

Diabetes Mellitus



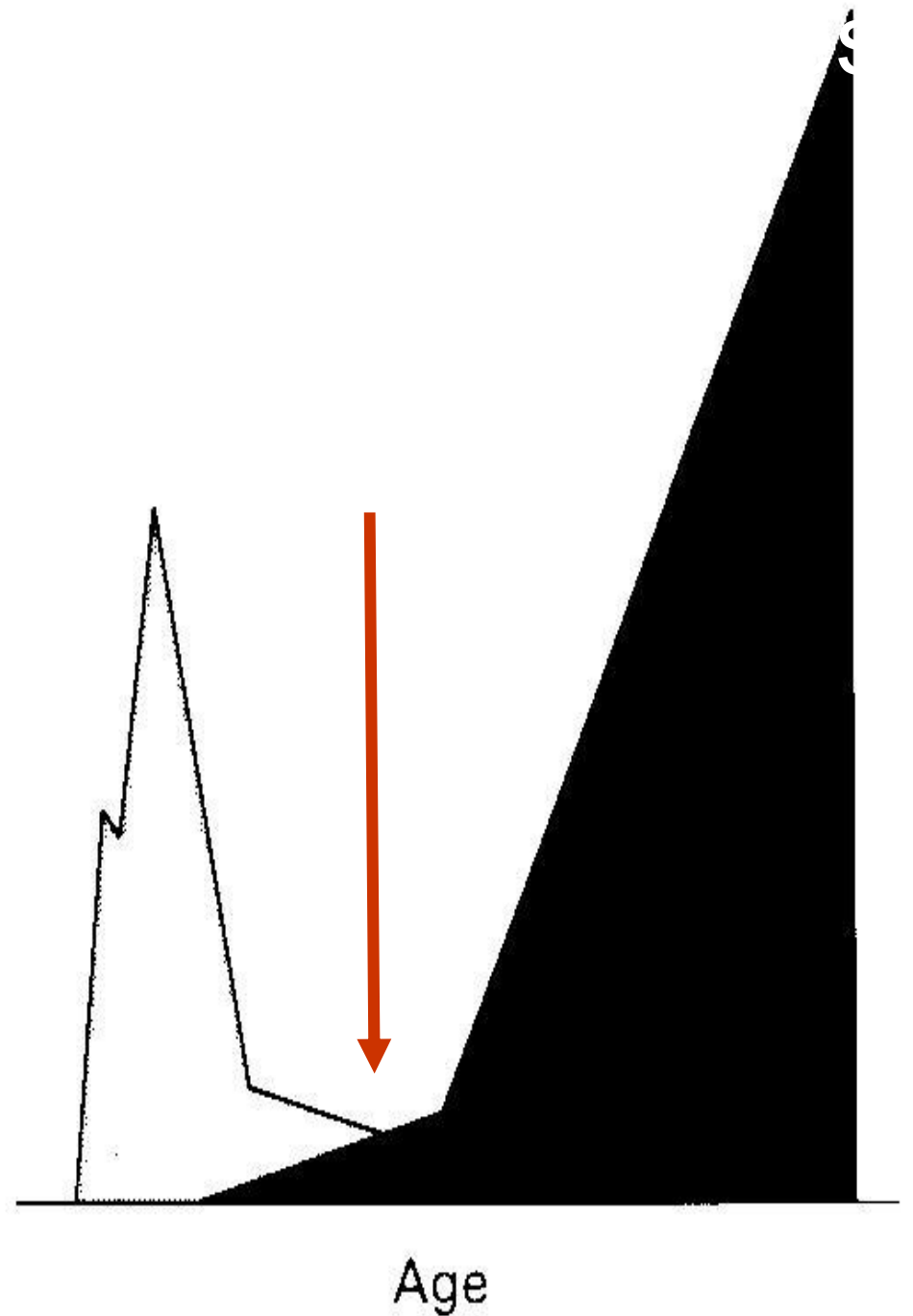
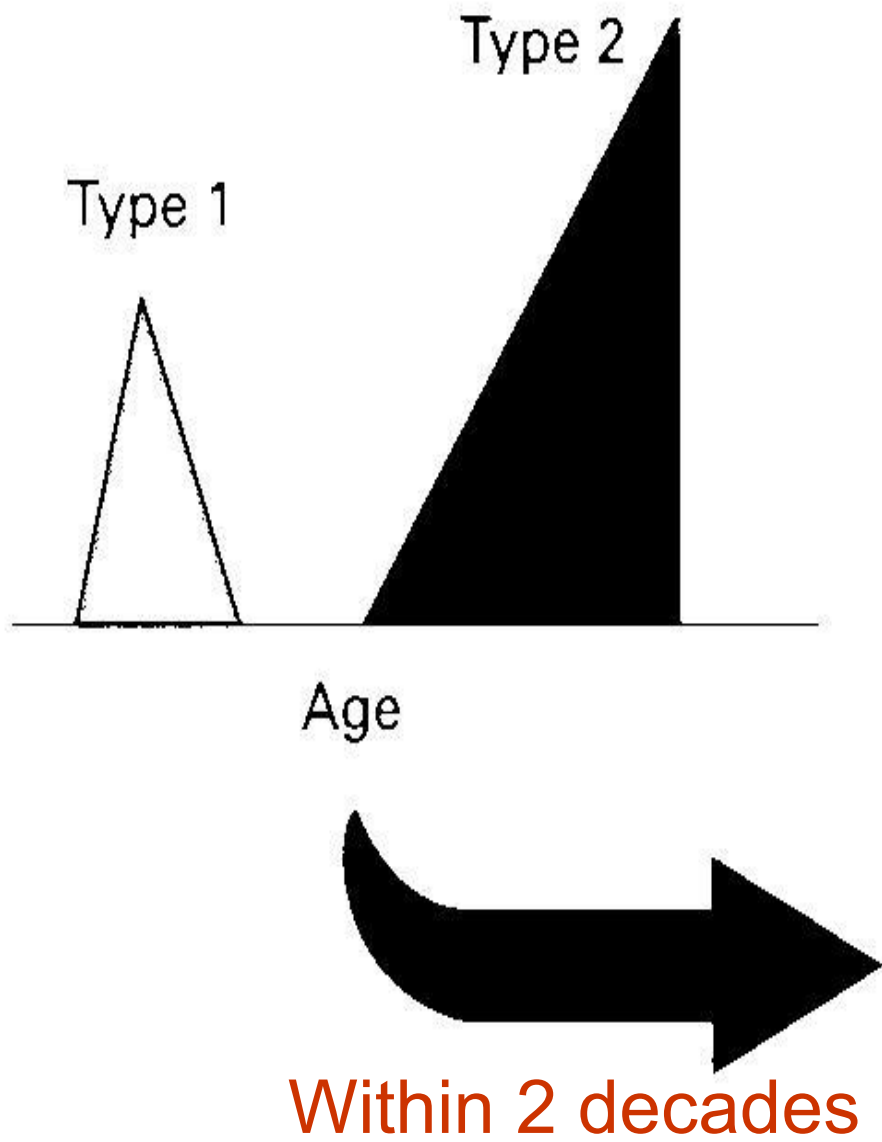
Background

- Diabetes mellitus (DM) is chronic metabolic disorder caused by absolute or relative deficiency of insulin
- Insulin is produced by β cells of islets of Langerhans located in the pancreas, and the absence, destruction, or other loss of these cells results in type 1 diabetes (insulin-dependent diabetes mellitus IDDM)
- Most children with diabetes have IDDM and a lifetime dependence on exogenous insulin
- IDDM occurs most commonly in children & adolescents but can occur in adults, in their late 30s and early 40s “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 20% of new patients with DM in childhood & adolescence have NIDDM, a change associated with increased rates of obesity
- Other patients may have inherited disorders of insulin release leading to maturity onset diabetes of the young (MODY)

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

Criteria for the Diagnosis of Diabetes

- Symptoms of diabetes plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l)
 - The classic symptoms of diabetes include:
 - polyuria, polydipsia, and unexplained weight loss
- Fasting glucose ≥ 126 mg/dl (7.0 mmol/l)
 - Fasting is defined as no caloric intake for at least 8 h.
- 2-h PG ≥ 200 mg/dl (11.1 mmol/l) during OGTT
 - The test should be performed as described by WHO using a glucose load containing equivalent of 75-g anhydrous glucose dissolved in water
- Hemoglobin A1c $\geq 6.5\%$



Pathophysiology

“Polygenic disorder”

Genetic issues:

- Clear evidence exists for a genetic component to IDDM
- Monozygotic twins have 60% lifetime concordance for developing IDDM
- Dizygotic twins have an 8% risk of concordance, which is similar to the risk among other siblings
- The frequency of diabetes developing in children with a diabetic mother is 2-3% and 5-6% if the father has IDDM
- The risk to children rises to almost 30% if both parents are diabetic

- HLA class II molecules DR3 & DR4 are associated strongly with IDDM
- More than 90% of whites with IDDM express 1 or both of these molecules, compared to 50-60% in the general population
- Patients expressing DR3 also risk developing other autoimmune endocrinopathies & celiac disease
- These patients are more likely to develop diabetes at a later age, to have positive islet cell antibodies, and to appear to have a longer period of residual islet cell function

HLA – CLASS II antigens

- DR – antigens DR 3 & DR 4
- DQ – antigens stronger > DR – antigens
 - DQ 2 & DQ 8
 - DQB 1 Alleles * 02 / 0302
- DP - antigens

Environmental factors:

- Environmental factors are important because even identical twins have only 60% concordance for IDDM
- No single factor has been identified, but infections & diet are considered the 2 most likely environmental candidates
 - Viral infections e.g., mumps, rubella, Coxsackie B4
 - Nutritional factors e.g. cow's milk in infancy
 - Recent evidence suggests role for vitamin D deficiency in pathogenesis & prevention of DM
 - ? Toxic chemicals e.g. food preservatives

- Currently, autoimmunity is considered the major factor in pathogenesis of type 1 DM
- Approximately 85% of patients have circulating islet cell antibodies (ICA) & insulin autoantibodies (IAA)
- Most islet cell antibodies are directed against glutamic acid decarboxylase (GAD) & other auto-antigens within β -cells (IA2)

Other causes:

- Congenital absence of the pancreas or islet cells
- Post pancreatectomy
- IDDM secondary to pancreatic damage (i.e., cystic fibrosis, chronic pancreatitis, Thalassemia major, hemochromatosis, hemolytic uraemic syndrome)
- Wolfram syndrome (diabetes insipidus, DM, optic atrophy, deafness (DIDMOAD))
- Chromosomal disorders such as Down syndrome, Turner syndrome, Klinefelter syndrome, or Prader-Willi syndrome

History:

- The main symptoms of hyperglycemia are secondary to osmotic diuresis & Glucosuria which leads to increased urinary frequency & volume (polyurea), nocturia & leads to enuresis in a previously dry child
- Polydypsea: Increased thirst, which is secondary to the osmotic diuresis causing dehydration
- Some children report general malaise, headache, weakness, irritable & become bad-tempered
- Weight loss: Insulin deficiency leads to uninhibited gluconeogenesis, causing breakdown of protein and fat
- Weight loss may be dramatic, even though the child's appetite usually remains good
- Failure to thrive and wasting may be the first symptoms noted in an infant or toddler & may precede frank hyperglycemia

- Symptoms of ketoacidosis

- Severe dehydration
- Smell of Acetone
- Acidotic breathing (Kussmaul respiration)
- Abdominal pain
- Vomiting
- Drowsiness & coma

- Other nonspecific symptoms

- Hyperglycemia impairs immunity & renders a child more susceptible to recurrent infection, particularly of the urinary tract, skin, and respiratory tract
- Candidiasis may develop, especially in mouth, groin and flexural areas

Physical examination

- Apart from wasting & mild dehydration, children with early diabetes have no specific clinical findings
- Examination and review should include the following:
 - Growth assessment
 - Injection site examination
 - Fundoscopy or other retinal screening such as photography
 - Examination of hands, feet & peripheral pulses for signs of limited joint mobility, peripheral neuropathy, and tendon reflexes
 - Evaluation for signs of associated autoimmune disease
 - Blood pressure
 - Urine examination for microalbuminuria

Lab Studies:

- Blood glucose
- Urine glucose
- Urine ketone
- Glycosylated hemoglobin (HbA1c)
 - A strong correlation exists between average blood-glucose concentrations over 3 months period
 - The Diabetes Control and Complications Trial (DCCT) has demonstrated that patients with HbA1c levels around 7% had the best outcomes relative to long-term complications
 - values > 9% carry an increased risk of long-term complications
- Renal function tests
- Thyroid function tests & antithyroid antibodies
- Celiac antibodies
- Lipid profile
- Urinary microalbuminuria
- Liver function test

Management

➤ Education

➤ Insulin therapy

- human insulin Vs insulin analogues
- 2 - 4 injections / day (depending on age, social and intellectual status)

➤ Blood glucose monitoring

- minimum 4 / day and to keep logbook record

➤ Food planning

➤ Exercise

➤ Psychological support

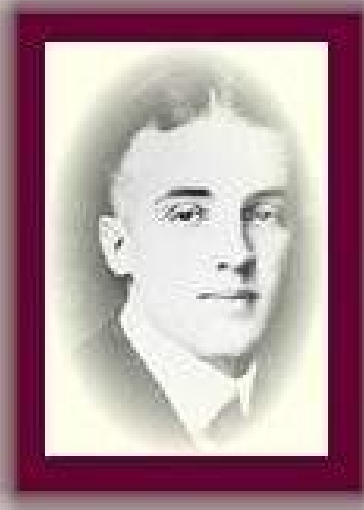


Discovery of Insulin

1920



Banting



Best

Insulin was first discovered (late 1920's) by 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

Insulin Types

Many formulations of insulin are available:

Short-acting insulin

- Actrapid , Humulin R

Rapid-acting insulin analog

- Lispro, Aspart, Glulisine

Intermediate-acting insulin

- Protaphane, Humulin N, Lente

Long-acting insulin

- Ultratard, Ultralente

Basal insulin analog

- Glargine , Detemir

Insulin Type	Action Begins	Peak	Duration
Humalog	5-15 minutes	1 hour	2-4 hours
Regular	30 - 60 minutes	2-4 hours	6-8 hours
NPH	1-2 hours	4-8 hours	12-18 hrs
Lente	1-2 hours	8-12 hours	20-24 hours
UltraLente	1-2 hours	9-15 hours	24hours
Levimer	2-4 hours	No peak	12-18 hours ?? 24 hours
Lantus	2 hours	No peak	24hours

- Pre-mixed insulin are popular for twice daily regimens
- Although they reduce potential errors in drawing up insulin, they lack the flexibility offered by separate adjustment of the two types (R & NPH)
- Such flexibility is especially useful for children with variable food intake and glucose control is not as good on these insulin comparing to other types

Insulin Therapy

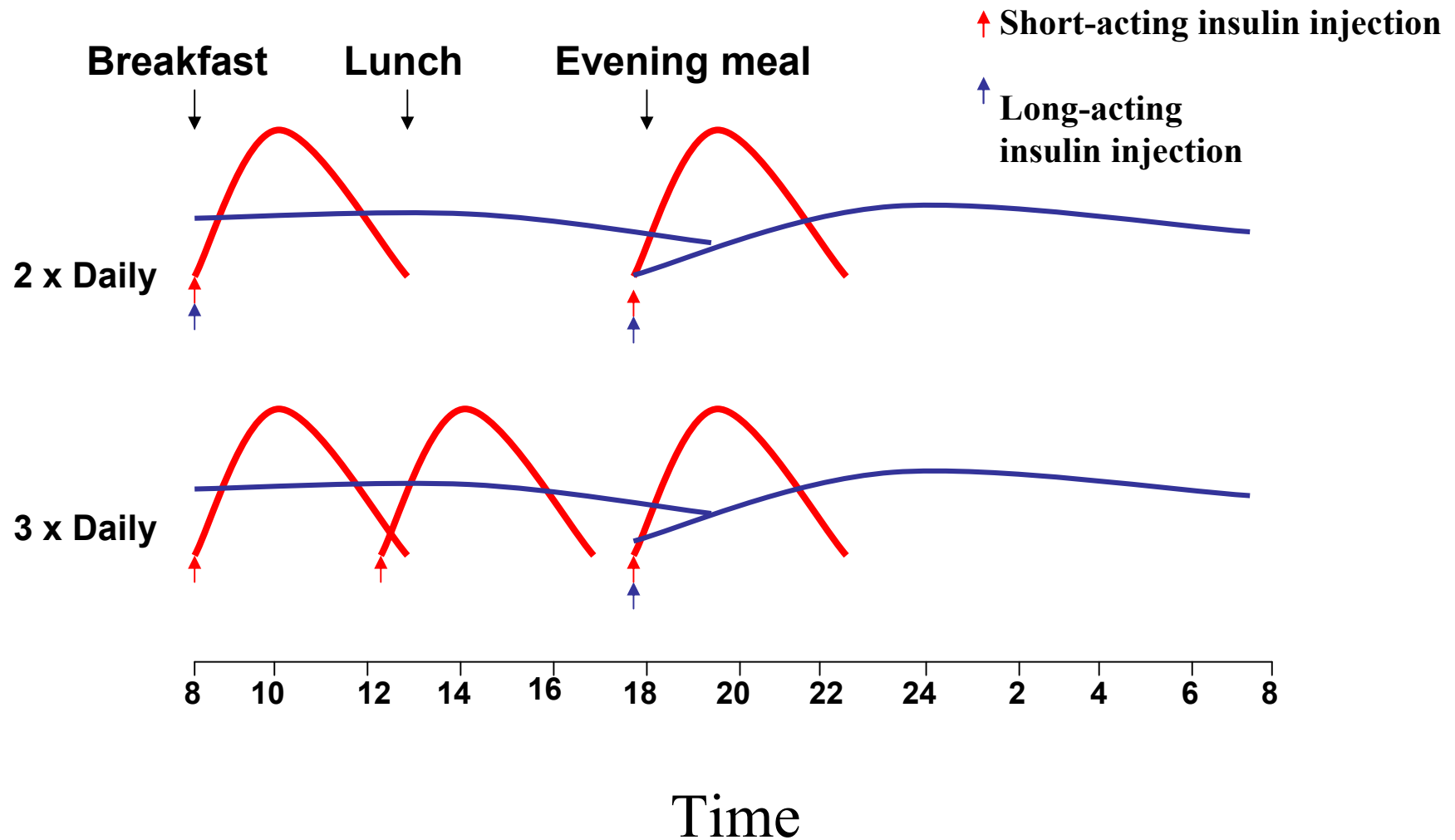
- Two main methods
 - Conventional therapy
 - BD insulin injections
 - Intensive therapy
 - More than 2 injections /day
 - Multiple daily injections (basal – bolus regimen)
 - Insulin Pump Therapy

Insulin regimens

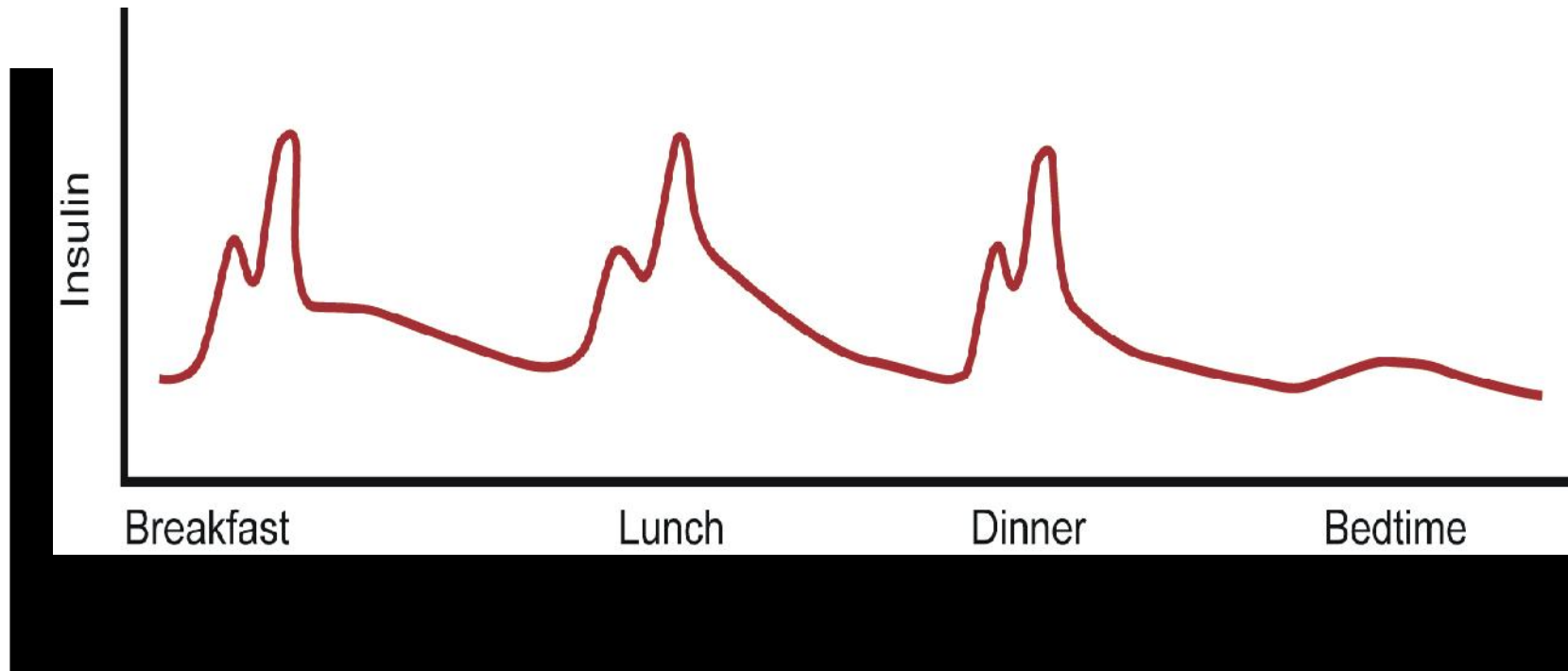
Frequently used regimens

- Two injections daily
 - mixture of short and intermediate-acting insulin (before breakfast and before evening meal)
- Three injections daily
 - using a mixture of short and intermediate acting insulin before breakfast & dinner
 - short-acting insulin alone before Lunch
- Basal-bolus regimen
 - short-acting insulin 20–30 min before main meals
 - intermediate or long-acting insulin at bedtime
- Insulin pump

Typical insulin injection profiles



Normal secretion of insulin



Target BG Ranges

Target ranges:

- Pre-prandial: 80 - 120 mg/dl
- 2 hr post-prandial: < 180 mg/dl
- Bedtime: 100 - 140 mg/dl

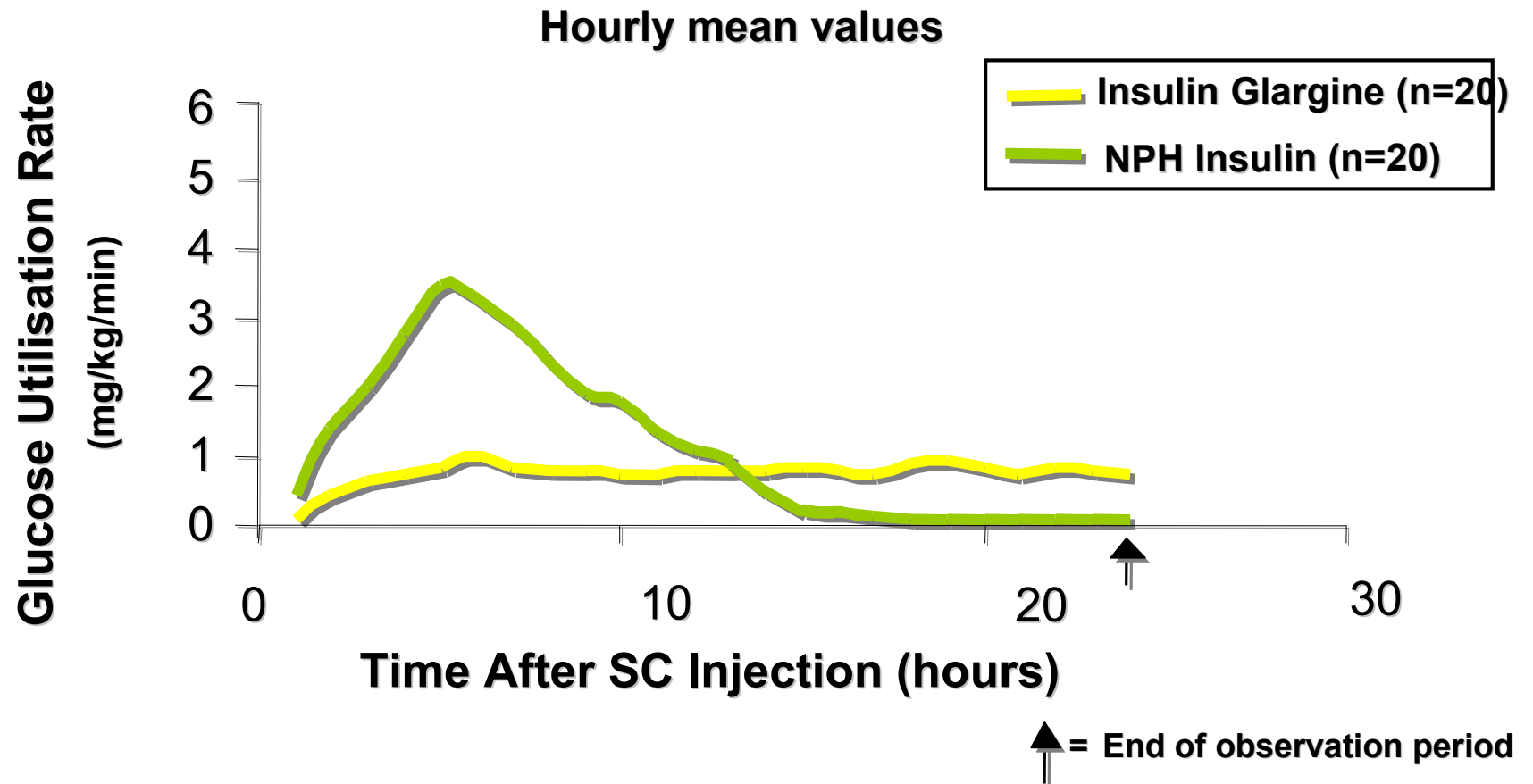
Rapid – acting insulin analogue

- There are now three 'rapid-acting' insulin analogues commercially available:
 - insulin lispro (Humalog)
 - insulin aspart (Novorapid)
 - insulin glulisine (Apidra)
- Advantages:
 - Rapid acting analogues can be given immediately before meals because of rapid onset
 - Reduces postprandial hyperglycemia & nocturnal hypoglycemia
 - In addition, they offer the useful option of being given after food to toddlers who reluctant to eat

Long – acting insulin analogue

- Two basal analogues are currently available:
 - Insulin detemir (Levimer)
 - Insulin glargine (Lantus)
- Both of them have not been approved for children below the age of 6 years
- Long acting insulin analogues show more predictable insulin effect with less day to day variation, compared to NPH insulin
- Both of them have advantages of being peakless insulin, thus reduced risk of hypoglycemia & no need for snacks

Peakless Profile



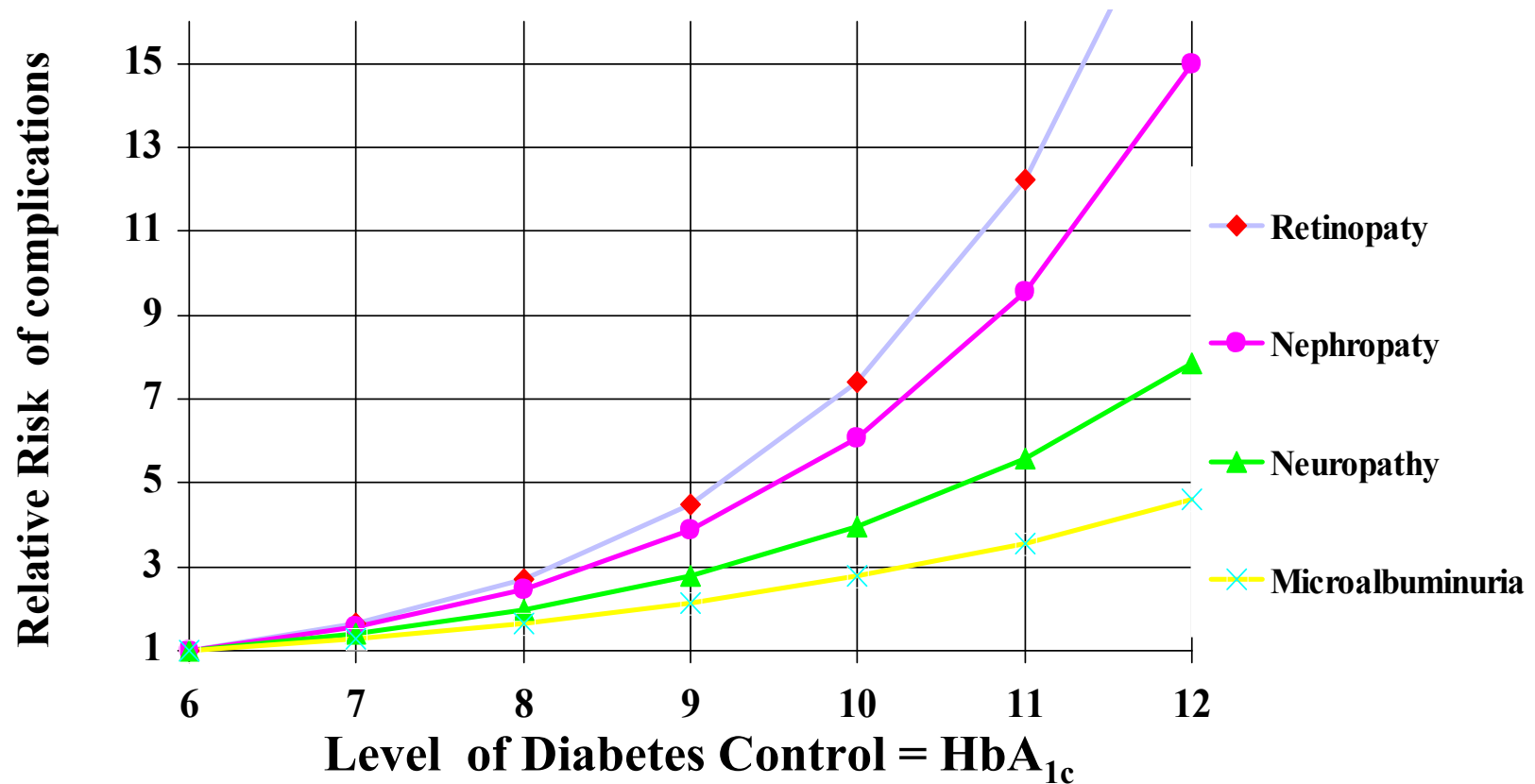
Advantages of intensive insulin therapy

- Gain of 15.3 years of complication free living compared to conventional therapy

Disadvantages of intensive insulin therapy

- Hypoglycemia
 - Peaked profiles result in uncontrolled glycaemic excursions
- Injection issues
 - Variability of absorption from different sites of injection
 - Patients' fear of multiple injections
- Weight gain

Relative Risk of Progression of Diabetes Complications by Mean HbA_{1c}: based on DCCT Data



Guideline on dosage

- During the partial remission phase the daily insulin dose is often <0.5 IU/kg per day
- Prepubertal children (outside the partial remission phase) usually require 0.7–1.0 IU/kg per day
- During puberty, requirements may rise substantially above 1(1–1.5) IU/kg per day

Dawn phenomenon

- Blood glucose levels tend to rise in the hours of the morning (usually after 5.00 am) prior to waking
- In non-diabetic individuals the mechanisms include increased nocturnal growth hormone secretion, increased resistance to insulin action and increased hepatic glucose production. These mechanisms are more potent in puberty
- Treatment by increasing night intermediated insulin dose

Somogyi rebound phenomenon

- Somogyi speculated (1930s) that hypoglycemia induced by insulin could cause a counter-regulatory hormone response that produces hyperglycemia
- Unappreciated nocturnal hypoglycemia could lead to morning hyperglycemia
- Treatment by increasing night intermediated insulin dose

“Honey - Moon phase”

- Transient partial remission of the pancreas
- Occurs in 60% of type 1 DM
- As early as 1-2 weeks of starting insulin therapy
- HbA1C returns back to normal levels (< 6%)
- 99% requires insulin therapy again
- Can lasts for months – one year

Diabetic Complications

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

Diabetic Retinopathy



Diabetic nephropathy

- Microalbuminuria is state of sub clinical increase in AER higher than normal but below the level of overt Proteinuria
- Causes increased morbidity and mortality
- Defined as AER > 200 mcg / min or 300 mg/d in patients with out other non - diabetic renal disease or UTI, or cardiac failure
- Microalbuminuria is an early predictor of diabetic nephropathy as well as retinopathy

Insulin pump



Insulin Pump Therapy

- Continuous insulin delivery over 24 hr
- Mimics physiological insulin production
- Improves glucose control
- Reduces incidence of hypoglycaemia
- Normalisation of lifestyle
- No insulin injections
- Flexible insulin adjustment
- Almost normal life style

How does it work

- By delivering 3 modes of insulin:
 - 1) Basal insulin through 24 hours
 - ❖ Pumping insulin according to patient's life style
 - 2) Bolus food insulin
 - ❖ Pumping insulin according to carbohydrate-to-insulin ratio
 - 3) Correction Bolus
 - ❖ Pumping insulin for correction of high glucose readings according to correction factor programmed

Type 2 Diabetes in Children

Clinical presentation

- Children with type 2 diabetes are usually diagnosed over the age of 10 years and are in middle to late puberty
- Milder symptoms than type 1 with mild polydypsea, polyurea, little or no weight loss
- Glucosuria with /without ketonuria
- Up to 33% have ketonuria at diagnosis
- 5–25% of patients who are subsequently classified as having type II diabetes have ketoacidosis at presentation

- Associated problems with type 2 DM
 - Obesity
 - Insulin resistance
 - Hyperinsulinism
 - Arterial hypertension
 - Hyperlipidemia
 - Acanthosis nigricans
 - PCOS

Acanthosis Nigricans

- Acanthosis nigricans is a cutaneous finding frequently in darker-skinned obese individuals
- Characterized by velvety hyperpigmented patches most prominent in intertriginous areas and is present in as many as 90% of children with type 2 diabetes

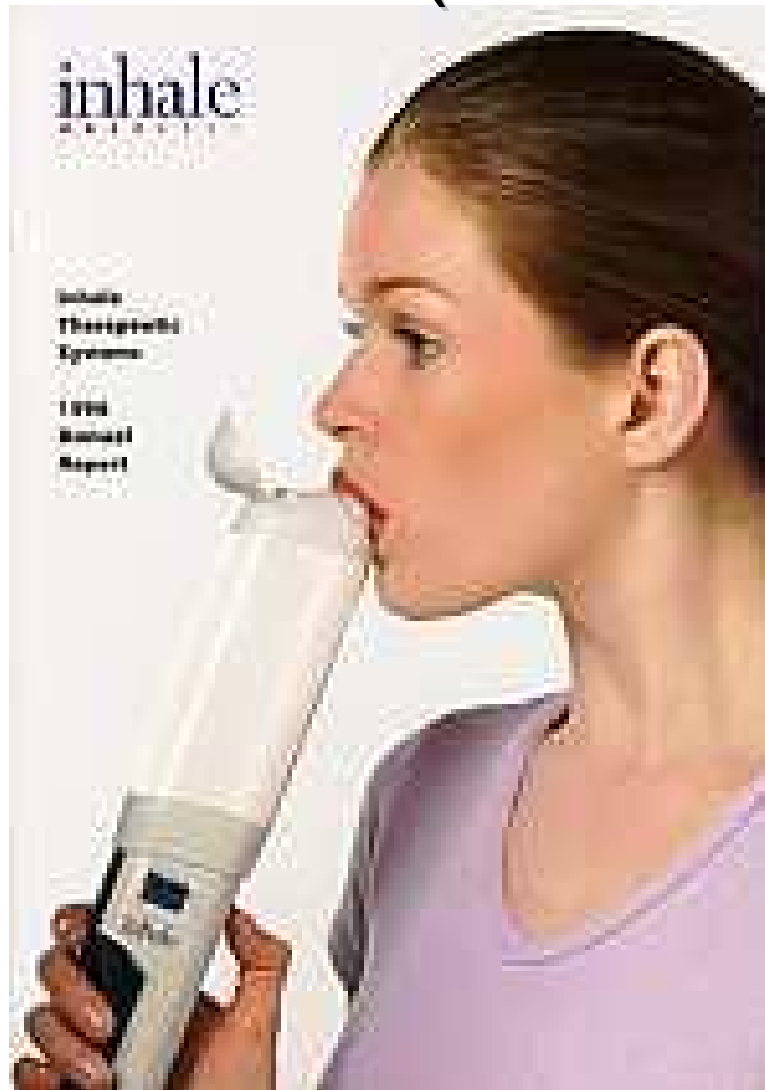




Metformin (Glucophage)

- Only approved oral hypoglycaemic in children above 10 years of age
- Can be used in pre-diabetes stage in children with hyperinsulinism
- Mechanism of actions:
 - increased peripheral glucose uptake
 - inhibition of hepatic gluconeogenesis
 - delays glucose absorption from the GIT
- Side Effects:
 - GI symptoms (nausea, diarrhoea, metallic taste)
 - Lactic Acidosis (rare, mainly in those with renal impairment)

"Exubera insulin (inhaled insulin)



Not any more
available

*I feel **like** I'm free. It's a miracle'*



William Lackey and Doris Holzman answer questions about how their islet cell transplants changed their lives

Islet cell transplantation

- The 1st. Pancreas transplant was in 1966
- Despite significant medical advances in surgical techniques & immunosuppressant protocols, pancreas transplantation is not successful
- Focus on islet cell transplantation through infusion through portal vein
- In year, 1999, Shapiro (Edmonton protocol) reported all 7 patients have normal fasting glucose for 12 months post transplant
- Using non-glucocorticoid immunosuppressive agents (sirolimus, tacrolimus) & anti – CD25 monoclonal antibody (Daclizumab)

Islet cell transplantation

- Barriers:
 - Shortage of human cadaveric islet cells
 - Requirement of immunosuppressive therapy to prevent rejection
 - Function of transplanted islet decreases with time
- To overcome these barriers, extensive research is going on including:
 - β - cells from animal (xenografts)
 - Encapsulation of islet cells
 - Stem cells / embryonic cell transplant
 - Genetically engineered β cells

Stem cell Transplant

- Stem cells of adult origin have been used clinically for 40 years in the treatment of hematological neoplasm such as leukemia.
- These cells were originally obtained from bone marrow, but are now also being derived from umbilical cord blood
- Adult stem cells, however, have limited potential to differentiate into different cell types
- Human embryonic stem cells can be converted into cells of all lineages
- They first became available for research in 1998 but are yet to be used in clinical trials

