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 mutions
- 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

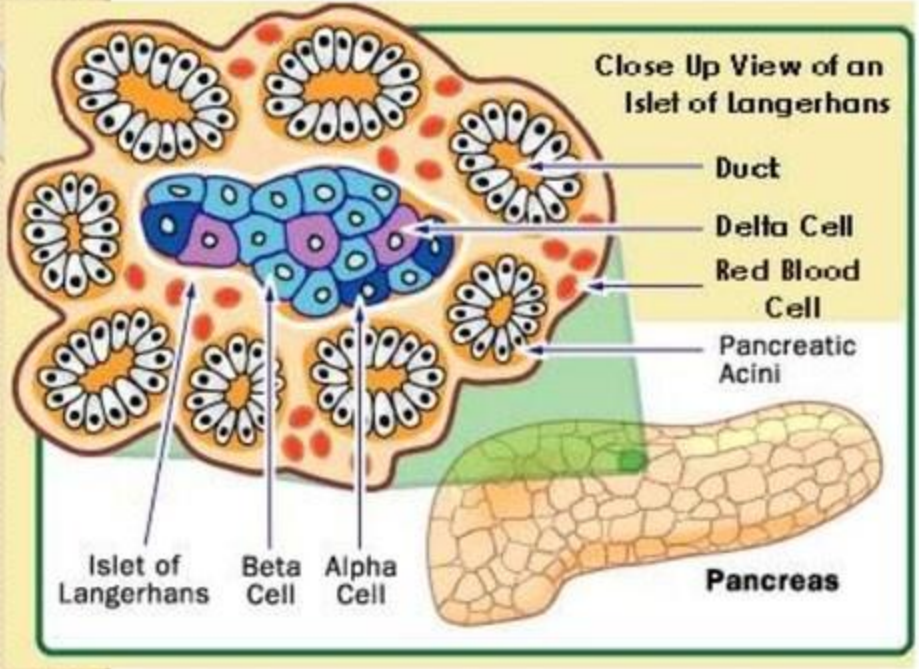
- If mother has Type1DM risk in child is 2%.
- If father is affected risk is 7%.
- In a sibling of the index case is estimated as 6%.
- Risk is 6-10% in diazygotic twins & 30-65% in monozygotic twins

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

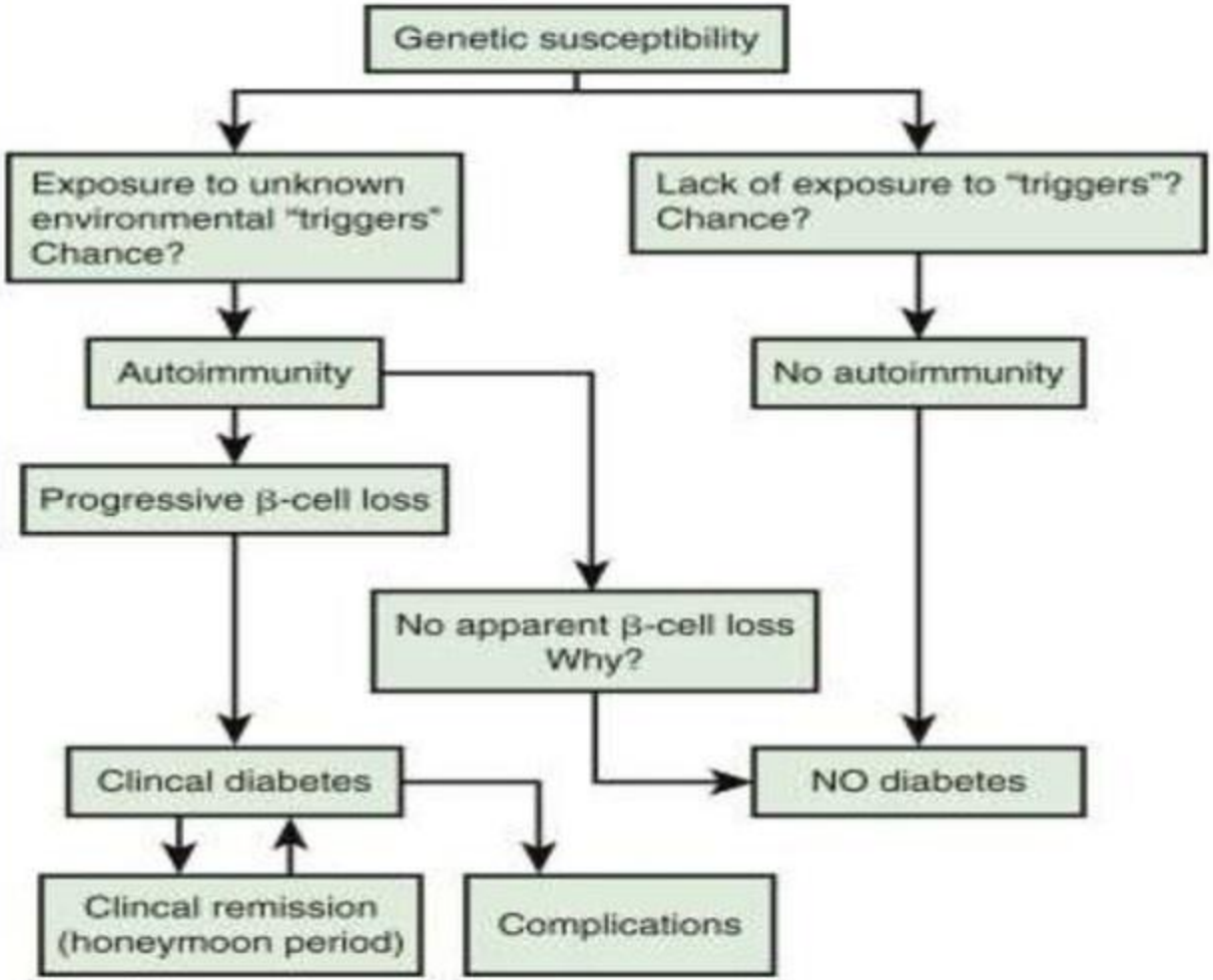
The Pancreas



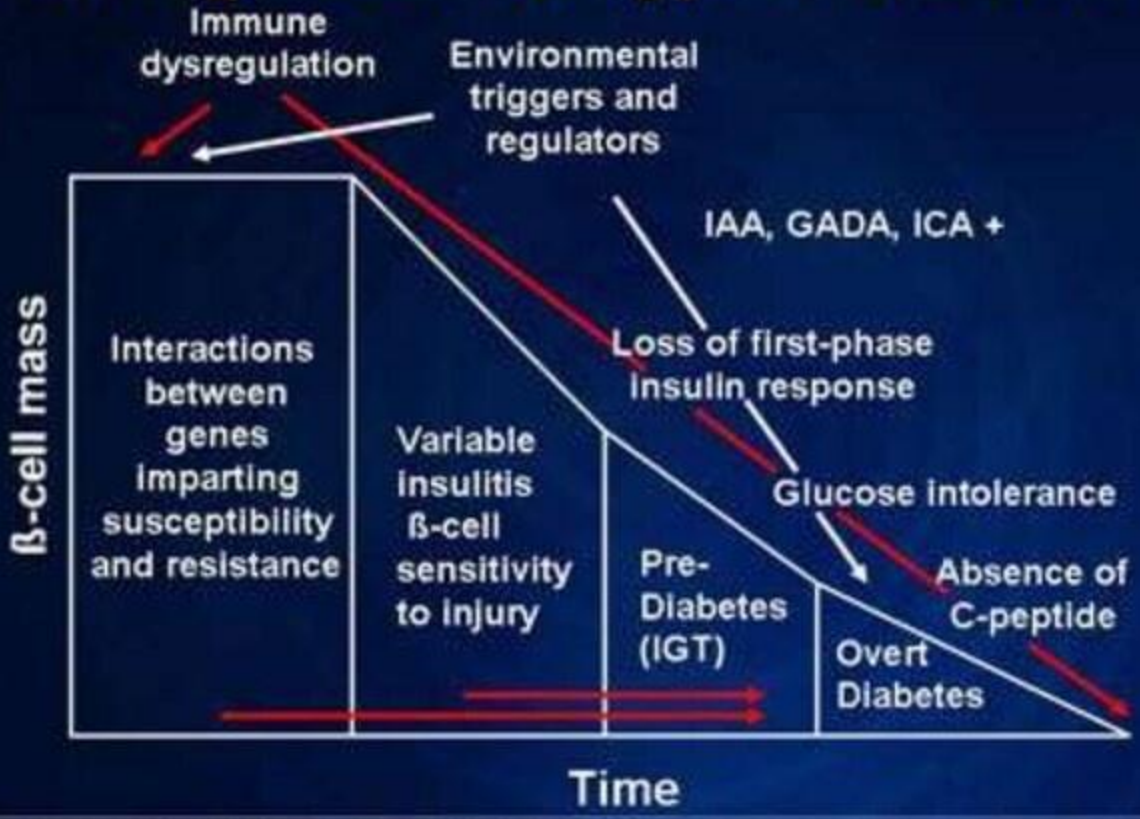
Beta Cells: secrete insulin.

Alpha Cells: secrete glucagon

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


Genetic susceptibility
Exposure to unknown environmental "triggers" Chance?
Lack of exposure to "triggers"? Chance?
Autoimmunity
No autoimmunity
Progressive β-cell loss
No apparent β-cell loss Why?
Clincal diabetes
NO diabetes
Clincal remission (honeymoon period)
Complications

Pathogenesis of Type 1 Diabetes



Atkinson & Eisenbarth. *Lancet.* 2001;358:221.

Joslin Diabetes Center

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 dectection 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

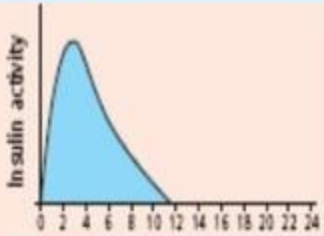
Examples: insulin glargine

Onset: Reaches the bloodstream 6-10 hours after injection

Duration: Usually effective for 20-24 hours

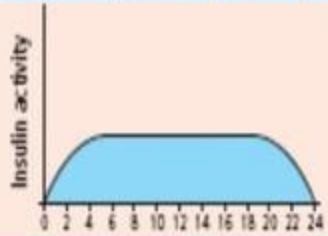
Soluble Human Insulin: Actrapid, Humulin S

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



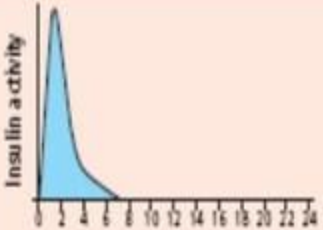
Long Acting Basal Analogues: Glargine (Lantus), Detemir (Levemir)

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



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

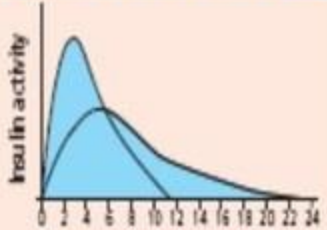
Onset: 0-15 mins
Peak: 1-2 hours
Duration: 3-5 hours



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

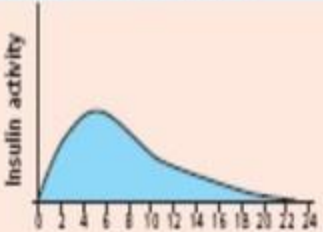
Onset: See above
Peak: See above
Duration: See above

Mixtard 30, M3 refers to % of soluble insulin ie. 30% Soluble 70% Isophane



Intermediate Human Isophane Insulin's: Insulatard, Humulin I

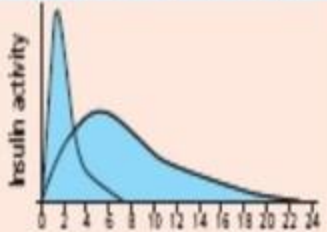
Onset: -
Peak: 4-8 hours
Duration: 14-16 hours



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

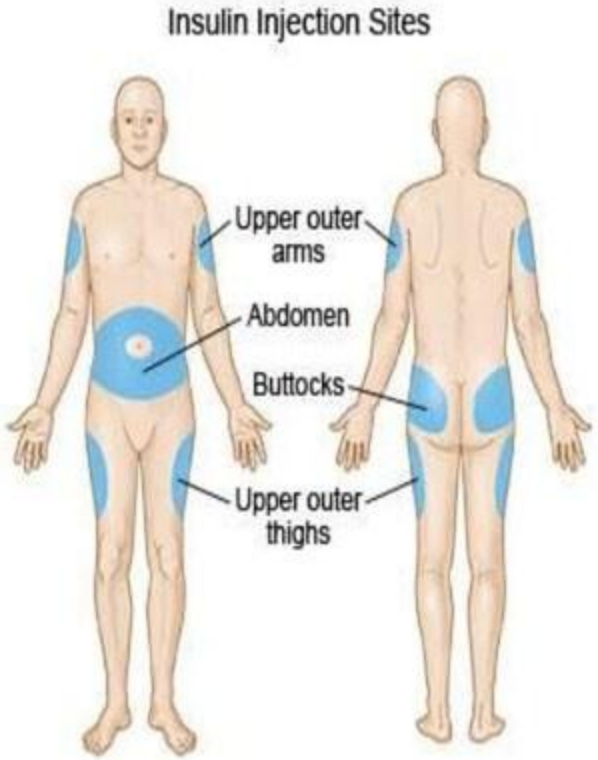
Adolescents-(9-14 yrs) 0.8-1.5unit/kg/day

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 carohydrate in gram covered by one unit of insulin
  - Initial calculation-500/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/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 IU * 33=26 IU

Carbohydrate to Insulin Ratio = 500/26=20

Insulin sensitivity factor = 1800/26 = 70

Inj Glargine 40% = 11 IU

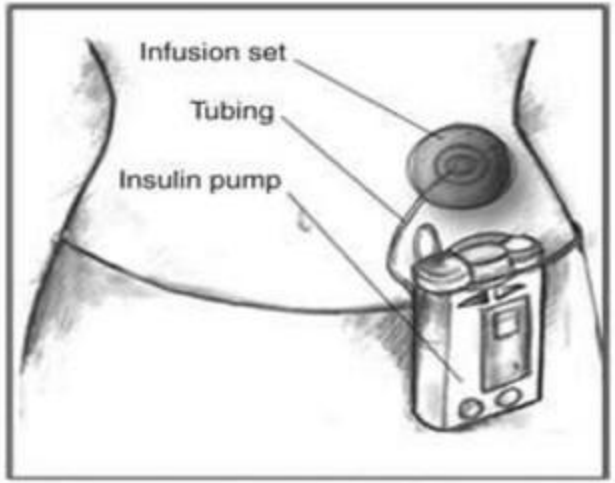
If child is taking 80 gm carbohydrates in lunch , insulin needed is 80/ CIR =4 IU

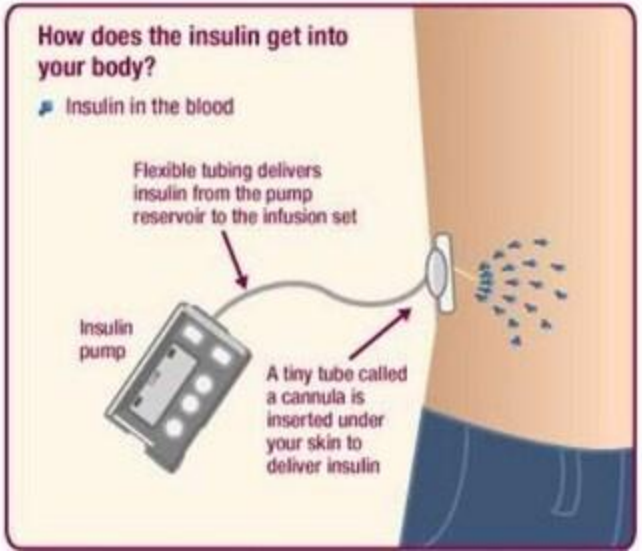
If pre lunch BS is 200 than to correct pre lunch BS insulin needed is 200-130/ISF = 1

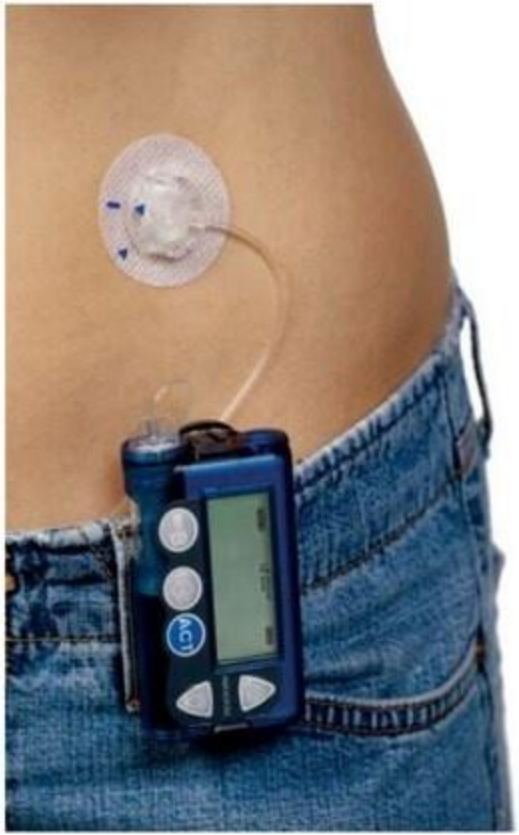
So Inj lispro is given 5 IU before lunch.

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


Infusion set
Tubing
Insulin pump


How does the insulin get into your body?
Insulin in the blood
Flexible tubing delivers insulin from the pump reservoir to the infusion set
Insulin pump
A tiny tube called a cannula is inserted under your skin to deliver insulin



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 theshold 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 monitered 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 TIDM 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.

MANAGEMENT OF ACUTE COMPLICATIONS

Diabetic Ketoacidosis

- DKA,a life threatning complication of diabetes mellitus,occurs more commonly in children with type 1 DM than type 2 DM.
- DKA in children is defined as hypgerglycemia(serum glucose conc. >200-300mg/dl) in the presence of metabolic acidosis (blood pH<7.3 with serum bicarbonate level<15 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 Kussumaul respiration(met. Acidosis)

Classification of diabetic ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE
Co2 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
1ST 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.Usefloe sheet. Have Mannitol at bedside;1 g/kg IV push for cerebral edema
2nd 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+maintainence-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;CO2> 16 mEq/L;normal electrolytes

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