Childhood diabetes

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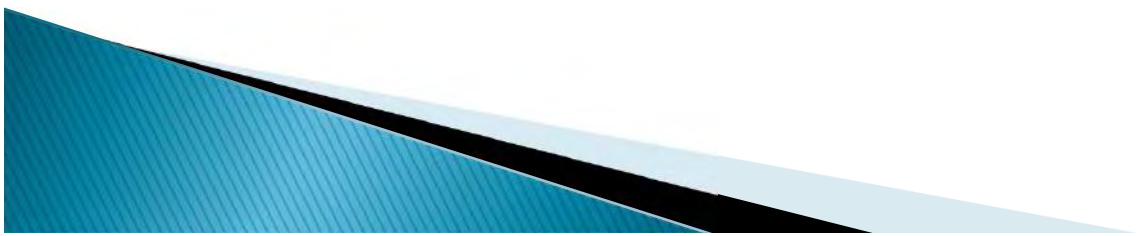
True stories from our Department

		7yrs, boy	2.5 yrs, girl	4 yrs, girl	10 yrs, boy	15 yr, girl
Symptoms		Low grade fever, cough X 2 days Fast breathing X 7 hours	Excessive thirst, lethargy, urinary urgency & increased frequency X 1 week	Irritability, fast breathing X 4 hours Direct questioning, nocturia, weight loss X 2 weeks	Injury to L toe x 2 weeks GP checked RBS for non-healing, RBS at 3 pm 350, referred to CMCH	Breathing difficulty, altered sensorium 15 kg weight loss over 1 month
Findings		Moderately dehydrated Markedly acidotic Chest clear	Not dehydrated, very lethargic, not acidotic, systems N	Moderately dehydrated Acidotic No focus of infection	Appears well, but wasted Wound L toe	Markedly acidotic, comatose
Lab	RBS	756	435	648	550	1230
	Urine ketones	4+	3+	3+	2+	3+
	ABG	pH 6.9 ABE - unrecordable	pH 7.4 HCO3 : 22	pH 7.2 HCO3 : 5	pH 7.4 HCO3: 18	pH 6.8 HCO3 < 5

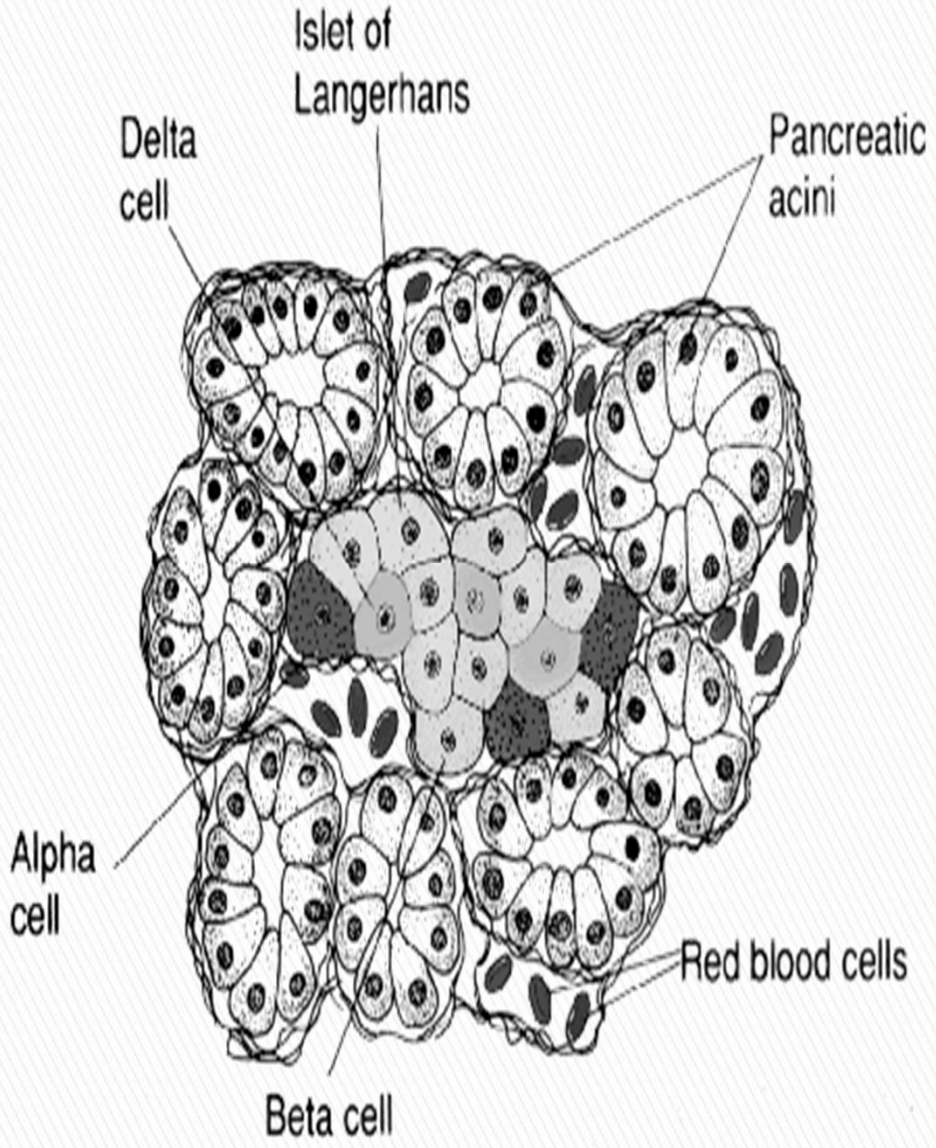
Introduction

- Clinical condition resulting from absolute or relative insulin deficiency
- Characterized by abnormalities in the metabolism of carbohydrate, protein and lipids



Pancreas – functional anatomy of endocrine portion

- Insulin produced by the β cells in the islets of Langerhans
- Islets make up 2% of the volume of pancreas, 80% by the exocrine portion of the pancreas



Classification

- **Type 1 diabetes**

  Absolute insulin def resulting from progressive β cell destruction

  1. immune mediated
  2. idiopathic

- **Type 2 diabetes**

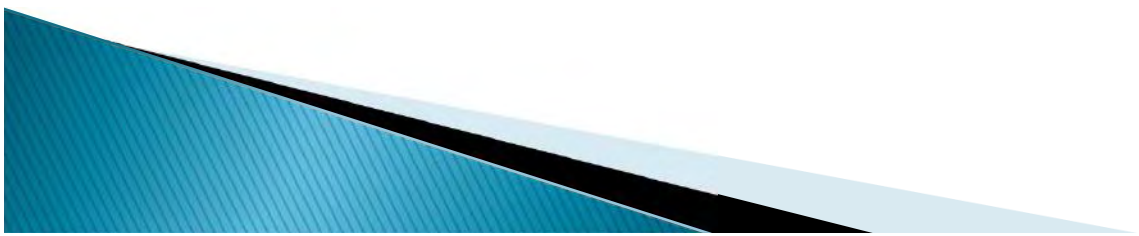
  Relative insulin def with insulin resistance

- **Secondary diabetes**

Secondary diabetes

- Genetic defects in **β cell function**
  1. MODY (1-6)
  2. mitochondrial diabetes

- Genetic defects in **insulin action**
  1. Type A insulin resistance
  2. leprechaunism
  3. Rabson-Mendenhall syndrome
  4. Lipoatrophic diabetes



Secondary diabetes contd—

- **Diseases of the exocrine pancreas**
    1. Cystic fibrosis
    2. Pancreatitits
    3. Haemochromatosis
    4. Neoplasm etc

- **Endocrinopathies**
    1. Cushing syndrome
    2. Thyrotoxicosis
    3. Phaeochromocytoma etc

Secondary diabetes contd—

- **Drugs**
  - glucocorticoids , thiazides
  - diazoxide, dilantin, pentamidine etc

- **Infections**
  - congenital rubella
  - CMV

- **Syndrome related**
  - Turner, Klinefelter, Down
  - Prader Willi , Lawrence-Moon-Biedl etc

Type I diabetes

- Commonest type in children
- Incidence varies :

  Finland : 40/yr/100,000

  Japan : 1/yr/100,000

  S.India : 10.5/yr 100,000

  (Ramachandran A, 1996)

- Alarming rate of increase in incidence worldwide compared to 1997, 40% higher incidence expected by 2010

- Severe insulin def- exogenous insulin absolutely essential to prevent ketosis and death

- Peak incidence

  1. at 5-7 yrs : ? Infection exposure at school entry

  2. during puberty : ? Insulin anatagonising effects of pubertal hormones(gonadal steroids, GH)

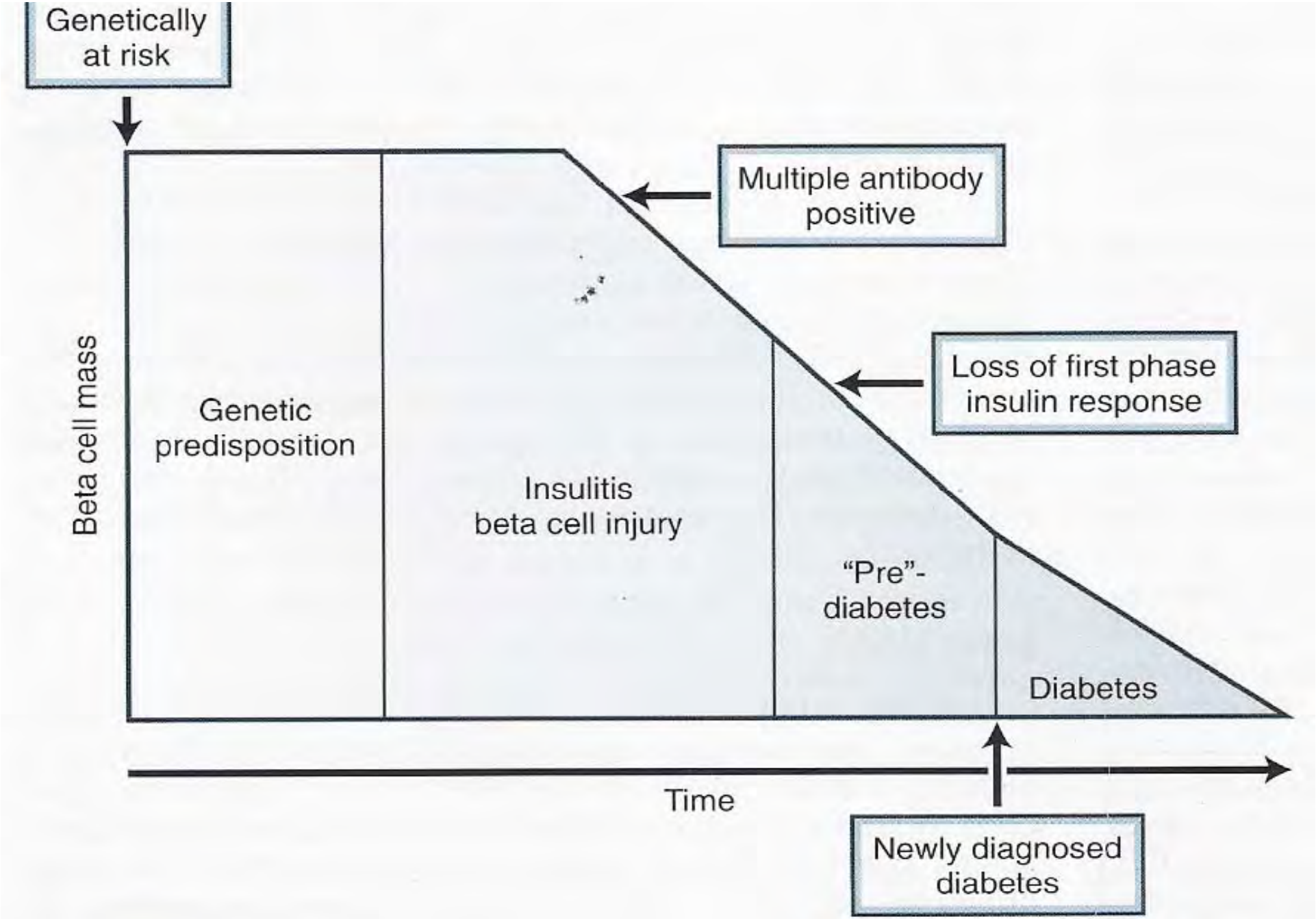
- No gender difference, no socioeconomic bias

Steps in pathogenesis

- **Genetic predisposition (HLA region)**
- **Environmental trigger**

  (viruses, dietary agents, toxins & stress)
- **Initiation of autoimmunity**
  against insulin, islet cell, GAD
  (ICA, GAD, IAA)
- **Prediabetic phase** of progressive islet cell destruction
- **Clinical onset of diabetes**

(when>90% of pancreas cells get destroyed)



Adapted from Atkinson MA et al,Lancet 2001;358:221-229

How do we maintain euglycaemia?

- **Normal plasma glucose**

  Interplay between Insulin & Glucagon (also other counter regulatory hormones like cortisol, GH, adrenaline)

- **Insulin – most important anabolic hormone**

  During fasting: Low insulin levels result in catabolism and mobilisation of stored energy

  Postprandial: High insulin levels result in an anabolic state, with excess energy stored as fuel for future use

Some terminologies

- Glycogenesis : glycogen synthesis from glucose
- Glycolysis : breakdown of glycogen to release glucose
- Gluconeogenesis : glucose synthesis from non-CHO substrates like amino acids, lactate etc
- Lipogenesis : synthesis of lipids
- Lipolysis : breakdown of lipids to fatty acids & glycerol

Main sites of insulin action

Skeletal muscle

1. stimulates glucose uptake
   glycogen synthesis
   glycolysis
2. stimulates aa uptake & protein synthesis

Adipose tissue

1. stimulates glucose uptake & storage as TG
2. inhibits lipolysis

Liver

1. Promotes glycogenesis & suppresses glycolysis
2. suppression of gluconeogenesis
3. stores FA as TG

What are the anabolic effects of Insulin?

Glucose

1. promotes utilisation as energy source
2. promotes storage as glycogen for future fuel
3. Inhibits glycogen breakdown in liver
4. Inhibits gluconeogenesis

Aminoacids

1. Stimulates protein synthesis

Lipids

1. Enhances fat storage
2. Prevents mobilisation of fat as energy

T1 diabetes is a progressive catabolic state due to insulin deficiency

Effects of insulin deficiency

All symptoms are due to effects on

- Carbohydrate Metabolism
- Protein Metabolism
- Lipid Metabolism

Consequences on CHO metabolism

- Hyperglycaemia exceeding renal threshold
- Glucose leak in urine (glucosuria)
- Osmotic diuresis (polyuria, nocturia), loss of electrolytes in urine
- Dehydration and increased thirst(polydypsia)
- To maintain energy balance, increased food intake(polyphagia)

Consequences on lipid metabolism

- Increased lipolysis and decreased lipid synthesis

- Loss of adipose tissue

- Unsuppressed lipolysis with excessive FFA production ⟶ increased Acetyl CoA

- Elevated plasma and urine ketones

Consequences on protein metabolism

- Increased protein breakdown & decreased synthesis

- Muscle wasting

Role of counterregulatory hormones

- Insulin deficiency

- Wasting, dehydration, loss of electrolytes (physiologic stress state)

- Hypersecretion of counterregulatory hormones

- Metabolic decompensation

Pathophysiology of DKA

Insulin def + Excess counterregulatory hormones

- Accelerated lipolysis → Increased FFA
- Accumulation of ketone bodies(acetone, acetoacetate, βhydroxybutyrate)
- Metabolic acidosis, compensatory Kussmaul's breathing
- Progressive dehydration, acidosis, hyperosmolarity → coma & death (if untreated)

Clinical features

- Of hyperglycaemia: Polyuria, polydypsia, polyphagia, nocturia, weight loss & weakness

- + Ketosis : abdominal discomfort, nausea, vomiting

  progressive & rapid deterioration

- Diabetic ketoacidosis : moderate to severe dehydration, acidotic breathing, fruity odour of the breath

  shock, cerebral obtundation & death if left untreated

Diagnosis

- **Plasma sugar (mg%)**

	Normal	Impaired	DM
Fasting	<110	111-125	≥126
2hr post glucose	<140	141-199	≥ 200

OR

- **Any random blood sugar≥ 200mg% with the classic symptoms**

American Diabetes Association criteria, Diabetes care, 1999

Other investigations

- Baseline HbA1C (at diagnosis)
  - duration of hyperglycaemia
  - to evaluate treatment efficacy over time
- Autoantibodies to β cell
  - not essential in non-obese children
- Other autoantibodies
  - coeliac disease (TTG IgA)
  - thyroid (TPO, TG)
- TSH, TFT
  - few weeks after stabilisation

Management

Needs a multidisciplinary team :

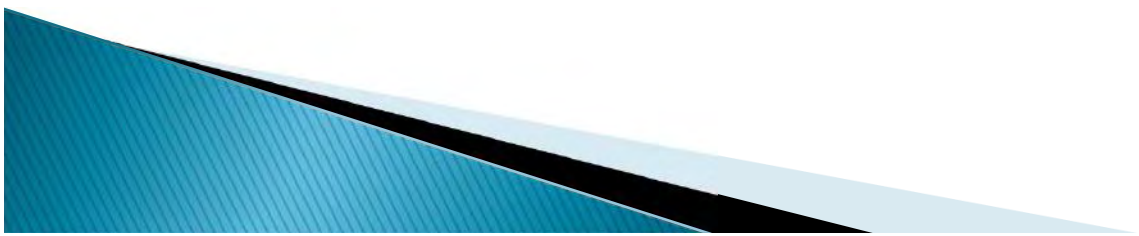
paediatrician/paediatric endocrinologist, diabetes nurse educator, dietitian, social worker, psychologist

Goals

- Adequate glycaemic control while avoiding hypoglycaemia
- Permit normal growth & development with minimal effect on lifestyle
- Prevent ketoacidosis

Principles of management

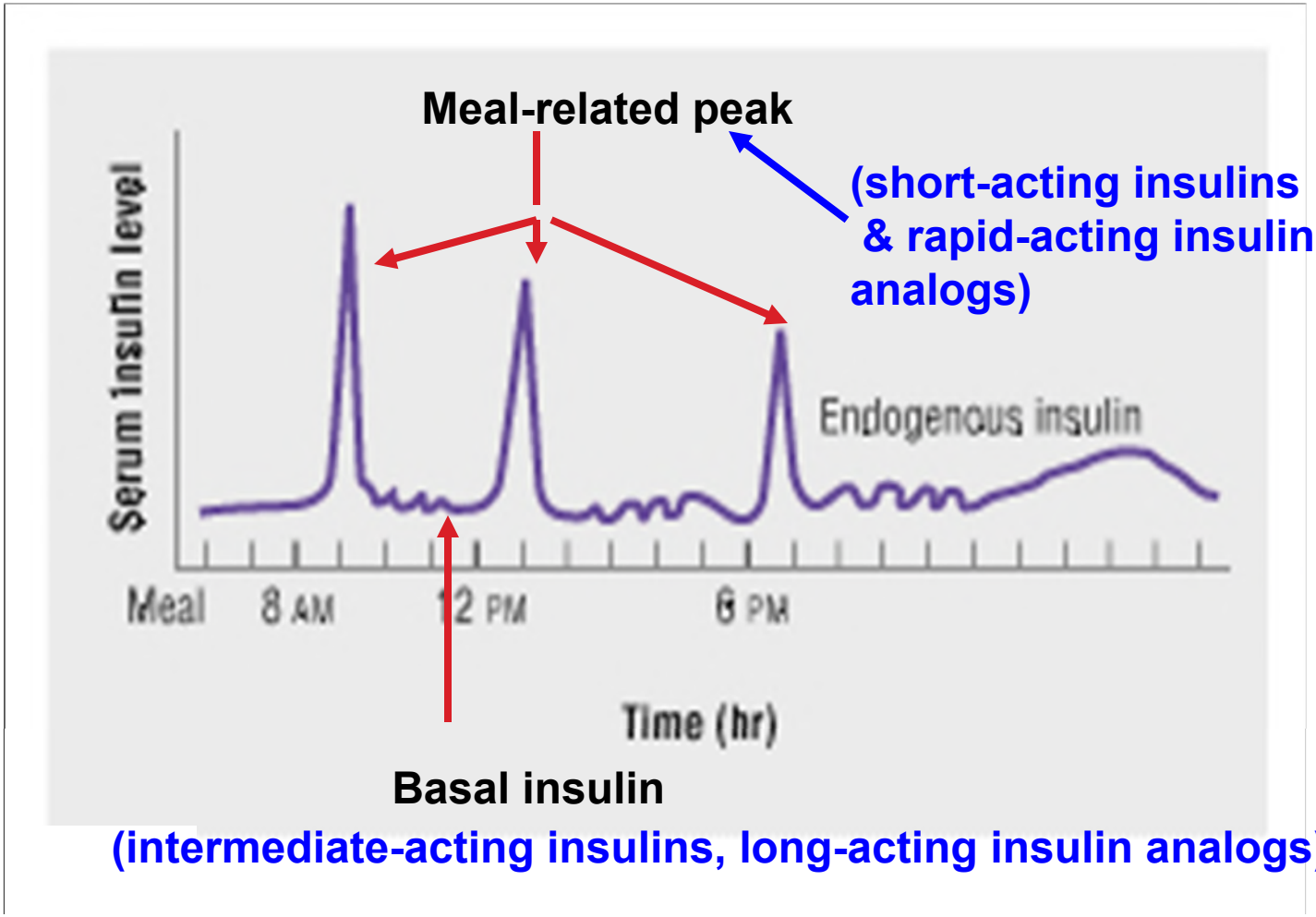
- Insulin therapy
- Balanced diet
- Regular exercise
- Regular monitoring



Insulin therapy

- Forms the cornerstone of management of Type1 DM
- Initiation at 0.7 unit/kg/day for pre-pubertal children, 1-1. 5units/kg/day during puberty
- Injection at least twice a day (2-4 times/ day)

Physiological insulin secretion



Ultimate goal of insulin therapy
- to mimic endogenous insulin secretion

Commonly used insulins

Classification on the basis of their peak effect and duration of action:

- Short acting: Regular insulin
- Intermediate acting: NPH/ Lente
- Long acting : Ultralente
- Premixed:(30/70), (50/50) – **not recommended in children**

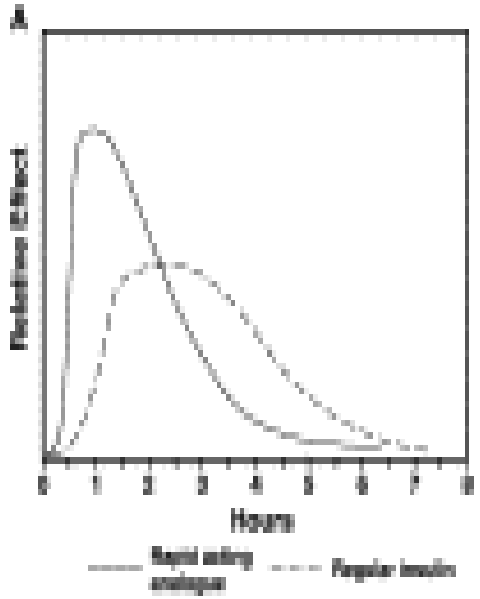
Insulin analogs

- Short acting : Lispro /Aspart
- Long acting : Glargine

Physiologic prandial response
Intraportal, biphasic & rapid

Regular insulin

- an initial lag phase
- plasma insulin level peaks after 1 to 2 hrs
- returns to basal levels after ~ 6 to 8 hrs



Insulin analogs –lispro and **aspart**

- faster onset (5–10 min)
- shorter duration of action
- more closely resemble endogenous insulin secretion
- particular importance among **infants and preschool-aged children**, whose food intake may be inconsistent

Basal insulins

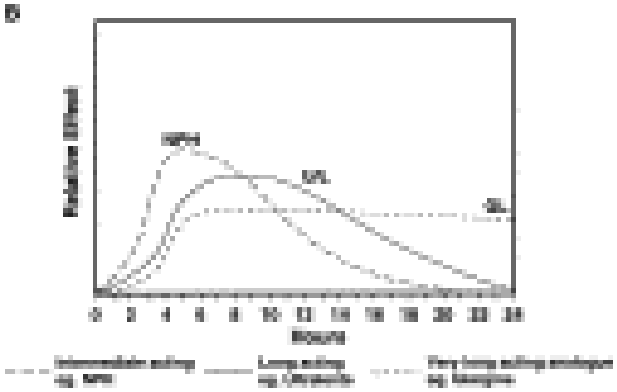
NPH/ULtralente
reduced solubility at physiologic pH – slower absorption

Disadvantages
➢considerable **dose-to-dose variation**
➢ **not "peakless"** – can cause nocturnal hypoglycemia

Glargine/Detemir

- prolonged absorption
- more consistent diurnal release of insulin – no pronounced peak over 24 hours
- flatter & longer action profile

- **Glargine: Inc IGF-1 receptor affinity ? Mitogenic potency**



Insulin action profile

Insulin	Onset	Peak	Duration
Regular	30min	2-4hrs	6-8 hrs
NPH	2-4hrs.	5-7 hrs	12- l 6 hrs
Lente	2-4hrs.	6-8 hrs	12-18 hrs
Ultralente	6-l2hrs	No Peak	18-30 hrs

Insulin regime

Split-mix

- combination of an intermediate acting with a short acting insulin given twice a day

- Lispro preferred in toddlers with erratic food intake

- pre-BF : 2/3rd total dose of insulin
  - 2/3 intermediate acting
  - 1/3 short acting

  pre-dinner : 1/3rd total dose of insulin

Insulin regime

Basal-bolus regime

- using single dose Glargine in the evening with twice or thrice a day short acting
- particualrly useful in children with risk of nocturnal hypoglycaemia

Insulin therapy

- Proper storage
- Strength of insulin & syringe(U 40/ U100)
- Correct sequence of insulin in the syringe- regular followed by intermediate acting
- Roll syringe gently to warm insulin (to bring it to room temp)
- Correct technique of administration (45 deg subcut) & regular rotation of the sites

Insulin injection sites

A case scenario

- 6yrs old, newly diagnosed Type 1 diabetic child (hyperglycaemia, ketonuria, no acidosis)
- Weight 18 kg
- Commence on

pre-BF	Insulotard	6
	Actrapid	4
pre-dinner	Insulotard	3
	Actrapid	2

Insulin dose adjustment– an example

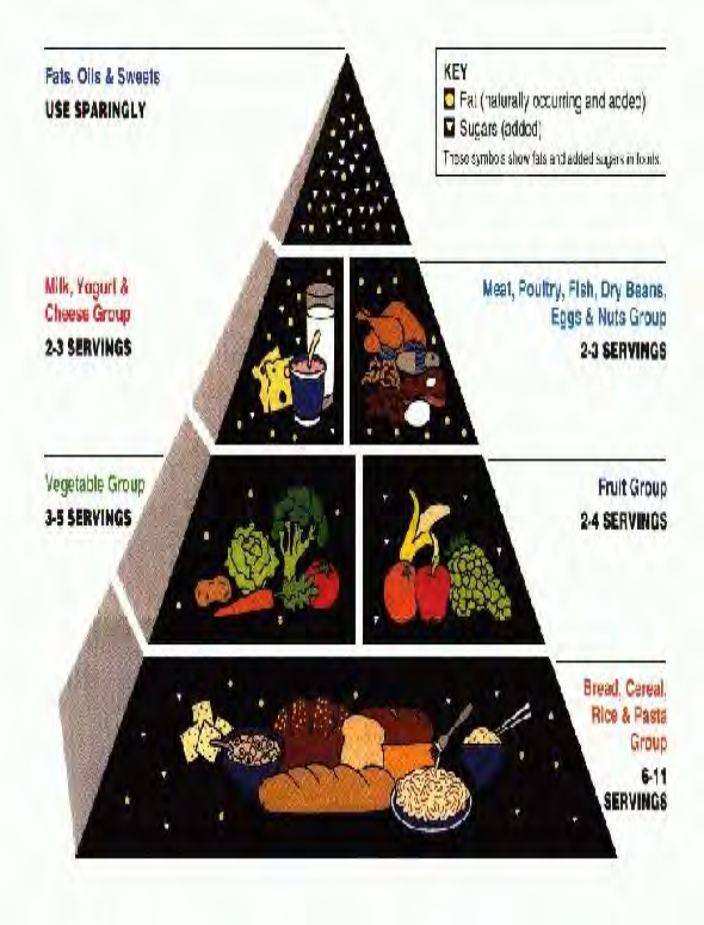
Pre-BF - Insulotard 6
Actrapid 4

Pre-dinner – Insulotard 3
Actrapid 2

Date	Pre-BF	2hrPC	Pre-lunch	Pre-dinner	Bed-time
29/06/09	212	280	200	225	130

Diet

- To maintain ideal body wt and promote growth
- 3 main meals (BF, lunch & dinner) and 3 midmeal snacks
- Split up of calories
  CHO : 50-65%
  proteins :10-20%
  fats : 25-30%
- Carbohydrate counting (carb count)



Diet

- Main restriction is for highly refined sugars or foods with high glycaemic index
- Family pot feeding, food exchange lists with glycemic index
- Special treats

Exercise/physical activity

Children should be encouraged to participate in all games and sports activities

- Stimulates glucose uptake into the skeletal muscle
- Plays a very important role in the management of diabetes
- Risk of hypoglycaemia with vigorous exercise- add on an extra carb exchange before and after exercise / reduction of insulin dose by 10-15% on that day

Another important guideline

- 3 year old, diagnosed as T1 diabetes a year ago. Has developed fever, cough and post tussive vomiting. How will you advise the mother?

Sick day issues

- Aims

  Prevent dehydration

  Prevent ketoacidosis

  Prevent hypoglycaemia

Ketonemia/ketonuria suggests

a. either insulin deficiency

stress hormones, inadequate insulin doses, missed insulin doses

b. or Low glucose levels due to fasting or starvation

eg. Acute gastroenteritis

Sick day guidelines

Any infection in a diabetic child can precipitate DKA

- Maintain dehydration
- Frequent blood glucose monitoring at home
- Check for urine ketones- if positive , will need more short acting insulin and careful monitoring till ketonuria clears
- Hospitalisation if ketonuria/hyperglycaemia persists or child develops persistent vomiting

Monitoring

Home blood glucose monitoring(HBGM)

- ideally ≥4 times a day
- in our set-up, monitoring for 3 days at least twice a month (pre-BF, pre-lunch, pre-dinner, bedtime)
- midnight & 3 am monitoring for nocturnal hypoglycaemia (CGMS ideal)

During follow-up

- Growth and pubertal assessment
- Glycosylated Hb (HbAIC)
- BP, Injection sites

Screening for complications

Complications

- Diabetic ketoacidosis
- Hypoglycemia
- Impact on growth and puberty

Complications

- Long term complications due to uncontrolled diabetes

  Nephropathy

  Retinopathy

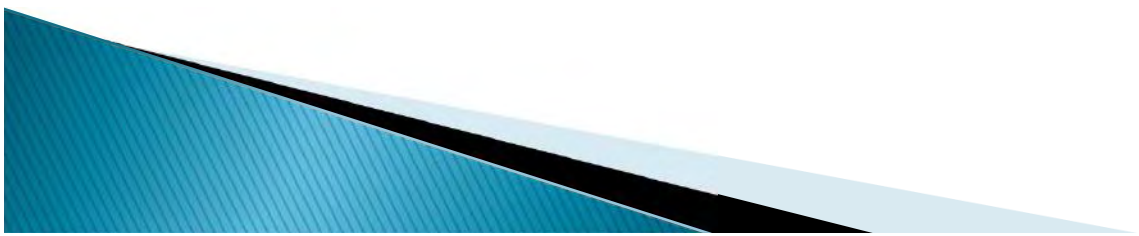
  annually after 5 yrs of onset in pre-pubertal children, after 2 yrs of onset in pubertal children

  Neuropathy

  Limited joint mobility

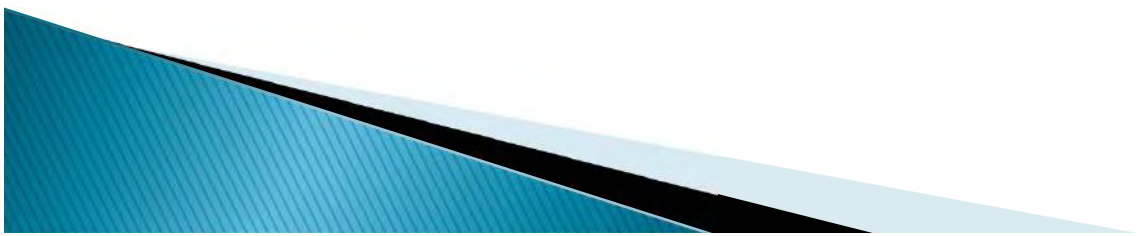
Associated autoimmune conditions

- Thyroiditis
- Coeliac disease
- Addison's disease



Honeymoon period

- Most children have partial remission following the diagnosis
- Transient improvement in β cell fn
- Insulin dose < 0.5 u/kg
- Duration – few months from diagnosis upto 2 years
- Maintain low dose insulin treatment even during the honeymoon period



(Newer) techniques
(not yet used in children with Type 1 diabetes in our unit)

Other modalities of insulin administration

- As nasal spray
- Follow-up studies upto 10 weeks and 6 months **in adults** promising
- Trial on in children & adolescents
- Long term efficacy & safety not known

CSII

Inhaled insulin

Monitoring devices

- **Continuous blood glucose monitoring (CBGM)**
  - measures interstitial blood glucose via an indwelling cannula in the abdomen/buttocks
  - expensive
- **Non-invasive blood glucose monitoring**
  - reverse iontophoresis
  - Device worn like a wristwatch approved for patients>7 years in the US
  - expensive

Miniglucagon therapy

- For home based management of hypoglycaemia especially during sick days
- Avoids need for hospitalisation to a large extent

Increasingly prevalent scenario

- 14 yr old boy
- Foul smelling urine X 2 months
- Nocturia X 3 weeks
- Some lethargy
- O/E : Wt> 97th percentile
  BMI 27 kg/m^2
  Acanthosis nigricans
  Not dehydrated or acidotic

What investigations would you like to do?

- Random blood glucose : 385

  If inconclusive, Fasting & 2 hr postprandial blood glucose

- Urine ketones

  negative

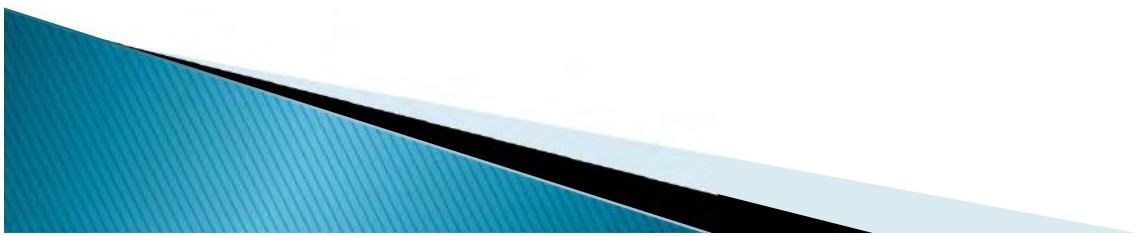
- Arterial blood gas

  not done because urine ketones neg

- Type 1 diabetes autoantibodies

  especially if ketonuria

Most recent advance in insulin?



Supramolecular insulin assembly II for a sustained treatment of type 1 diabetes mellitus

Sarita et al, National Academy of Sciences,July 2010

- "Administration of a single dose of the insulin oligomer(supramolecular insulin assembly II (SIA-II)), to experimental diabetic animals released insulin capable of maintaining physiologic glucose levels for > 120 days for bovine and > 140 days for recombinant human insulin without fasting hypoglycemia

- The novel SIA-II not only improved the glycemic control, but also reduced the extent of secondary diabetic complications"

- *Adapted version of the abstract*