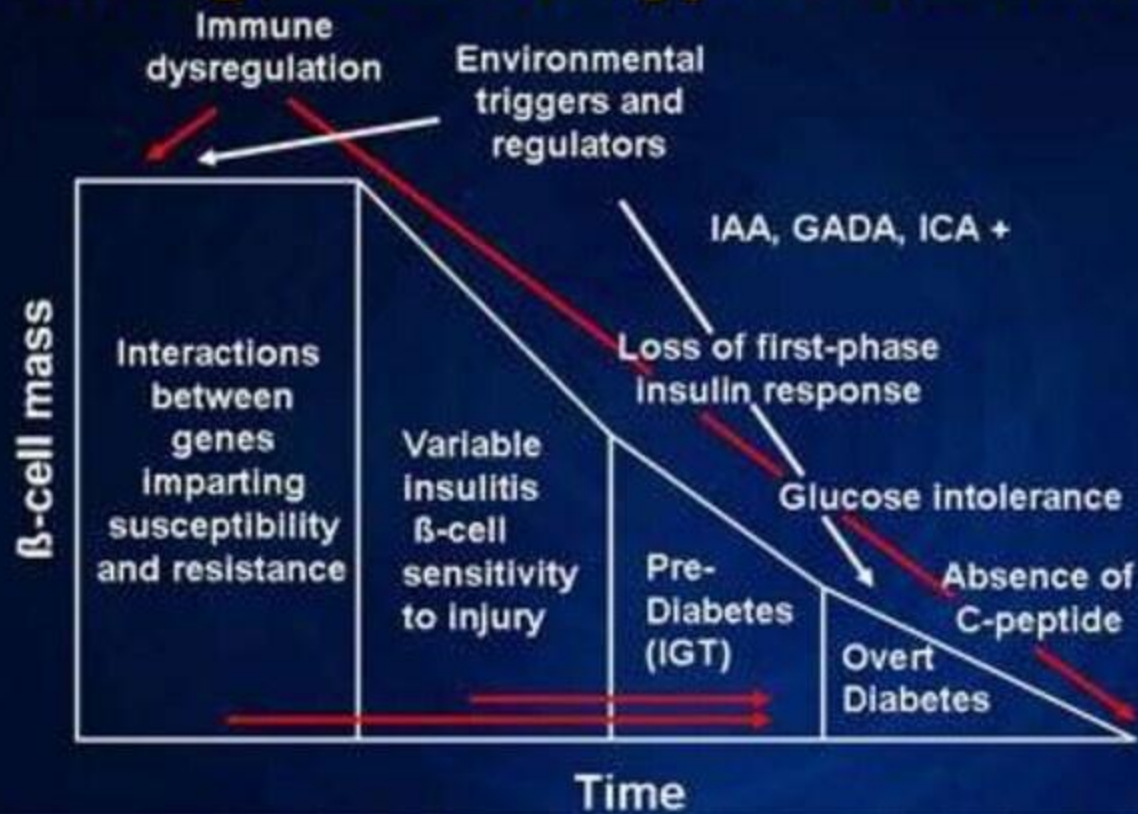
Beta Cells: secrete insulin.

Alpha Cells: secrete glucagon

Autoimmunity occurs in islet of Langerhans against the beta cells...



Pathogenesis of Type 1 Diabetes



CLINICAL PRESENTATIONS

- DKA (most common presentation in pediatrics)
- Classical symptom triad:
 - ✓ polyuria, polydipsia and weight loss
- Accidental diagnosis

DIAGNOSTIC CRITERIA

- In symptomatic (polydipsia , polyurea, weight loss) children a random plasma glucose >11.1 mmol (200 mg) is diagnostic.
- Hemoglobin A_{1c} ≥ 6.5 %

Remember: acute infections in young non-diabetic children can cause hyperglycemia without ketoacidosis.

DIAGNOSTIC CRITERIA

modified OGTT (oral glucose 1.75gm/kg max 75 gm) may be needed in

- Asymptomatic children with hyperglycemia (RBS >140)
- Symptomatic with hyperglycemia (RBS between 140 to 200)

- Fasting blood glucose level

IGT (Impaired glucose tolerance)

6.0-6.9 mmol (100-126 mg/dl)

Diabetic

≥ 7.0 mmol (126mg/dl)

- 2 hours after oral glucose

IGT (Impaired glucose tolerance)

7.8-11.0 mmol (140-200 mg/dl)

Diabetic

≥ 11.1 mmol (200 mg/dl)

TREATMENT ELEMENTS

- Education
- Insulin therapy
- Glycemic control Monitoring
- Diet and meal planning
- Prevention and early detection of complication

EDUCATION

- **Educate child & care givers about:**
 - Diabetes type 1
 - life long Insulin therapy
 - self monitoring and maintaining records
 - Recognition of Hypoglycemia & DKA
 - Meal plan
 - Sick-day management
 - Possible long term complication

INSULIN Therapy

Insulin

- A polypeptide made of 2 β -chains.
- Discovered by Bants & Best in 1921.
- Animal types (porcine & bovine) were used before the introduction of human-like insulin (DNA-recombinant types).
- Recently more potent insulin analogs are produced by changing aminoacid sequence.

Rapid-acting Insulin

Examples: insulin lispro or insulin aspart

Onset: Begins to work at about 5 minutes

Peaktime: Peak is about 1 hour

Duration: Continues to work for about 2-4 hours

Regular or Short-acting Insulin

Examples: insulin regular

Onset: Reaches the bloodstream within 30 minutes after injection.

Peaktime: Peaks anywhere from 2-3 hours after injection.

Duration: Effective for approximately 3-6 hours.

Intermediate-acting Insulin

Examples: NPH, Lente

Onset: Reaches the blood stream about 2 to 4 hours after injection.

Peaktime: Peaks 4-12 hours later.

Duration: Effective for about 12 to 18 hours

Long-acting Insulin

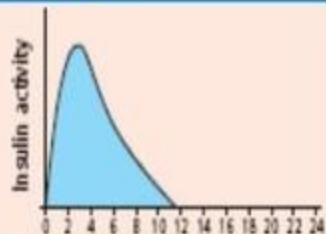
Examples: insulin glargine

Onset: Reaches the bloodstream 6-10 hours after injection

Duration: Usually effective for 20-24 hours

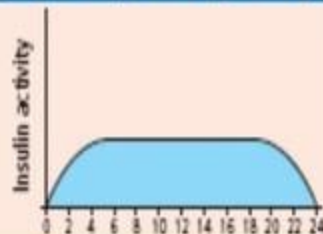
Soluble Human Insulin: Actrapid, Humulin S

Onset: 30 mins
Peak: 2-4 hours
Duration: 6-8 hours



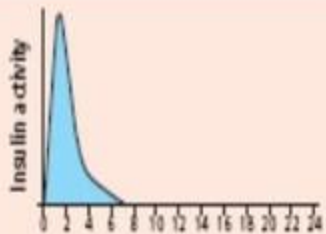
Long Acting Basal Analogues: Glargine (Lantus), Detemir (Levemir)

Onset: ~ 2 hours
Peak: None
Duration: 18-24 hours



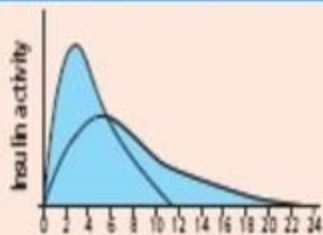
Rapid Acting Insulin Analogue: Novorapid Aspart, Humalog Lispro, Apidra

Onset: 0-15 mins
Peak: 1-2 hours
Duration: 3-5 hours



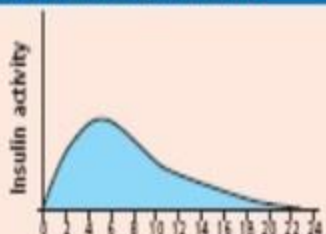
Pre-mixed Human Soluble/Isophane: Mixtard 30, Humulin M3 etc

Onset: See above
Peak: See above
Duration: See above
Mixtard 30, M3 refers to % of soluble insulin ie. 30% Soluble 70% Isophane



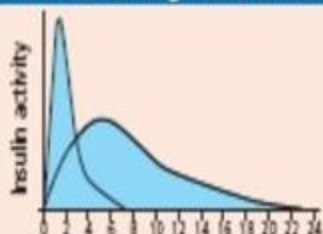
Intermediate Human Isophane Insulin's: Insulatard, Humulin I

Onset: -
Peak: 4-8 hours
Duration: 14-16 hours



Pre-mixed Analogues/Isophane: Novo Mix 30, Humalog Mix50, Mix25

Onset: See above
Peak: See above
Duration: See above
Novo Mix 30, Humalog Mix50/ Mix25 refers to % of rapid acting analogue insulin



INSULIN CONCENTRATIONS

- Insulin is available in different concentrations 40, 80 & 100 Unit/ml.
- WHO now recommends U 100/ml to be the only used insulin to prevent confusion.
- Special preparation for infusion pumps is soluble insulin 500 U/ml.

Suggested target blood glucose range

	Time of checking	Target plasma glucose(mg/ dl)
1	Fasting or preprandial	90-145
2	Postprandial	90-180
3	Bedtime	120-180
4	Nocturnal	80-162

For children < 5 yrs of age 90-200mg/dl during the day time and between 150-200mg/dl at bed time and during the night are optimal

Key aspect of Insulin Therapy

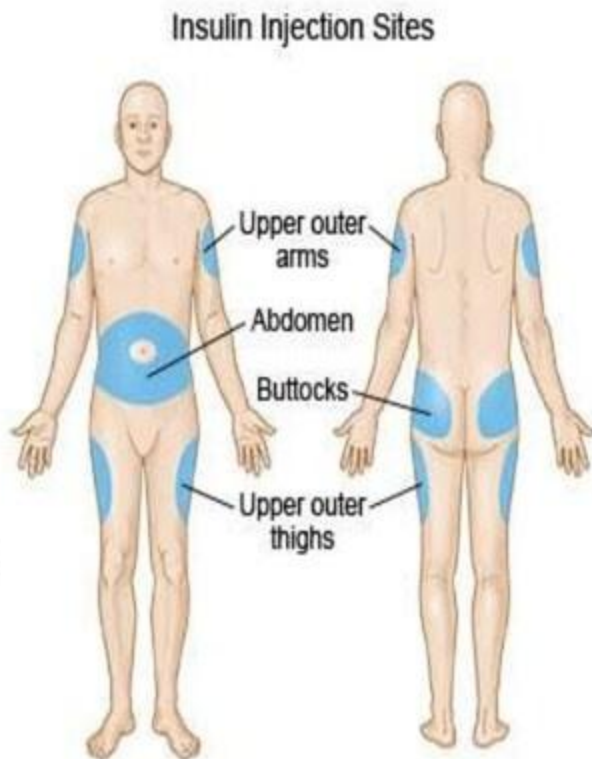
- Aim-To mimic natural pattern of insulin secretion
- Administration- insulin is administered subcutaneously using insulin syringes, pens, or insulin pumps.
- Dose-
 - DKA/with overt symptoms:
 - Total daily dose(TDD)-0.8 to1 unit/kg/day
 - Incidentally diagnosed: at lower dose
 - Toddlers & pre-school (2-5 yrs)-0.2-0.4unit/kg/day
 - Pre-pubertal children(5-9 yrs)-0.5-0.8 unit/kg/day
 - Adolescents-(9-14 yrs) 0.8-1.5unit/kg/day

Key aspect of Insulin Therapy

Injection sites

- Anterolateral thighs
- Anterior and lateral abdominal wall
- Posterior aspect of upper arms
- Superolateral aspects of buttocks.

(site rotation : following a regular pattern of using the different sites and different areas within the same site is important)



Key aspect of Insulin Therapy

- **Regimes-**

- Split mix regime (mixtard 30:70 or NPH 2/3 + Regular insulin 1/3; twice a daily)

 - 2/3 dose-45 min BBF

 - 1/3 dose-45 min BD

 - 1 IU of Mixtard takes care of BS 50mg/dl above target

- Basal bolus regime with multiple daily injection(MDI)

 - 30-50% of Total daily dose as one dose- long action (Glargine, Detemir)

 - 3-4 doses of rapid insulin as remainder

Key aspect of Insulin Therapy

Calculation of Bolus Dose –

➤ **CIR (carbohydrate to insulin ratio)**

- Amount of carbohydrate in gram covered by one unit of insulin
- Initial calculation- $500/\text{Total daily dose}$

more accurate estimation is based on

- amount of carbohydrate consumed in a meal
- units of insulin administered
- pre and post prandial blood glucose

➤ **ISF-insulin sensitivity factor**

- Reduction in blood glucose by one unit of insulin
- Initial calculation as $1800/\text{Total daily dose}$

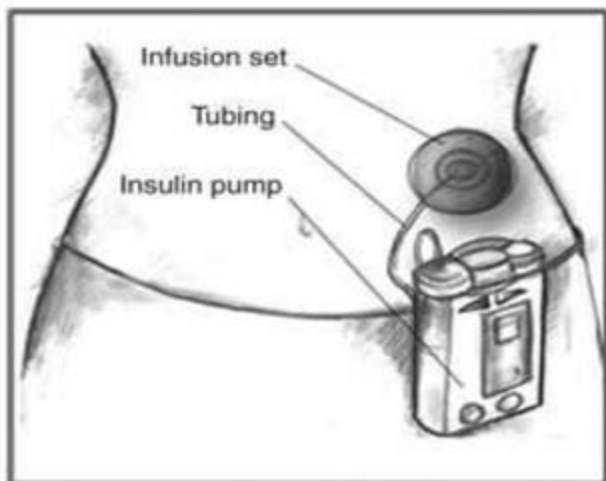
- For correcting Pre meal high sugar (actual BS- Target BS/ISF)

Key aspect of Insulin Therapy

- Example for 10 yrs old 33 kg wt child
Total insulin requirement $0.8 \text{ IU} * 33 = 26 \text{ IU}$
Carbohydrate to Insulin Ratio = $500/26 = 20$
Insulin sensitivity factor = $1800/26 = 70$
Inj Glargine 40% = 11 IU
If child is taking 80 gm carbohydrates in lunch , insulin needed is $80/ \text{CIR} = 4 \text{ IU}$
If pre lunch BS is 200 than to correct pre lunch BS insulin needed is $(200 - 130)/\text{ISF} = 1$
So Inj lispro is given 5 IU before lunch.

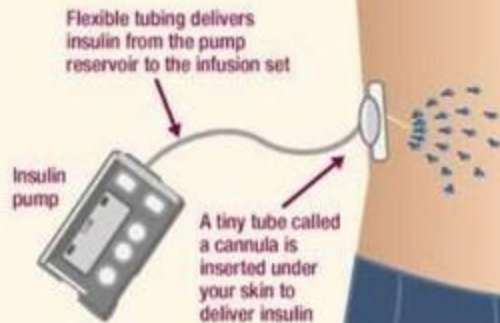
Insulin Pump Therapy

- Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles.
- It accurately deliver a small baseline continuous infusion of insulin, coupled with parameters for bolus therapy.
- The bolus insulin determined by amount of carbohydrate intake and blood sugar level



How does the insulin get into your body?

➤ Insulin in the blood



Monitoring of glycemic control

- Self monitoring of blood glucose(SMBG)
 - fasting
 - before and 2 hours after meals
 - during night
- Real time continuous glucose monitoring
- Urinary Glucose
 - Reflects glycemic level over the preceding several hours
 - It is positive if renal threshold is exceeded.
 - Crude indicator of hyperglycemia

Monitoring of glycemic control

- Measuring ketones in urine-More sensitive and accurate
 - In-BG > 250 mg/dl
 - Illness with fever and or vomiting
 - abdominal pain , polyurea,
 - drowsiness, rapid breathing
- Glycosylated Hemoglobin (HbA1C)
 - every 3-4 monthly

ADVERSE EFFECTS OF INSULIN

- Hypoglycemia
- Lipoatrophy
- Lipohypertrophy
- Obesity
- Insulin allergy
- Insulin antibodies

PRACTICAL PROBLEMS

- Non-availability of insulin in poor countries
- injection sites & technique
- Insulin storage & transfer
- Mixing insulin preparations
- Insulin & school hours
- Adjusting insulin dose at home
- Sick-day management
- Recognition & Rx of hypoglycemia at home

Management on Sick days

- Insulin requirement may increase or decrease during illness.
- Fever, dehydration, and the stress of illness can cause hyperglycemia due to increase production of counterregulatory hormones , whereas vomiting and loss of appetite can lead to hypoglycemia.
- The risk of Ketosis is increased due to starvation and dehydration.

Management on Sick days

- Take plenty of fluids.
- Blood glucose and urine ketones monitored frequently.
- “moderate” or “large” ketones in the urine in the presence of hyperglycemia indicate insulin deficiency and risk of DKA.
- Child should be given rapid acting analog or regular insulin and oral fluids and ketones should be rechecked in the next urine.
- If there is vomiting with hyperglycemia and large ketones , or persistent hypoglycemia, child should be taken to emergency department.

Management on Sick days

URINE KETONE STATUS	INSULIN	CORRECTION DOSE	COMMENT
Negative or small	q2hr	q2hr for glucose >250mg/dl	Check ketones every other void
Moderate to large	q1hr	q1hr for glucose >250 mg/dl	Check ketones each void go to hospital if emesis occurs.

RBS 2hrly
INSULIN short acting (0.1u/kg) or if
RBS >250

DIET REGULATION

- Regular meal plans with calorie exchange options are encouraged.
- 50-60% of required energy to be obtained from complex carbohydrates.
- Distribute carbohydrate load evenly during the day preferably 3 meals & 2 snacks with avoidance of simple sugars.
- Encouraged low salt, low saturated fats and high fiber diet.

DIET REGULATION

- Avoid simple sugar
- In patient with split mix regime-
6 meals-3 major(70% of total calories)
-3midmeal(30% of total calories)
- In children with MDI(multiple dose regime)
mid meal is not essential
majority of the calories should be consumed as a part of the meals,
mid meal should have less than 10-15 gm of carbohydrate.

DIET REGULATION

Glycemic Index :

- ranking of carbohydrates on a scale from 0 to 100 according to the extent to which they raise blood sugar levels after eating.
- Foods with a high GI are those which are rapidly digested and absorbed and result in marked fluctuations in blood sugar levels. Like corn flakes, potato, watermelon, biscuits, chocolates
- Low-GI foods, by virtue of their slow digestion and absorption, produce gradual rises in blood sugar and insulin levels, and have proven benefits diabetics. Like Most fruits and vegetables (except potato & water melon), pasta, pulses, milk, curd,

EXERCISE

- Decreases insulin requirement in diabetic subjects by increasing both sensitivity of muscle cells to insulin & glucose utilization.
- It can precipitate hypoglycemia in the unprepared diabetic patient.

PITFALLS OF MANAGEMENT

- Delayed diagnosis of IDDM
- The honey-moon period
- Problems with diagnosis & treatment of DKA & hypoglycemia
- Somogyi's effect & dawn phenomenon may go unrecognized.

Dawn Phenomenon

- Blood glucose levels increase in early morning hours before breakfast due to **decline in insulin levels**. Which results in elevated morning glucose.
- This phenomenon mainly caused by overnight growth hormone secretion and increased insulin clearance.
- It's a normal physiologic process seen in most adolescents without diabetes, who compensate with more insulin output. Child with T1DM cannot compensate.

Somogyi Phenomenon

- It's a theoretical rebound from late-night or early morning hypoglycemia, thought to be from an exaggerated counter-regulatory response.
- Continuous glucose monitoring systems or night time blood glucose may help clarify ambiguously elevated morning glucose levels.

COMPLICATIONS OF DIABETES

- Acute:
 - DKA
 - Hypoglycemia
 - Hyperosmolar Coma
- Late-onset:
 - ☐ Retinopathy
 - ☐ Neuropathy
 - ☐ Nephropathy
 - ☐ Ischemic heart disease & stroke

Guidelines regarding monitoring for complications

Parameter	Recommendation
HbA1c	3-4 times per year
Height and Weight	3-4 times per year
Nutritional counseling	At diagnosis, 4-6 weeks later ,then annually.
Lipid profile	Prepubertal child :every 5 yr Pubertal child: within 6-12 months after diagnosis, then every 2 yrs.
Blood pressure	Annually after age 10 yrs.

Prevention and Early detection of complication

RETINOPATHY :

- Screening - after 5 yr duration in prepubertal children
 - after 2 yr in pubertal children
- Frequency- 1-2 yearly
- Method preferred- fundal photography

NEPHROPATHY:

- Screening - after 5 yr duration in prepubertal children
 - after 2 yr in pubertal children
- Frequency- annually
- Preferred method- spot urine sample for albumin:creatinine ratio

Prevention and Early detection of complication

NEUROPATHY:

- Screening-unclear in children ; adults at diagnosis in type 2 DM and 5yr after diagnosis in type 1DM
- Frequency- unclear
- Method preferred-physical examination

MACROVASCULAR DISEASE:

- Screening- after age 2 yrs
- Frequency- every 5 yrs
- Method preferred- lipid profile test

Prevention and Early detection of complication

THYROID DISEASE

- Screening- at diagnosis
- Frequency- every 2-3 yr or more frequently based on symptoms or the presence of antithyroid antibodies.
- Method preferred- TSH

CELIAC DISEASE:

- Screening- at diagnosis
- Frequency- every 2-3 yr
- Method preferred- tissue transglutaminase endomysial antibody.



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MANAGEMENT OF ACUTE COMPLICATIONS

Diabetic Ketoacidosis

- DKA, a life threatening complication of diabetes mellitus, occurs more commonly in children with type 1 DM than type 2 DM.
- DKA in children is defined as hyperglycemia (serum glucose conc. $>200-300\text{mg/dl}$) in the presence of metabolic acidosis (blood $\text{pH} < 7.3$ with serum bicarbonate level $< 15\text{ mEq/L}$) and ketonemia (presence of ketones in blood).

Diabetic Ketoacidosis

Signs and symptoms

- ❖ Nausea, vomiting, abdominal pain
- ❖ Fruity odour in breath
- ❖ Tachycardia
- ❖ Low volume pulses
- ❖ Hypotension
- ❖ Impaired skin turgor
- ❖ Delayed capillary refill time
- ❖ Dehydration
- ❖ Rapid, Deep sighing respiration Kussmaul respiration (met. Acidosis)

Classification of diabetic ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE
Co ₂ mEq/L (venous)	20-28	16-20	10-15	<10
pH	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

DIABETIC KETOACIDOSIS TREATMENT PROTOCOL.

TIME	THERAPY	COMMENTS
1 ST hr	10-20 ml/kg IV bolus 0.9% NaCl or LR Insulin drip at 0.05 to 0.10 u/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurological status. Use flow sheet. Have Mannitol at bedside; 1 g/kg IV push for cerebral edema
2 nd hr until DKA resolution	0.45% NaCl; plus continue Insulin drip 20 mEq/l Kphos and .5% glucose if blood sugar <250 mg/dl	IV rate= 85 ml/kg+maintenance-bolus/23hr
		If K<3mEq/L, give 0.5 to 1 mEq/kg as oral K solution OR increase IV K to 80 mEq/L
After correction of dehydration and acidosis	Oral intake with subcutaneous insulin	No emesis; CO ₂ > 16 mEq/L; normal electrolytes

References

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- Harrison's Textbook of Internal Medicine
- Case based reviews of paediatric endocrinology

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- World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of WHO. Department of Non-communicable Disease Surveillance. Geneva 1999