Type 1 diabetes in children

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Objectives

- Define diabetes including diagnostic criteria.
- Describe various types of diabetes in children including differences between type 1 & type 2.
- Identify genetic & environmental contributing factors.
- Develop an approach to a child with diabetes including, history, clinical examination, investigations (at diagnosis and follow up).
- Describe pillars of diabetes management including home glucose monitoring (invasive Vs non invasive methods).
- Awareness of various types of insulin and method of delivery (Basal-bolus regimen) including insulin pump.
- Identify various acute & chronic complications of diabetes and its relationship to glycaemic control (HbA1c).
- Awareness of associated disease with type 1 DM (celiac disease Addison and autoimmune thyroiditis).

Definition

The term “diabetes” represents chronic disease of impaired carbohydrate, protein and fat metabolism owing to insufficient secretion of insulin or target-tissue insulin resistance.

Diabetes in Children

- Type 1 diabetes mellitus (IDDM) is the result of insulin deficiency caused by destruction of the pancreatic beta cells by autoimmune antibodies.
- It accounts for approximately two-thirds of all cases of diabetes in patients younger than 18 years of age.
- IDDM occurs most commonly in children & adolescents but can occur in adults, in their late 30s “non - obese”.
- Most patients with type 2 DM (NIDDM) have insulin resistance, and their β cells lack the ability to overcome this resistance.
- Although type 2 DM was previously uncommon in children, in some, countries up to 20% of new patients of childhood & adolescence have it, as result of increased rates of obesity globally.
- Other patients may have inherited disorders of insulin release leading to maturity onset diabetes of the young (MODY).

- Maturity-onset diabetes of the young (MODY), results from genetic defect of insulin synthesis (not immunological) & as common among children as type 2 diabetes.
- Other varieties of diabetes mellitus in childhood include:
  - Neonatal diabetes (autosomal dominant condition occurs in neonates & infant below 6 months)
  - Secondary diabetes e.g. cystic fibrosis, Thalassemia major due to hemosiderosis, thyrotoxicosis. Cushing ….. Etc.
  - Syndromes e.g. Turner, Down, Prader Willi …etc.
  - Drug induced e.g. steroids, chemotherapy …etc.

Diagnosis

- Diagnostic criteria by the American Diabetes Association in a patient with classic symptoms of polyurea, polydipsia and unexplained weight loss in addition to the following:
  - Fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L) *or*
  - A 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT) *or*
  - A random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).
  - Glycosylated HbA1c ≥ 6.5 %.

Type 1 versus type 2 diabetes

- T1DM is characterized primarily by insulin deficiency.
- T2DM is characterized primarily by insulin resistance with relative insulin deficiency.
- As the incidence of T2DM increases in children and adolescents.
- It becomes increasingly important to distinguish type 1 from type 2 disease because long-term management differs.

Characteristic	Type 1	Type 2
Gender	Female = male	Female > male
Age at presentation	Childhood & adolescence	Adulthood, obese >10 years
Ethnic group	Caucasian	Pima Indians, African American Hispanic
Autoimmunity	Common	No
Obesity	Not present	Present
Acanthosis	Not present	Present
Family history	Infrequent	Frequent
Insulin resistance	No	Major factor

Pathophysiology

Polygenic “multifactorial”

Genetic susceptibility

- HLA class II molecules “DR3 & DR4” are associated strongly with IDDM.
- More than 90% of patients with type 1 diabetes express one or both molecules, compared to 50-60% in the general population.
- Patients expressing DR3 also risk of developing other autoimmune endocrinopathies , celiac disease, vitiligo, alopecia areata, pernicious anaemia and mucocutaneous candidiasis.

Genetic susceptibility

- The lifetime risk of developing T1DM is significantly increased in close relatives of a patient with T1DM:
- No family history: 0.4 %.
- Offspring of an affected mother: 1 - 4 %.
- Offspring of an affected father: 3 - 8 %.
- Offspring with both parents affected: as high as 30%.
- Non-twin sibling of affected patient: 3 - 6 %.
- Dizygotic twin: 8 %.
- Monozygotic twin: 30 %- 65%.

Environmental predisposing factors

- In genetically susceptible individuals, exposure to one or more environmental agents appears to trigger an immune response that ultimately causes destruction of the insulin-producing pancreatic beta cells.
- Identification of these factors should lead to a better understanding of the pathogenesis of the disease and help in developing strategies to prevent T1DM.
- No single factor has been identified; however, infections & diet are considered the commonest two environmental precipitating factors.

Environmental predisposing factors

- Viral infections particularly respiratory or enterovirus infections including, mumps, rubella, Coxsackie B4.
- Nutritional factors e.g. cow's milk bottle feeding in infancy (especially first 6 months of life).
- Recent evidence suggests the role of vitamin D deficiency in the pathogenesis & prevention of diabetes.
- ? Toxic chemicals (food preservatives & colouring agents).
- Recently, large for gestational age at birth may increase the risk for T1DM (unknown why?).
- Babies born by caesarean section at higher risk to develop type 1 diabetes later life than those born with vaginal delivery.
- ? Seasonal variation has been suggested in some studies, with a higher reported incidence of T1DM in colder as compared with warmer months, particularly in children.

Symptoms

- The main symptoms of hyperglycaemia are secondary to glucosuria which leads to osmotic diuresis with increased urinary frequency & volume (polyuria), nocturia & nocturnal enuresis in a previously dry child.
- Increased thirst (Polydipsia) , which is secondary to the osmotic diuresis causing dehydration.
- Some children report general malaise, headache, weakness, irritable & become bad-tempered.
- Failure to gain weight & unexplained weight loss may be the first symptoms.
- Candidiasis may develop, especially in mouth, groin & flexural areas.

- Hyperglycaemia impairs immunity & renders a child to be more susceptible to recurrent infection, particularly urinary tract, skin, and respiratory tract.
- Symptoms of diabetes ketoacidosis:
  - In addition to polyuria, polydipsia and weight loss, there could be of the following:
  - Nausea, vomiting & abdominal pain.
  - Rapid and shallow breathing “Kussmaul”.
  - Dehydration (moderate to severe).
  - Smell of acetone.
  - Change of consciousness (sleepy, drowsy, hallucinations, semi-coma or rarely coma).

DIABETES SYMPTOMS

Blurry Eyesight

Feeling Hungry

Sudden Weight Loss

Feeling Thirsty

Frequent Urination

Physical examination

- Apart from wasting & mild dehydration, children with diabetes usually have no specific clinical findings.
- Examination should include the following:
  - Vital signs including measuring blood pressure (supine &erect).
  - Growth assessment (by plotting weight & height on growth chart.
  - General look (signs of dehydration, consciousness, looking well or unwell, or ill, oriented or not).
  - Check for acetone breath.
  - Inspecting and palpating injection site examination.
  - Examination of peripheral pulses.
  - Looking for limited joint mobility.
  - CNS examination for peripheral neuropathy & tendon reflexes.
  - Look for signs of associated diseases (goitre, hyperpigmentation...etc).

Investigations

- Investigations to confirm diabetes initially include:
  - Fasting & 2 hours post prandial glucose.
  - Haemoglobin A1c.
  - Urinalysis (glucosuria & ketonuria).
  - Venous blood gas (if DKA is suspected).
  - Serum urea, creatinine and electrolytes.
  - C- peptide & insulin (if type 2 is suspected in an obese child).
  - Autoantibodies screening (if type 2 or MODY is suspected) including:
    - Autoantibodies (ICA) Insulin Autoantibodies (IAA) Glutamic Acid Decarboxylase Autoantibodies (GADA) GAD65 Autoantibodies Insulinoma-Associated-2 Autoantibodies (IA-2A) Zinc Transporter-8 Autoantibodies (ZnT8A)

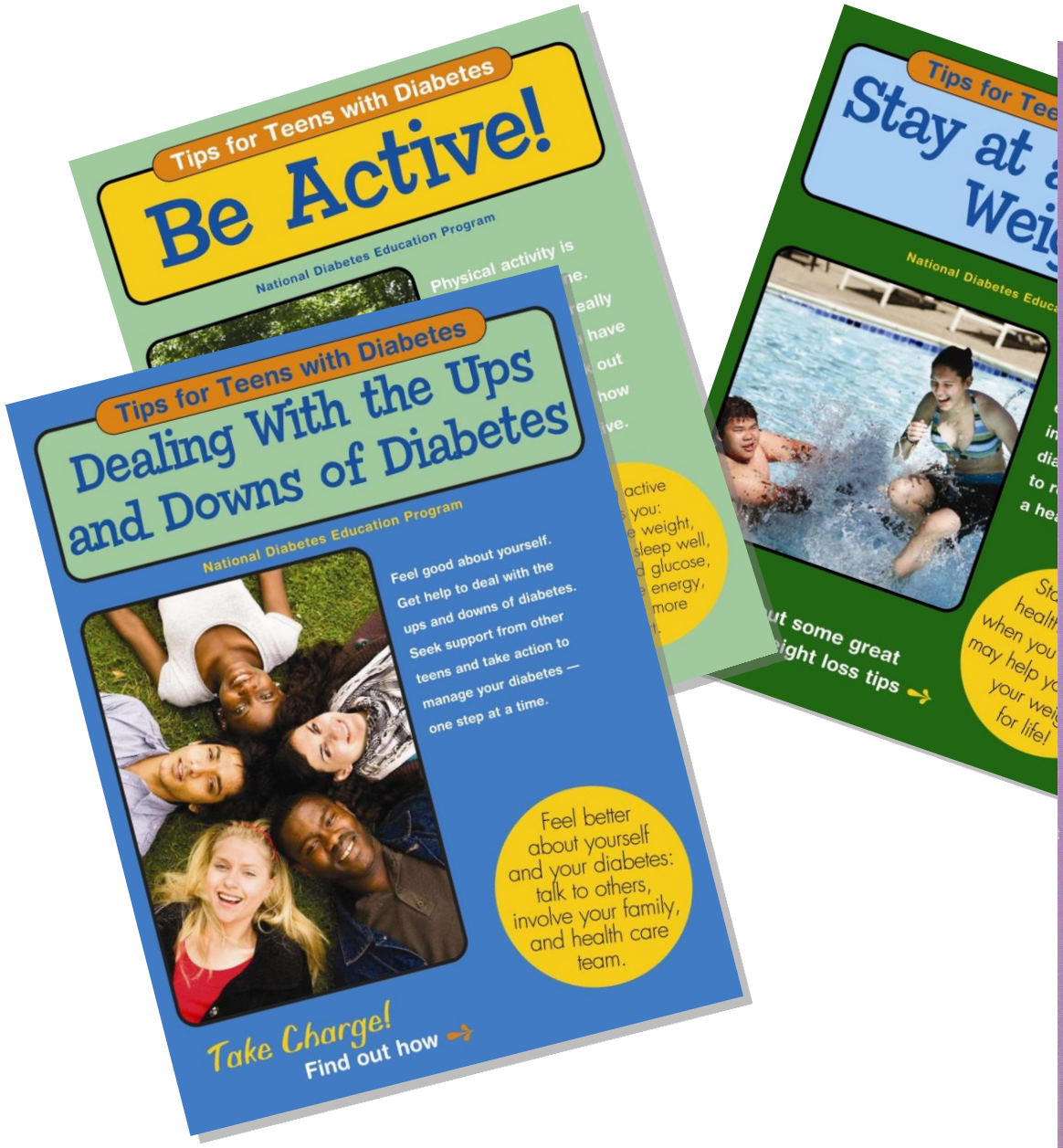
Investigations

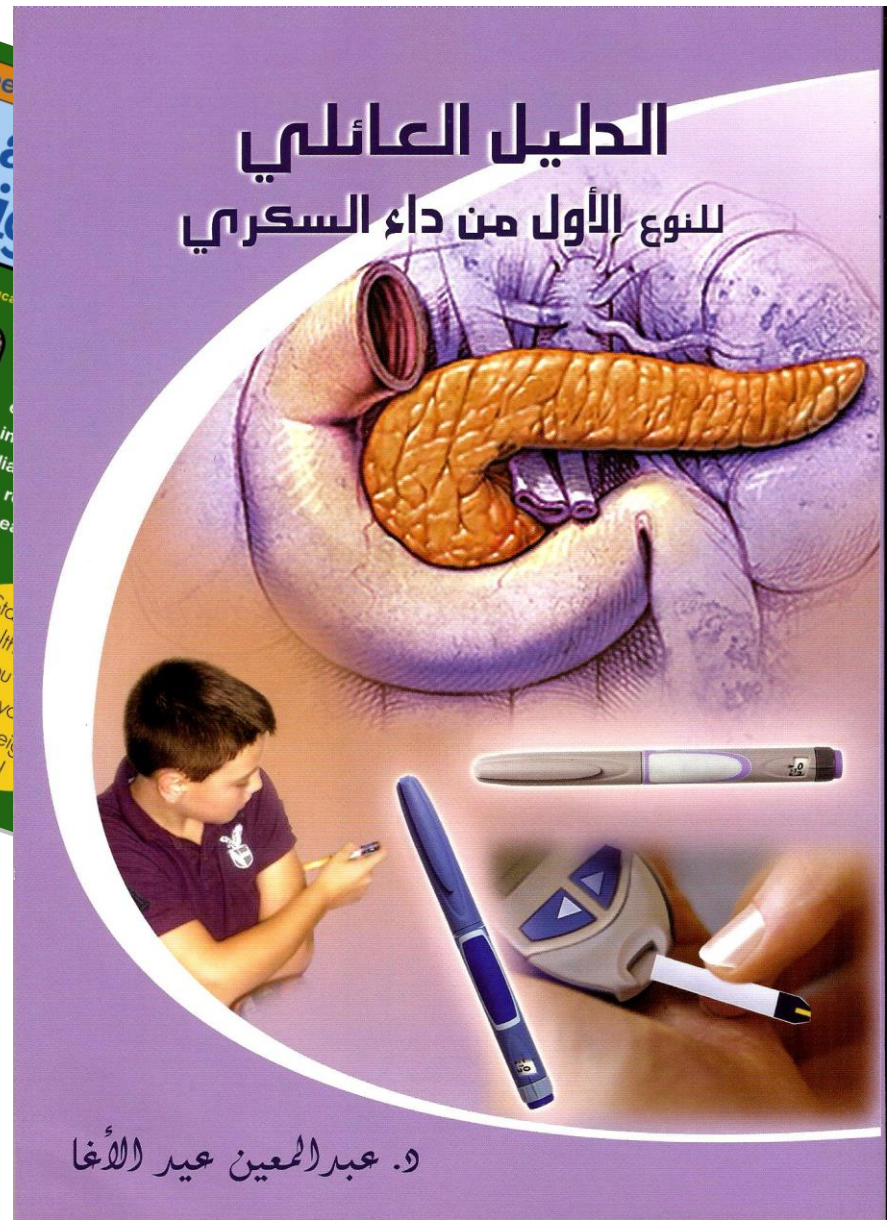
- Investigations to screen for associated diseases:
  - Thyroid function tests & thyroid antithyroid antibodies.
  - Celiac screening (IGA- anti tissue transglutaminase).
- Follow-up investigations include:
  - Glycosylated haemoglobin (HbA1c).
    - strong correlation exists between average blood-glucose concentrations
      over 3 months period.
    - The Diabetes Control and Complications Trial (DCCT) has demonstrated that children's with HbA1c levels around 7-7.5 % had the best outcomes relative to long-term complications.
    - values > 9% carry an increased risk of long-term complications.
  - Renal function tests (annually).
  - liver function test (annually).
  - Lipid profile test (annually).
  - Urine microalbuminuria and fundal examination at puberty or 3-5 years of diagnosis if child is pubertal.

Management pillars of Type 1 DM

- Education the child / caregivers fully.
- Insulin therapy.
- Healthy diet.
- Exercise.
- Home glucose monitoring (SMBG / CGMS).
- Behavioral / psychological supports.
- Screening for associated autoimmune diseases.
- Screening for complications.

Patient education has essential role in diabetes management

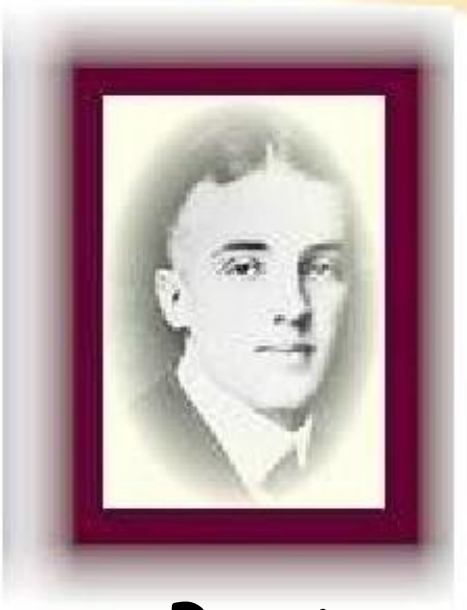




Discovery of Insulin

1922

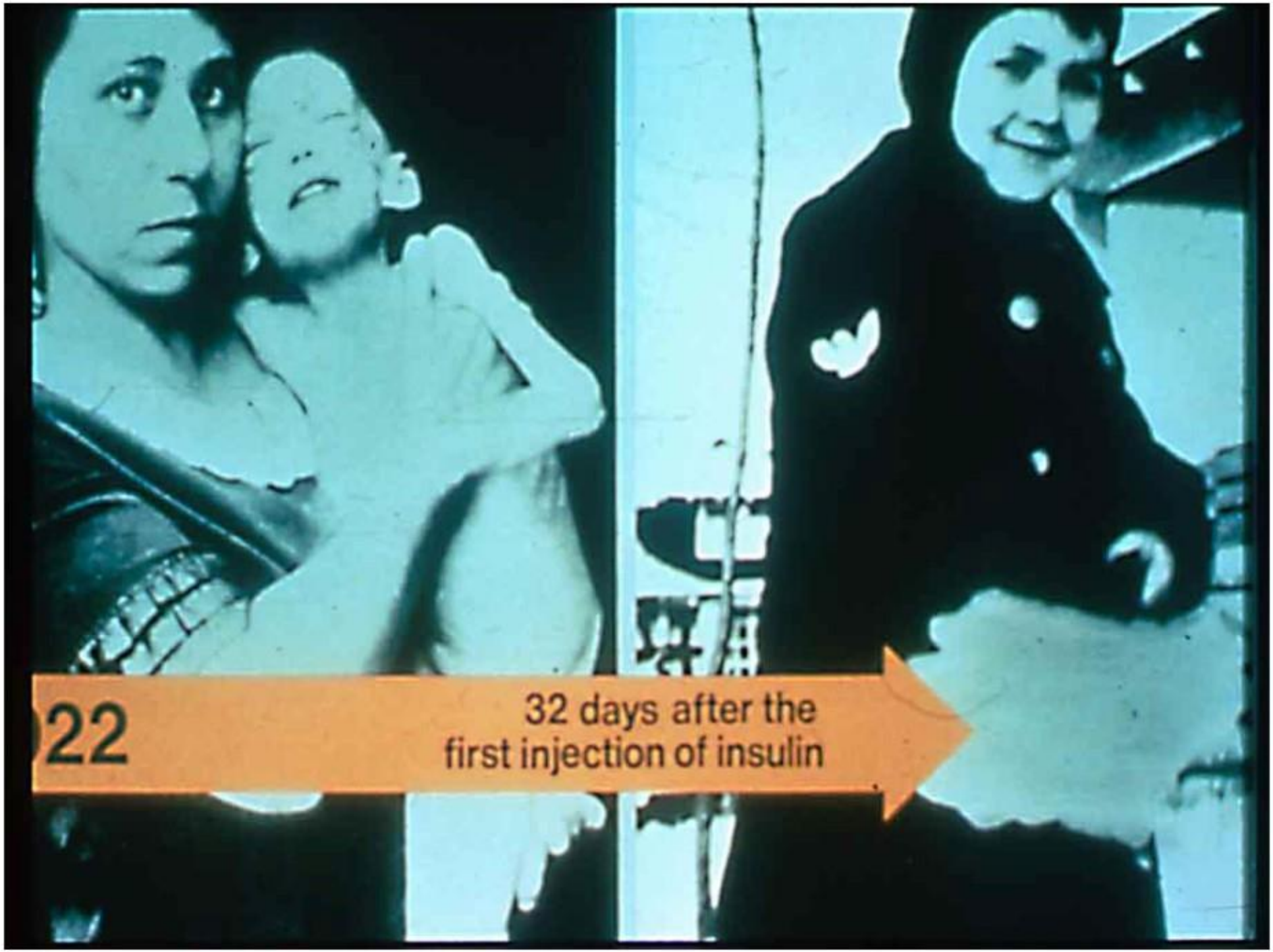
Banting



Best

Insulin was the first discovered (late 1920's) which won the doctor and medical student who discovered it the Nobel Prize (Banting and Best)

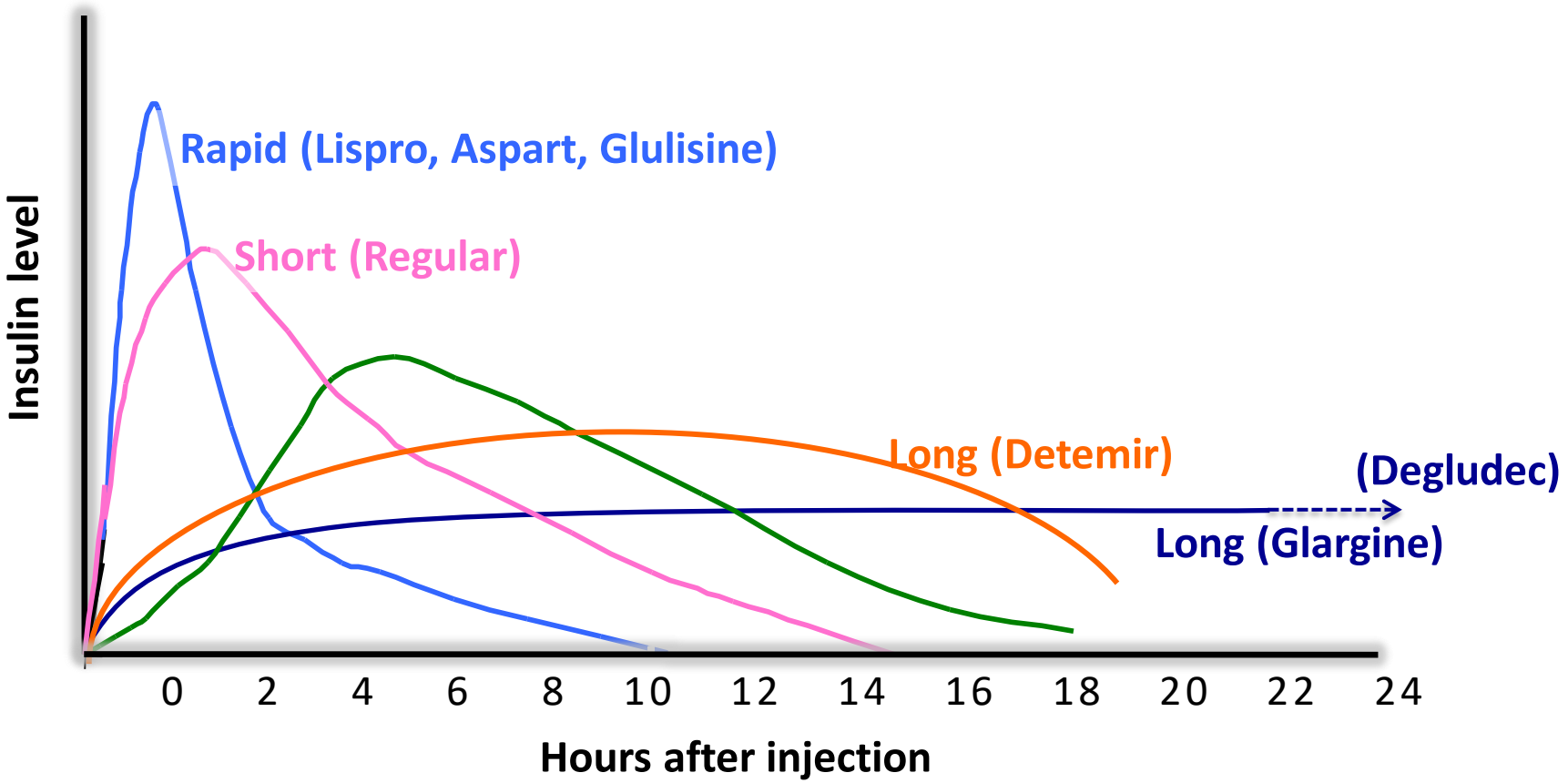
Banting & Best


22
32 days after the
first injection of insulin

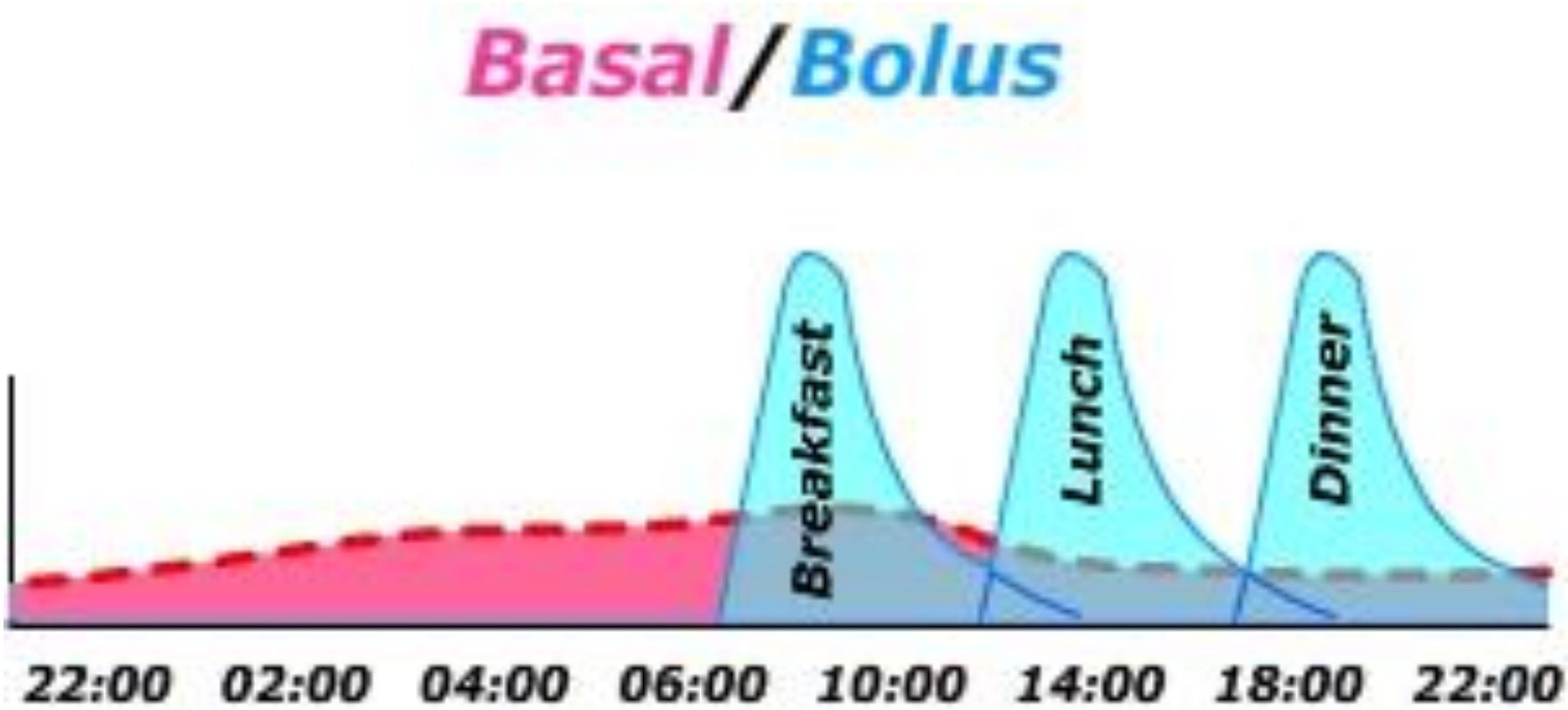
Types of Insulin

Category	Type	Onset	Peak	Duration
Ultrafast	Fiasp	5-15 min.	1-2 hours.	2-3 hours.
Rapid – acting	Lispro, Aspart, Glulisine	15-30 min.	1-2 hours.	3-4 hours.
Short - acting	Regular	30-60 min.	2-4 hours.	5-8 hours.
Intermediate	NPH, Humulin N	2-4 hours.	4-6 hours.	8-12 hours.
Long –acting analog	Glargine	2-4 hours.	Peak less.	18-24 hours.
Long –acting analog	Glargine 300	2-6 hours.	Peak less.	30-36 hours.
Long –acting analog	Degludec	0.5- 1.5 hours.	Peak less.	Up to 42 hours.

Various types of insulin preparations



Basal – Bolus Insulin Regimen



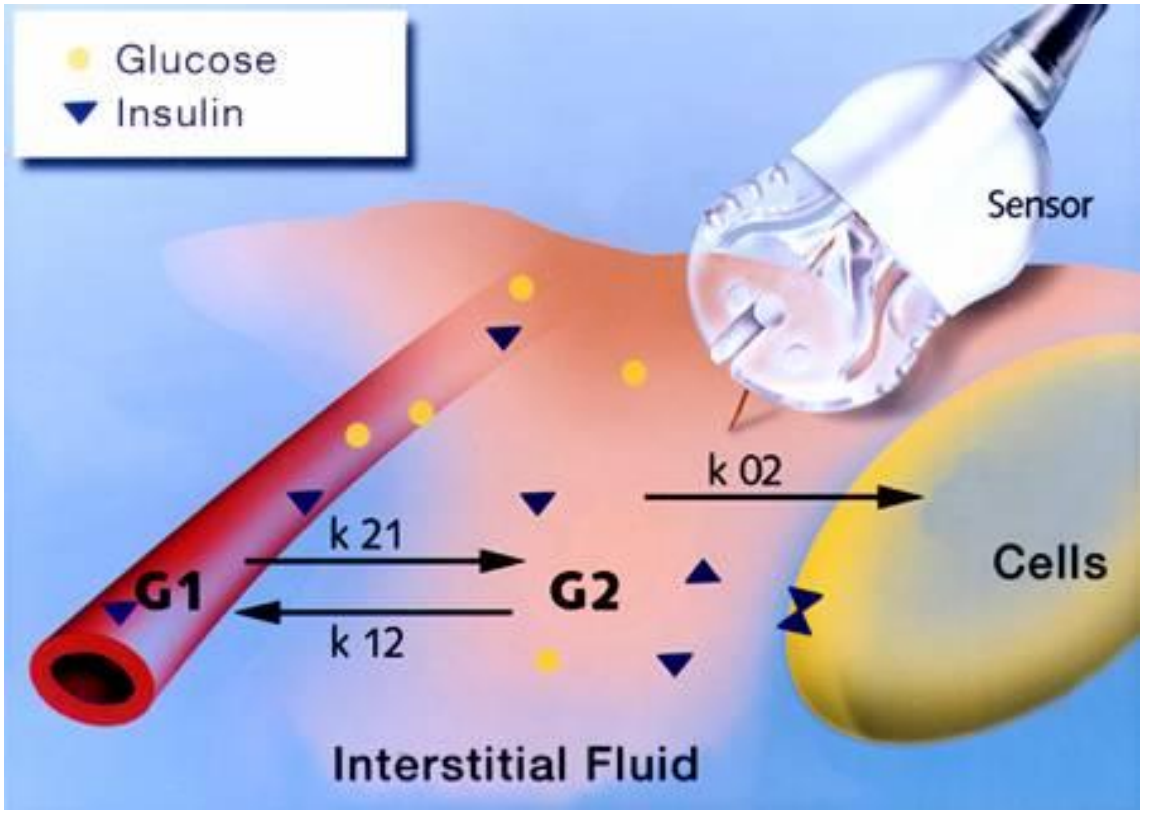
Self-monitoring of blood glucose levels (Invasive monitoring)

- Is essential component of treatment of type 1 diabetes in children.
- All children and adolescents with type 1 diabetes should have blood glucose levels monitored multiple times daily (up to 6–10 times/day), including:
  - pre-meals.
  - pre-bedtime.
  - as needed for safety in specific situations such as exercise, driving, illness, or the presence of symptoms of hypoglycemia.
- Is necessary for determination of insulin doses (e.g., mealtime), assessment of safety (e.g., corrective dose for or prevention of hyperglycemia), and longer-term adjustment in insulin dosing regimens based on blood glucose patterns and trends.

Continuous glucose monitoring (Non-invasive monitoring)

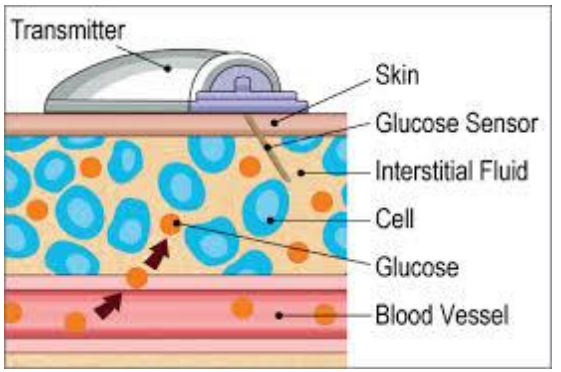
- Should be considered in all children & adolescents with type 1 diabetes, whether using injections or insulin pump therapy, as an additional tool to help improve glycemic control.
- Considered to be one of good methods for home glucose monitoring.

Interstitial Fluid Glucose Measurement



Interstitial fluid glucose (G2) is almost always comparable with blood glucose (G1)

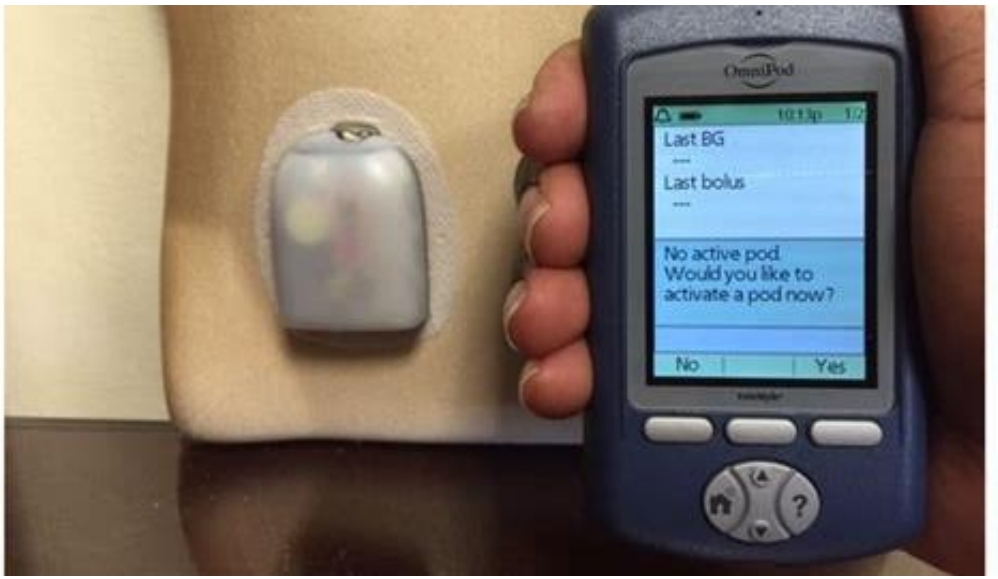
Availability of various CGMS



Insulin Pump

- Insulin pump therapy is considered the most nearly physiological type of treatment.
- Consists of continuous administration of insulin for the patient's basal requirement with additional boluses for mealtimes or for the correction of elevated glucose values.
- Insulin pump studies that incorporate continuous glucose monitoring (CGM) devices used continuously demonstrate significant improvement in both glycemic control and hypoglycemia with best glycemic control.

Various insulin pumps available



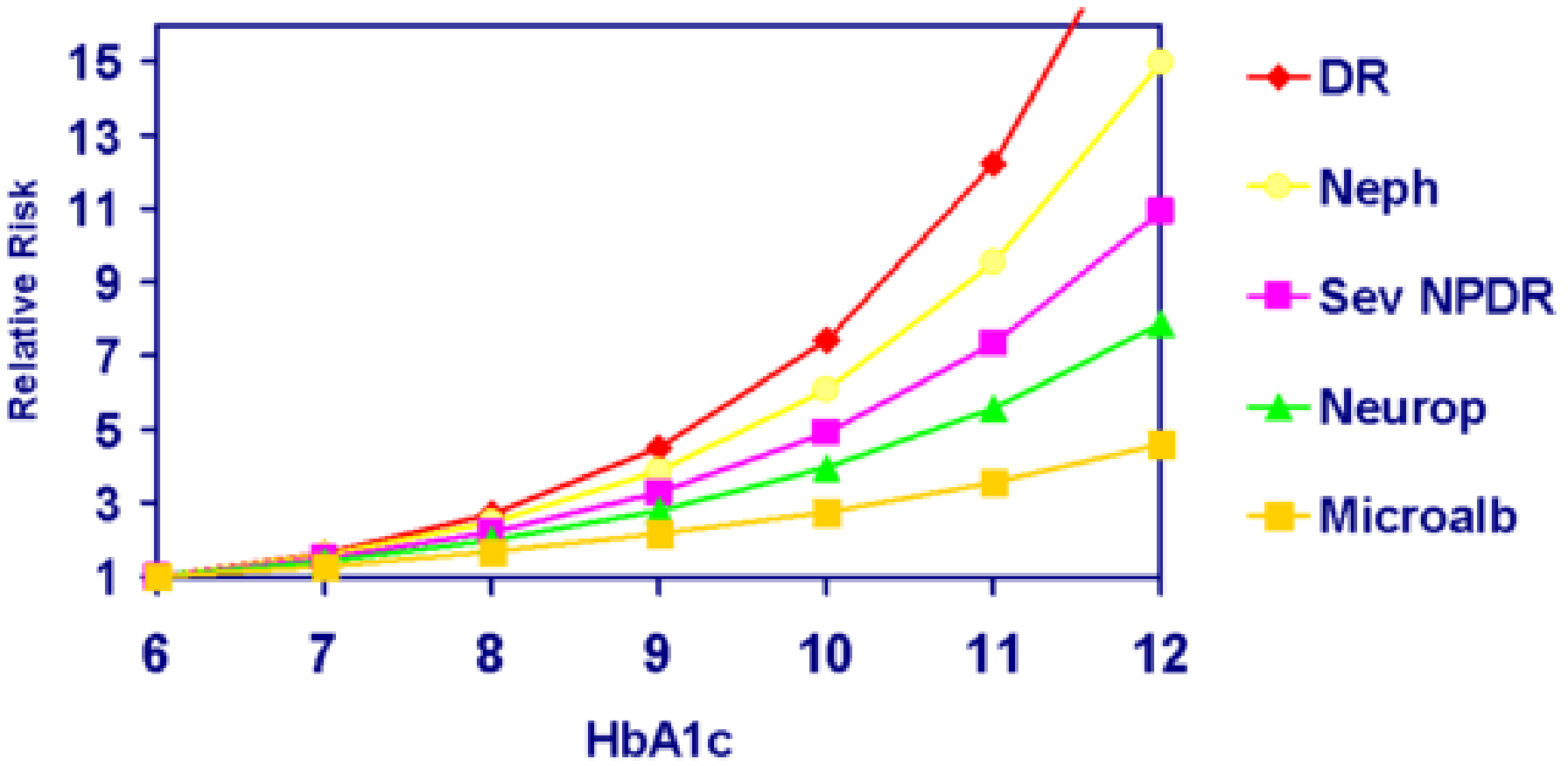
Indications for insulin pump therapy

- Neonates, infants, and preschool children.
- Dawn phenomenon (marked rise in blood sugar in the early morning hours).
- Severe, recurrent, and nocturnal episodes of hypoglycaemia.
- Poorly controlled diabetes.
- Brittle diabetes.
- Impaired quality of life under current modality of insulin therapy.
- Fear of needles
- Athletes.

Diabetic Complications (Not for any one Only for those with persistent high HbA1c !!)

- Retinopathy
- Cataracts
- Hypertension
- Progressive renal failure
- Early coronary artery disease
- Peripheral vascular disease
- Neuropathy, both peripheral and autonomic
- Increased risk of infection

DCCT: Relative Risk of Progression of Diabetic Complications by Mean HbA1c



Skyler JS: Endocrin Metab Clin N Am 1996; 25:243-254

Associated autoimmune diseases

- Autoimmune thyroid disease occurs in 15 - 30% of individuals with type 1 diabetes.
- Addison's disease is rare, even in those with type 1 diabetes.
- Celiac disease occurs in 4 - 9% of children with type 1 diabetes (60 - 70% of these children, the disease is asymptomatic).

Conclusions

- The incidence of type 1 diabetes mellitus in childhood & adolescence is steadily rising worldwide.
- Polydipsia, polyuria, and weight loss are the most common presenting symptoms of diabetes mellitus.
- Type 1 diabetes is the commonest type in 90% of affected children, however type 2 diabetes is increasingly happened in children owing to increased rate of obesity.
- Insulin therapy is given by subcutaneous injection or by needle or by insulin pump.
- The goals of treatment in children are the near-normalization of glucose metabolism and keeping HbA1c <7.5%.

Conclusions

- Diabetes control is essential in order to avoid short- and long-term complications including:
  - Short-term complications: hypoglycaemia & ketoacidosis.
  - Long-term complications: Retinopathy, nephropathy, neuropathy, hypertension, and hyperlipidaemia.


Wishing you
Best Success