Diabetes mellitus type1 TIDM

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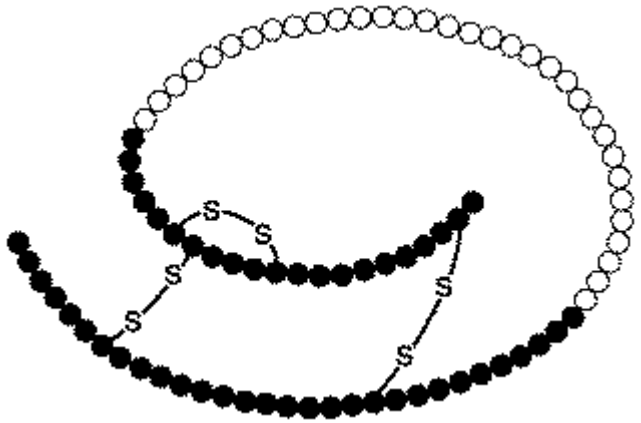
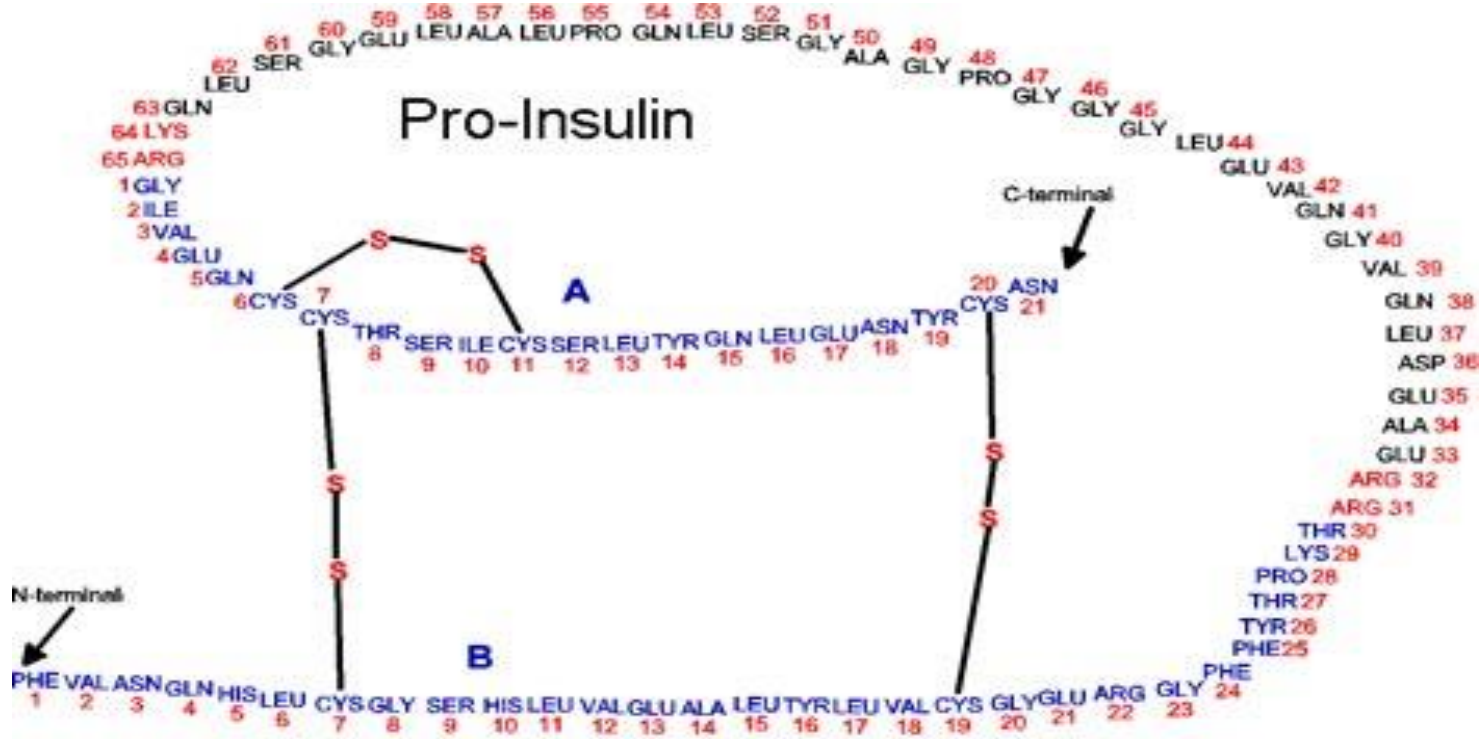
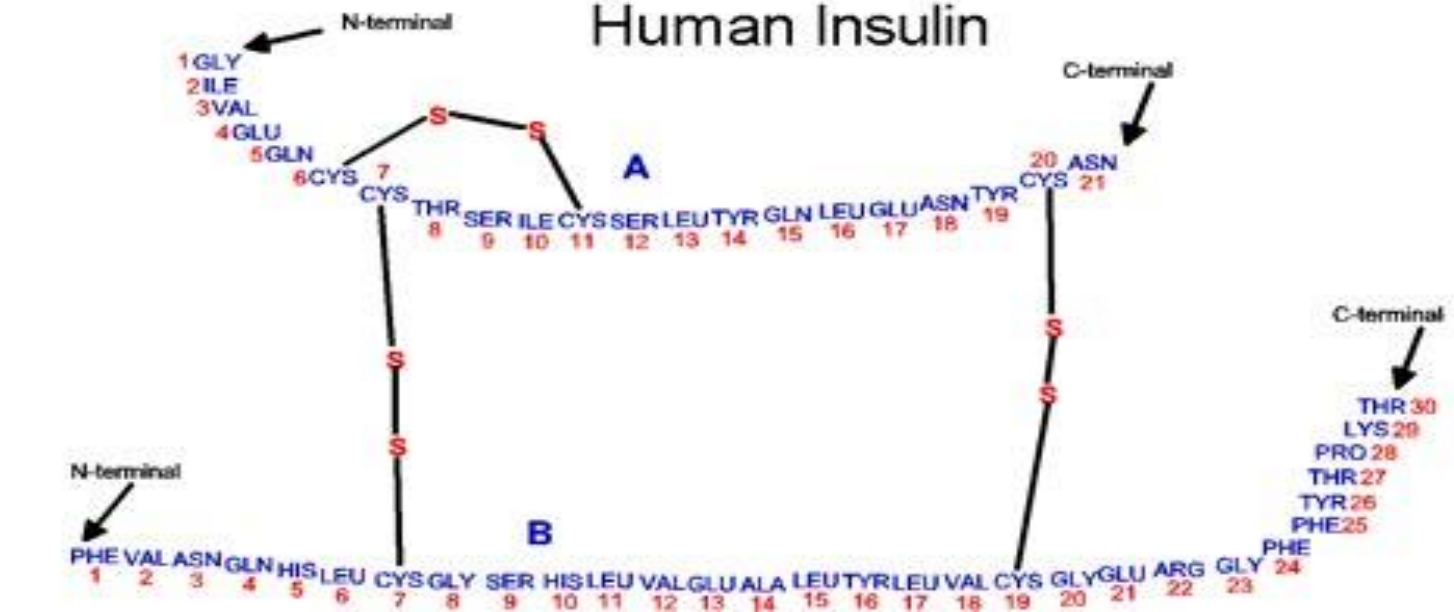


The C-peptide of proinsulin is depicted as open circles

Insulin is derived from proinsulin by cleavage of the C-peptide structure at the dipeptides Arg-Arg and Lys-Arg.
Insulin is composed of an A chain of 21 amino acids and a B chain of 30 amino acids, the chains being held together by two disulfide bonds. A third disulfide bond is present within the A chain.


Pro-Insulin
1 GLY 2 ILE 3 VAL 4 GLU 5 GLN 6 CYS 7 CYS 8 THR 9 SER 10 ILE 11 CYS 12 SER 13 LEU 14 TYR 15 GLN 16 LEU 17 GLU 18 ASN 19 TYR 20 CYS 21 ASN
A
B
N-terminal
C-terminal
PHE 1 VAL 2 ASN 3 GLN 4 HIS 5 LEU 6 CYS 7 GLY 8 SER 9 HIS 10 LEU 11 VAL 12 GLU 13 ALA 14 LEU 15 TYR 16 LEU 17 VAL 18 CYS 19 GLY 20 GLU 21 ARG 22 GLY 23 PHE 24 PHE 25 TYR 26 THR 27 PRO 28 LYS 29 THR 30 ARG 31 ARG 32 GLU 33 ALA 34 GLU 35 ASP 36 LEU 37 GLN 38 VAL 39 GLY 40 GLN 41 VAL 42 GLU 43 LEU 44 GLY 45 GLY 46 GLY 47 PRO 48 GLY 49 ALA 50 GLY 51 SER 52 LEU 53 GLN 54 PRO 55 LEU 56 ALA 57 LEU 58 GLU 59 GLY 60 SER 61 LEU 62 GLN 63 LYS 64 ARG 65


Human Insulin
1 GLY 2 ILE 3 VAL 4 GLU 5 GLN 6 CYS 7 CYS 8 THR 9 SER 10 ILE 11 CYS 12 SER 13 LEU 14 TYR 15 GLN 16 LEU 17 GLU 18 ASN 19 TYR 20 CYS 21 ASN
A
B
N-terminal
C-terminal
PHE 1 VAL 2 ASN 3 GLN 4 HIS 5 LEU 6 CYS 7 GLY 8 SER 9 HIS 10 LEU 11 VAL 12 GLU 13 ALA 14 LEU 15 TYR 16 LEU 17 VAL 18 CYS 19 GLY 20 GLU 21 ARG 22 GLY 23 PHE 24 PHE 25 TYR 26 THR 27 PRO 28 LYS 29 THR 30

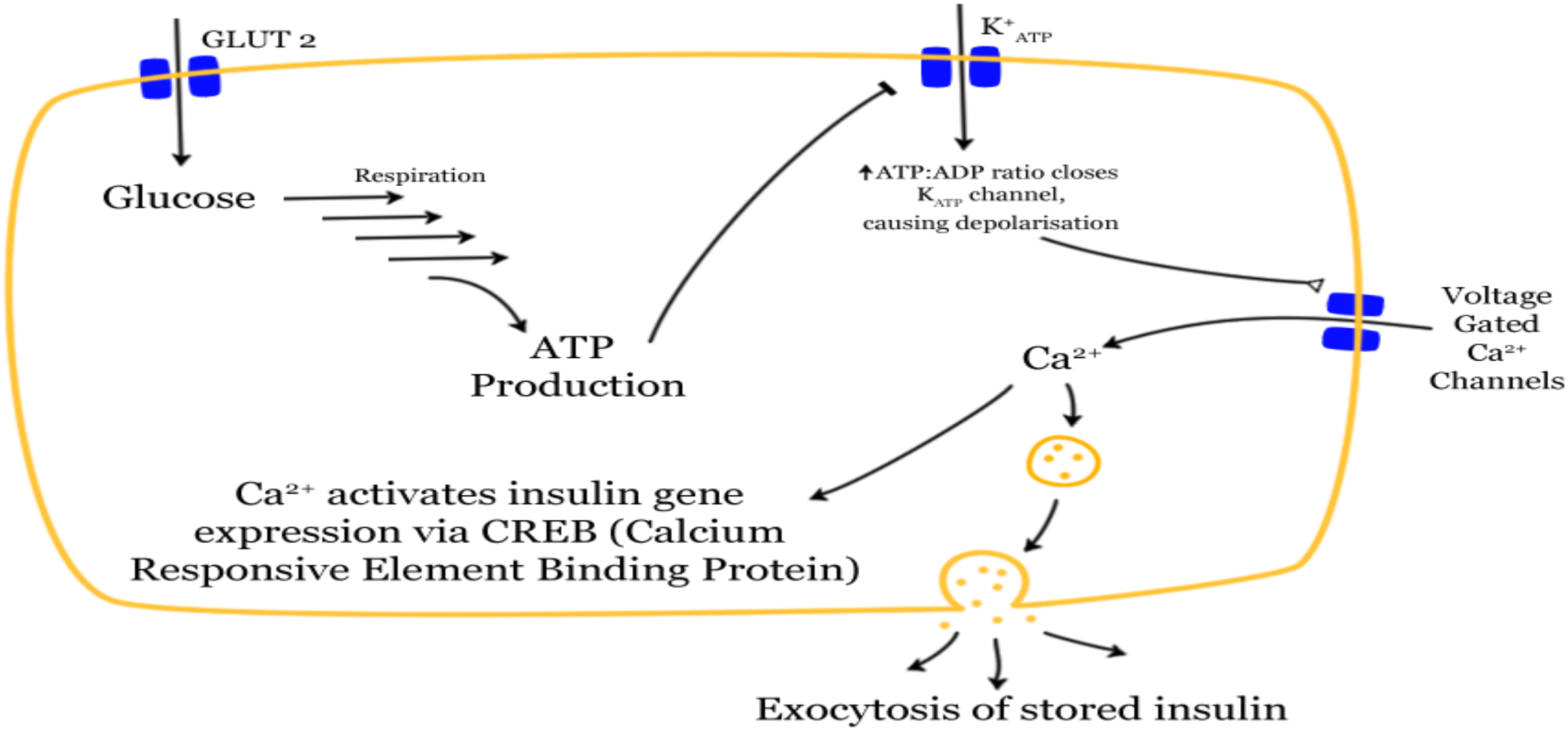
The actions of insulin on the global human metabolism level:

- Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about 2/3 of body cells)
- Increase of DNA replication and protein synthesis via control of amino acid uptake
- Modification of the activity of numerous enzymes (allosteric effect)
- Increased glycogen synthesis
- Increased fatty acid synthesis
- Increased esterification of fatty acids lack of insulin causes the reverse
- Decreased proteinolysis
- Decreased lipolysis
- Decreased gluconeogenesis.
- Increased amino acid uptake
- Increased potassium uptake absorption.
- Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract.

Mechanism of glucose dependent insulin release

Beta cells in the islets of Langerhans are sensitive to variations in blood glucose levels through the following mechanism:

1. Glucose enters the beta cells through the glucose transporter GLUT2
2. Glucose goes into the glycolysis and the respiratory cycle where the high-energy ATP molecule is produced by oxidation
3. Dependent on blood glucose levels and hence ATP levels, the ATP controlled potassium channels (K+) close and the cell membranes depolarize
4. On depolarisation, voltage controlled calcium channels (Ca2+) open and calcium flows into the cells



Mechanism of glucose dependent insulin release

Definition

Diabetes mellitus is disorder characterized by varying or persistent hyperglycemia, especially after eating. All types of diabetes mellitus share similar symptoms and complications at advanced stages.

Hyperglycemia itself can lead to dehydration and ketoacidosis.

Longer-term complications include cardiovascular disease chronic renal failure (it is the main cause for dialysis), retinal damage, and, nerve damage

Epidemiology TIDM

- In countries with higher incidence, the age of onset indicates that
  - diabetes under the age of 1 year is extremely uncommon
  - incidence increases with age
  - there may be a minor peak at age 4–6 years
  - there is a major peak at age 10–14 years
- In many countries the total incidence of type 1 diabetes has been shown to be increasing

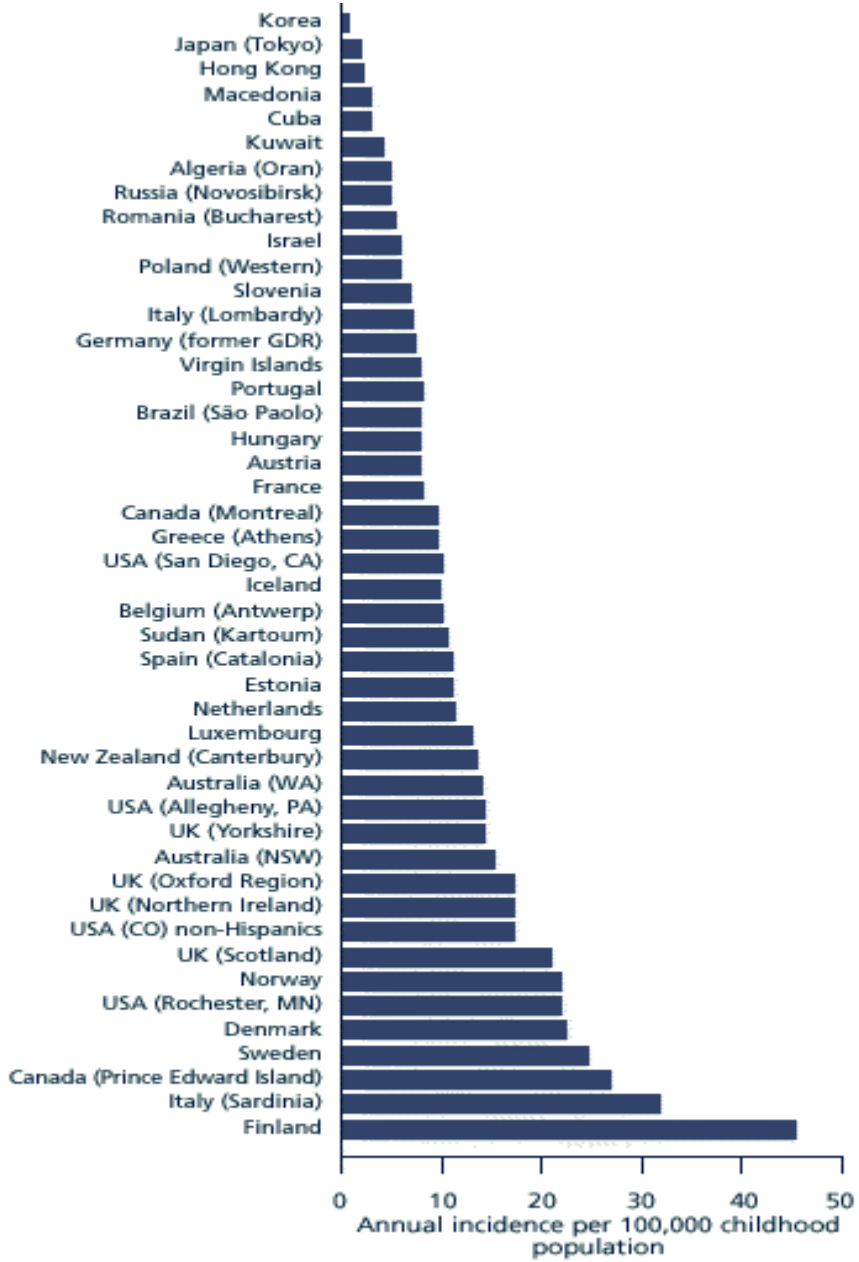


Figure 1: Annual incidence rates for childhood type 1 diabetes (0- to 14-year age group) in different regions of the world. [Source: Verge CF, Thesis, University of Sydney, 1994].

Etiologic classification of diabetes mellitus

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

- A. Immune mediated
- B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

- A. Genetic defects of β-cell function
  1. Chromosome 12, HNF-1α (MODY3)
  2. Chromosome 7, glucokinase (MODY2)
  3. Chromosome 20, HNF-4α (MODY1)
  4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
  5. Chromosome 17, HNF-1β (MODY5)
  6. Chromosome 2, *NeuroD1* (MODY6)
  7. Mitochondrial DNA
  8. Others

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Etiologic classification of diabetes mellitus

B. Genetic defects in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall syndrome
   4. Lipoatrophic diabetes
   5. Others

C. Diseases of the exocrine pancreas
   1. Pancreatitis
   2. Trauma/pancreatectomy
   3. Neoplasia
   4. Cystic fibrosis
   5. Hemochromatosis
   6. Fibrocalculous pancreatopathy
   7. Others

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Etiologic classification of diabetes mellitus

D. Endocrinopathies

1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others

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Etiologic classification of diabetes mellitus

E. Drug- or chemical-induced

1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

F. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others

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Etiologic classification of diabetes mellitus

G. Uncommon forms of immune-mediated diabetes

1. “Stiff-man” syndrome
2. Anti–insulin receptor antibodies
3. Others

H. Other genetic syndromes sometimes associated with diabetes

1. Down's syndrome
2. Klinefelter's syndrome
3. Turner's syndrome
4. Wolfram's syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others

IV. Gestational diabetes mellitus (GDM)

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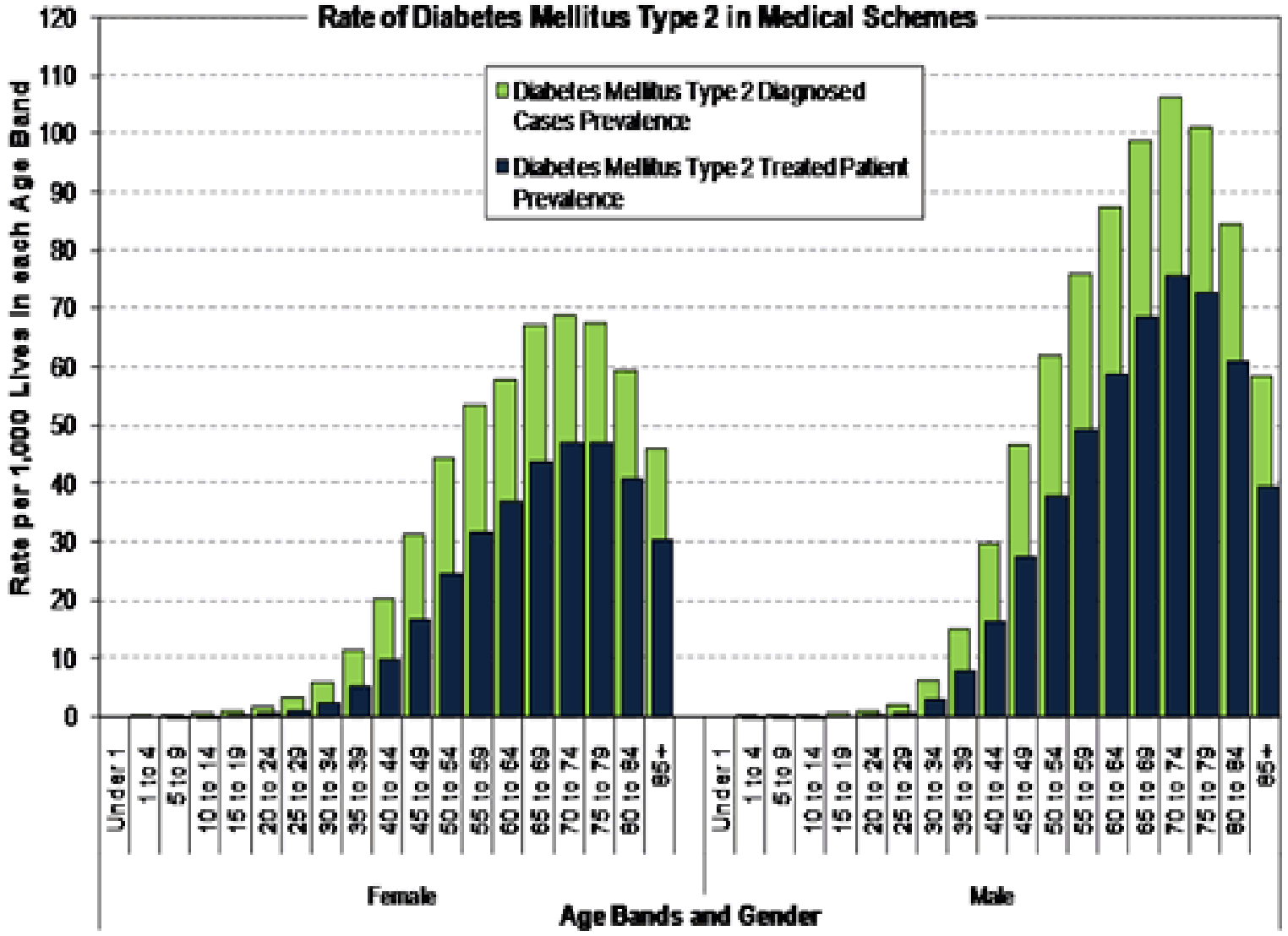
Differentiating between type 1 and type 2 diabetes at diagnosis

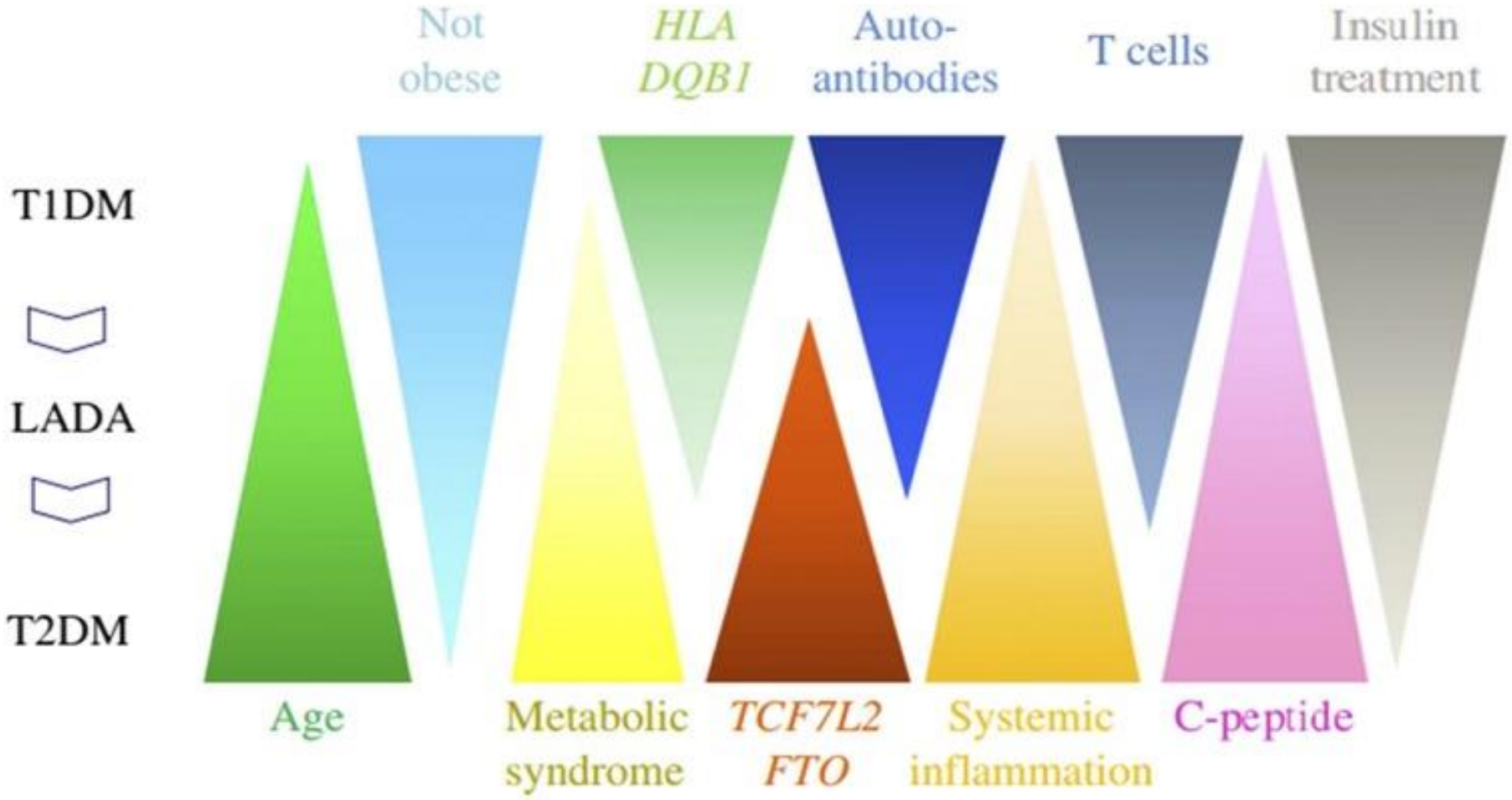
Features suggesting the diagnosis of type 2 diabetes rather than type 1 diabetes at diagnosis include:

- Overweight or obesity
- Age greater than 10 years
- Strong family history of type 2 diabetes
- Acanthosis nigricans
- High-risk racial or ethnic group
- Undetectable islet autoantibodies

Table 1: Characteristic features of type 1 compared with type 2 diabetes in young people.

Characteristics	Type 1	Type 2
Age	Throughout childhood	Pubertal (or later)
Onset	Most often acute, rapid	Variable: from slow, mild (often insidious) to severe
Insulin dependence	Permanent, total, severe	Uncommon, but insulin required when oral hypoglycemic agents fail
Insulin secretion	Absent or very low	Variable
Insulin sensitivity	Normal	Decreased
Genetics	Polygenic	Polygenic
Race/ethnic distribution	All groups, but wide variability of incidence	Certain ethnic groups are at particular risk
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% (Japan ~80%)
Associations		
Autoimmunity	Yes	No
Ketosis	Common	Rare
Obesity	No	Strong
Acanthosis nigricans	No	Yes


Rate of Diabetes Mellitus Type 2 in Medical Schemes
Diabetes Mellitus Type 2 Diagnosed Cases Prevalence
Diabetes Mellitus Type 2 Treated Patient Prevalence
Rate per 1,000 Lives in each Age Band
120
110
100
90
80
70
60
50
40
30
20
10
0
Under 1
1 to 4
5 to 9
10 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 59
60 to 64
65 to 69
70 to 74
75 to 79
80 to 84
85+
Female
Male
Age Bands and Gender



Qualitative illustration of the spectrum of factors associated with different forms of DM, including the variable age at onset, lack of obesity, metabolic syndrome, genetic associations,different forms of immune changes, C-peptide secretion, and the need for insulin therapy. T1DM, type 1 DM; T2DM, type 2 diabetes.

Type 1 diabetes mellitus - etiology

- Type 1 diabetes is most commonly diagnosed in children and adolescents, but can occur in adults as well.
- It is an autoimmune disorder, in which the body's own immune system attacks the beta cells in the Islets of Langerhans of the pancreas, destroying them or damaging them sufficiently to reduce insulin production.
- The autoimmune attack may be triggered by reaction to an infection, for example by one of the viruses of the Coxsackie virus family.

  A subtype of type 1 (identifiable by the presence of antibodies against beta cells) develops slowly and so is often confused with Type 2. In addition, a small proportion of type 1 cases has the hereditary condition maturity onset diabetes of the young (MODY).

The role of the environment in the pathogenesis of type 1 diabetes

- Congenital rubeola is a long standing recognized environmental trigger
- Enterovirus infections during pregnancy and childhood, and the introduction of multiple foreign antigens in the infant diet.
- In at-risk children, concurrent breast milk feedingat the time of cereal introduction may be protective
- Omega 3 fatty acids may also have a small protective effect. Vitamin D metabolism may play, as yet, an undetermined role

Genetics

Both type 1 and type 2 diabetes are at least partly inherited.

Type 1 diabetes appears to be triggered by infection, stress, or environmental factors (e.g. exposure to a causative agent). There is a genetic element in the susceptibility of individuals to some of these triggers which has been traced to particular HLA genotypes

.

Genetic markers

Certain HLA markers, particularly when identical to those of a family member with diabetes, indicate increased risk

- ***Examples of genetic markers conferring increased risk***

The highest-risk haplotypes are

- DRB1*03:01-DQA1*05:01-DQB1*02:01
- DRB1*04-DQA1*03:01-DQB1*03:02

- ***Examples of genetic markers conferring decreased risk***

HLA DR2–DQA1*0102-DQB1*0602

Immunological markers

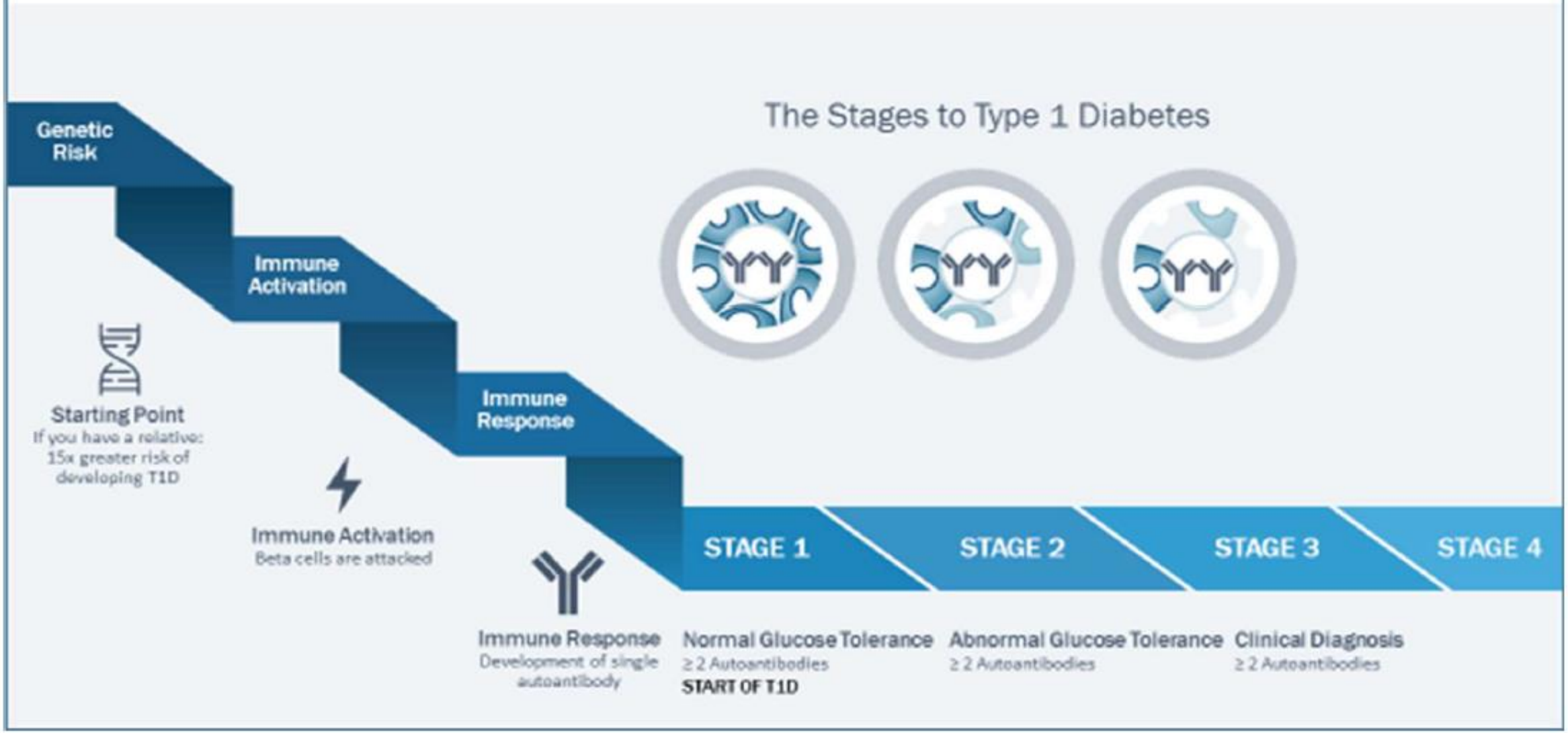
- Islet cell autoantibodies (ICA) at a high titer (>20 JDF units) predict a 40–60% risk of type 1 diabetes over the next 5–7 years
- When multiple autoantibodies are present the risk prediction rate increases greatly, e.g. glutamic acid decarboxylase (65 kD GAD isoform) plus IA2 (acid thyrosine phosphatase 2) antibodies predict a risk of >70% over 5 years.
- Insulin autoantibodies (IAA) at high titer may also increase the risk prediction
- β-cell-specific zinc transporter 8 autoantibodies (ZnT8).

Stages of diabetes

Type 1 diabetes is characterized by four stages.

- Stage 1 Multiple islet antibodies, normal blood glucose, pre-symptomatic
- Stage 2 Multiple islet antibodies, raised blood glucose, pre-symptomatic
- Stage 3 Islet autoimmunity, raised blood glucose, symptomatic
- Stage 4 Long standing type 1 diabetes

Type 1 Diabetes Disease Progression



Stages of type 1 diabetes in children and adolescents
ISPAD Clinical Practice Consensus Guidelines 2018

Recommendations and principles

- Individuals with a first degree relative with type 1 diabetes have an approximately 15-foldincreased relative risk of type 1 diabetes
- Individuals with two or more islet antibodies are classified as having the first stage of type 1 diabetes.
- Screening and intervention before the symptoms of type 1 diabetes should be conducted within the context of defined research studies.

Stages of type 1 diabetes in children and adolescents ISPAD Clinical Practice Consensus Guidelines 2018

- Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counseling and information regarding current prevention studies.
- Features suggesting the diagnosis of type 2 rather than type 1 diabetes include a family history of type 2 diabetes in first degree relatives, obesity, acanthosis nigricans, high-risk racial or ethnic group and undetectable islet autoantibodies.

Criteria for clinical manifestation

- Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of
- Two fasting plasma glucose levels above 7 mmol/l (126 mg/dl) on different days;
- Casual plasma glucose above 11.1 mmol/l (200 mg/dl) any time of day or two hours after a 75 g glucose load; or
- Symptoms of diabetes.
- Or hemoglobin HbA1c >6.5% or higher.

Criteria for the Diagnosis of Diabetes Mellitus and Impaired Glucose Homeostasis

Criteria for the Diagnosis of Diabetes Mellitus and Impaired Glucose Homeostasis

Diabetes mellitus-positive findings from any two of the following tests on different days:

- Symptoms of diabetes mellitus, plus casual plasma glucose concentration >=200 mg per dL (11.1 mmol per L**)**

  or

- IFG >=126 mg per dL (7.0 mmol per L)

  or

- 2hr >=200 mg per dL (11.1 mmol per L) after a 75-g glucose load **(**IGT)

(IFG -*impaired fasting glucose,* NGT -*normal glucose tolerance,* IGT -*impaired glucose tolerance*)

(FPG Fasting Prandial Glucose, PPG Post Prandial Glucose))

Criteria for the Diagnosis of Diabetes Mellitus and Impaired Glucose Homeostasis

- **Impaired glucose homeostasis**
  - Impaired fasting glucose FPG:

    FPG from 100 to <126 (5.55 to 7.0 mmol per L)
  - Impaired glucose tolerance IGT:

    2hrPPG from 140 to <200 (7.75 to <11.1 mmol per L)
- Normal
  - FPG <100 mg per dL (5.55 mmol per L)
  - 2hrPPG <140 mg per dL (7.75 mmol per L)

Signs and symptoms

Type 2 diabetes almost always has a **slow onset** (often years), **but in type 1, particularly in children,** onset may be quite fast (weeks or months).

Early symptoms of type 1 diabetes are:

1. polyuria (frequent urination)
2. polydipsia (increased thirst, and consequent increased fluid intake)
3. weight loss (despite normal or increased eating)
4. increased appetite, and irreduceable fatigue.

Signs and symptoms

Thirst develops because of osmotic effects — sufficiently high glucose (above the 'renal threshold') in the blood is excreted by the kidneys but this requires water to carry it and causes increased fluid loss, which must be replaced. The lost blood volume will be replaced from water held inside body cells, causing dehydration.

Signs and symptoms

- Another common presenting symptom is:
- Altered vision- prolonged high blood glucose causes changes in the shape of the lens in the eye, leading to blurred
- Especially dangerous symptoms in diabetics include the smell of acetone on the patient's breath (a sign of ketoacidosis), Kussmaul breathing (a rapid, deep breathing), and any altered state of consciousness. The most dangerous form of altered consciousness is the so-called "diabetic coma„.
- Early symptoms of impending diabetic coma include polyuria, nausea, vomiting and abdominal pain, with lethargy and somnolence a later development, progressing to unconsciousness and death if untreated.

MODY subtypes

Genetic defects of beta-cell function (formerly known as maturity-onset diabetes in the young, MODY subtypes)

Characteristics

- Early-onset hyperglycemia before age 25 years
- Monogenic, autosomal dominant mode of inheritance — at least two, preferably three, generations exhibiting a similar phenotype (although older relatives may not be diagnosed until older age)
- Non-insulin-dependent for at least 5 years after diagnosis of diabetes
- Impaired insulin secretion
- Absence of severe ketosis
- Some forms of these defects in beta-cell function may present with severe osmotic symptoms and may be misdiagnosed as type 1

But

- Not severely ketotic
- Family history (autosomal dominant)
- Good metabolic control with low insulin dose

Presentation and phases of diabetes

Type 1 diabetes in childhood and adolescence is characterized by the following phases

- Prediabetes
- Presentation of diabetes
- Partial remission (or ‘honeymoon’)
- Permanent insulin dependency

Clinical presentation
Prediabetes

- ***Definition***

  A state preceding the clinical onset of diabetes by months or even years, characterized by the presence of antibodies to several islet cell antigens which are often, but not always, predictive of the development of type 1 diabetes. The antibodies have been used as markers to identify people at risk of developing type 1 diabetes

Insulin secretion prediabetes

During the phase of prediabetes, before clinical onset of diabetes, beta-cell destruction progresses and insulin secretion diminishes.

Presentation

- Diabetes in young people most often has a sudden and acute onset with polyuria, polydipsia and evidence of ketosis
- A minority of young people have a slower onset with symptoms presenting over several months

- ***Additional clinical presentations***
- Recent-onset or persistent enuresis
- Abdominal pain with or without vomiting
- Vaginal candidiasis
- Poor weight gain or weight loss
- Fatigue, irritability, decreasing school performance
- Recurrent skin infections

Presentation

Diagnostic difficulties at onset

- Young infants with hidden symptoms
- Hyperventilation misdiagnosed as pneumonia
- Abdominal pain or vomiting misdiagnosed as abdominal ‘migraine’ or appendicitis
- Enuresis or polyuria misdiagnosed as urinary infection
- Polydipsia misdiagnosed as habit or psychogenic drinking

Recommendation

Weight loss or excessive thirst in a child or adolescent should always be investigated immediately by at least a urinary glucose test to rule out diabetes mellitus

Partial remission phase

Definition

The phase after the diagnosis of type 1 diabetes during which there may be continuing and effective secretion of endogenous pancreatic insulin
Often called the 'honeymoon period' when glycemic control seems inappropriately easy

- Has been defined in the past as when the insulin dose required to maintain excellent metabolic control is less than 0.5 units/kg body weight per day and HbA1C <7,0 %
- Approximately 30–60% of children and adolescents demonstrate a partial remission phase most often during the first 1–6 months after starting insulin treatment
- Opinion has varied about whether insulin treatment should be withdrawn temporarily during this phase
- Currently there is no clear evidence of any treatment strategy which significantly prolongs the partial remission phase (there is weak evidence to suggest that maintenance of normal BG levels with insulin injections helps to protect islet cell function)
- Beta-cell function becomes almost unmeasurable in the great majority of children by 1–2 years after diagnosis

Permanent total insulin dependency

When beta-cell function becomes unmeasurable, the individual is then totally dependent on exogenous insulin injections

Treatment

- ***Insulin***
- ***Nutritional management***
- ***Physical activity***

Assessment and monitoring of metabolic control

- **Monitoring of BG**
- **Glycated hemoglobin**
- **Monitoring of urinary ketones**

Table 5: Target indicators of glycemic control

Level of control	Ideal (non-diabetic)	Optimal	Suboptimal	High risk (action required)
Clinical assessment				
Raised BG	Not raised	No symptoms	Polyuria Polydipsia Enuresis Poor weight gain Poor school attendance	Blurred vision Cramps Poor growth Delayed puberty Skin or genital infections Signs of vascular complications
Low BG	Not low	Few mild, no severe hypos	Episodes of severe hypoglycemia (unconscious ± convulsions)	
Biochemical assessment[a]				
Preprandial or fasting BG (mmol/l)	3.6–6.1	4.0–7.0[b]	>8.0	>9.0
Postprandial BG (mmol/l)	4.4–7.0	5.0–11.0	11.1–14.0	>14.0
Nocturnal BG[c] (mmol/l)	3.6–6.0	Not <3.6	<3.6 or >9.0	<3.0 or >11.0
HbA_{1c} (%) (DCCT standardized)	<6.05	<7.6	7.6–9.0	>9.0

[a]These population-based target indicators must be adjusted according to individual circumstances. Different targets will be appropriate for various individuals such as young children, those who have experienced severe hypoglycemia or those with hypoglycemic unawareness

[b]If fasting morning BG is <4 mmol/l, consider the possibility of antecedent nocturnal hypoglycemia

[c]These figures are based on clinical studies but no strict evidence-based recommendations are available

Glycated hemoglobin

- Glucose attaches itself to the molecule of hemoglobin (Hb) during the life-cycle of the circulating red cell, forming glycated hemoglobin (HbA1 or HbA1c)

- HbA1c level reflects levels of glycemia over the preceding 6–12 weeks

- HbA1c monitoring has been shown to be the most useful measure in evaluating metabolic control and is the only measure for which good data are available in terms of its relationship with later microvascular complications

Recommendation
Facilities for the measurement of HbA1c should be available to all centers caring for young people with diabetes

Assessment and monitoring of metabolic control HbA1c

Targets

- The DCCT showed that as HbA1c rises above 7.5% (or more than approximately 120% above the upper level of the normal reference range), the risk of later microvascular complications increases steeply [In the DCCT intensive treatment group of adolescents, fewer than 50% achieved a mean HbA1c <8% (reference range <6.05%)

- *The Diabetes Control and Complications Trial (DCCT) was a major clinical study conducted from 1983 to 1993 and funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The study showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of the eye, kidney, and nerve damage caused by diabetes. The study compared the effects of standard control of blood glucose versus intensive control on the complications of diabetes. Intensive control meant keeping hemoglobin A1C levels as close as possible to the normal value of 6 percent or less*

Insulin

Insulin availability

- Children and adolescents with type 1 diabetes are dependent on insulin for survival
- Insulin treatment must be started as soon as possible after diagnosis (usually within 24 h if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis

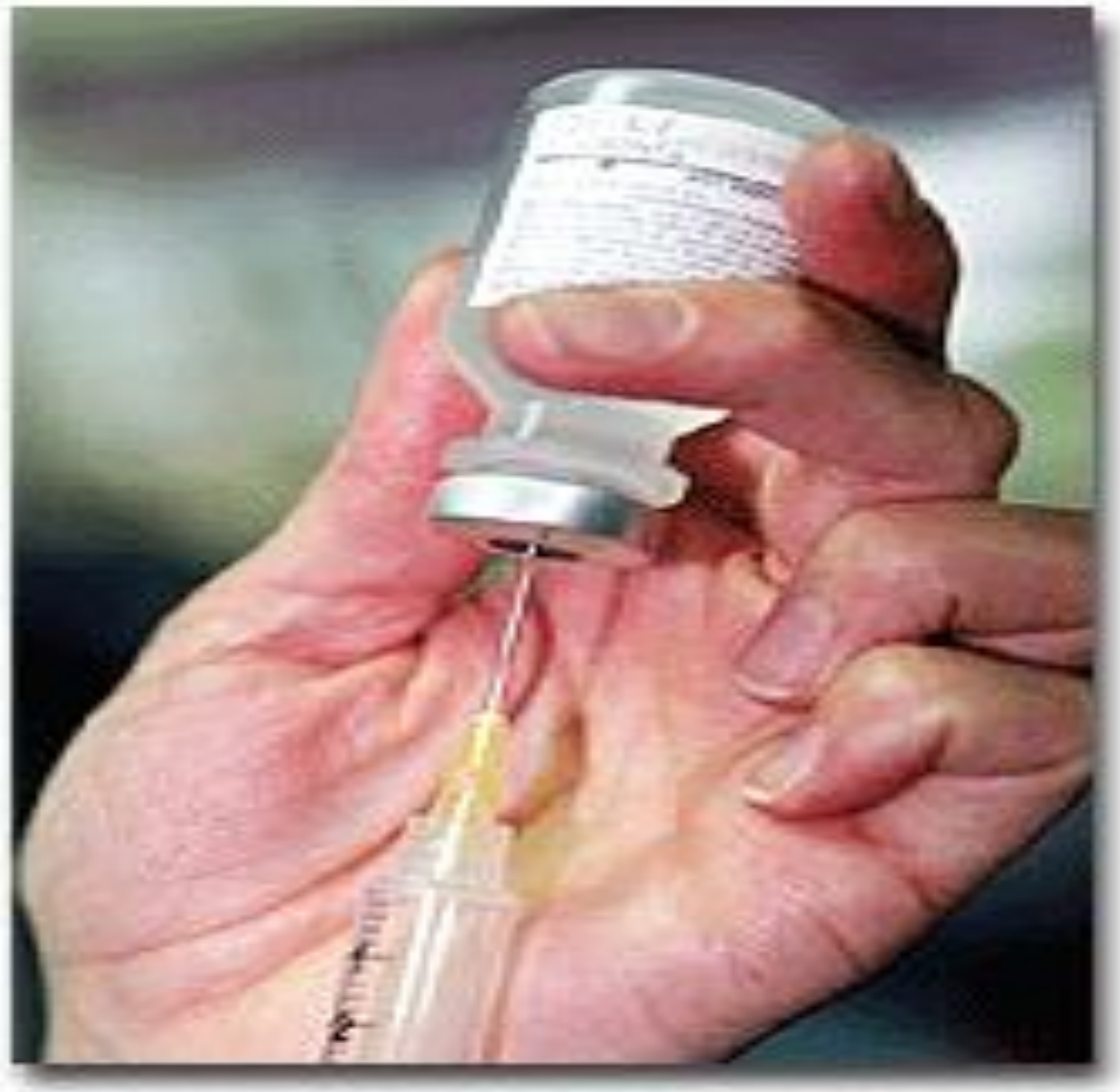
Table 6: Types of insulin preparations and suggested action profiles

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogs	0.15–0.35	1–3	3–5
Short-acting			
Regular/soluble	0.5–1	2–4	5–8
Intermediate-acting			
Semi-lente (pork)	1–2	4–10	8–16
Isophane NPH	2–4	4–12	12–24
IZS lente type	3–4	6–15	18–24
Long-acting			
Ultralente type	4–8	12–24	20–30
Analog	2–4	none	24

NPH, neutral protamine Hagedorn insulin; IZS, insulin zinc suspension

Table 1. Types of insulin preparations and suggested action profiles for s.c. administration

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Ultra-Rapid acting analog (Faster aspart)** &****	0.1-0.2	1-3	3-5
Rapid-acting analogs (aspart, glulisine and lispro)	0.15-0.35	1-3	3-5
Regular/soluble (short acting)	0.5-1	2-4	5-8
NPH*	2-4	4-12	12-24**
Basal long-acting analogs			
Glargine***	2-4	8-12 (not pronounced)	22-24**
Detemir	1-2	4-7 (not pronounced)	20-24**
Long-acting			
Glargine U300*+*	2-6	nearly peakless	30-36
Degludec ****	0.5-1.5	nearly peakless	>42



i.v. soluble insulin

- **Regular and rapid-acting and ultra-rapid** insulins are equally suited for IV therapy in the following crisis situations:
- Diabetic ketoacidosis.
- Control of diabetes during surgical procedures.
- However, regular insulin is less expensive

Short acting Insulin

Short-acting insulin

- Short-acting (soluble, regular) insulin is used as an essential component of most daily replacement regimens
either

  - in combination with intermediate-acting insulin in a twice-daily regimen

or

  - as pre-meal bolus injections in basal-bolus regimens (20–30 min before meals)

Rapid-acting insulin analogs

- Rapid-acting analogs can be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycemia but that postprandial and nocturnal hypoglycemia may also be reduced. In selected children they offer the useful option of being given after food to toddlers who are reluctant to eat
- Rapid-acting analogs may also be used during sick days with hyperglycemia and potential ketosis
- Rapid-acting analogs are most often used as prandial or snack boluses in combination with longer acting insulins given twice or more times daily

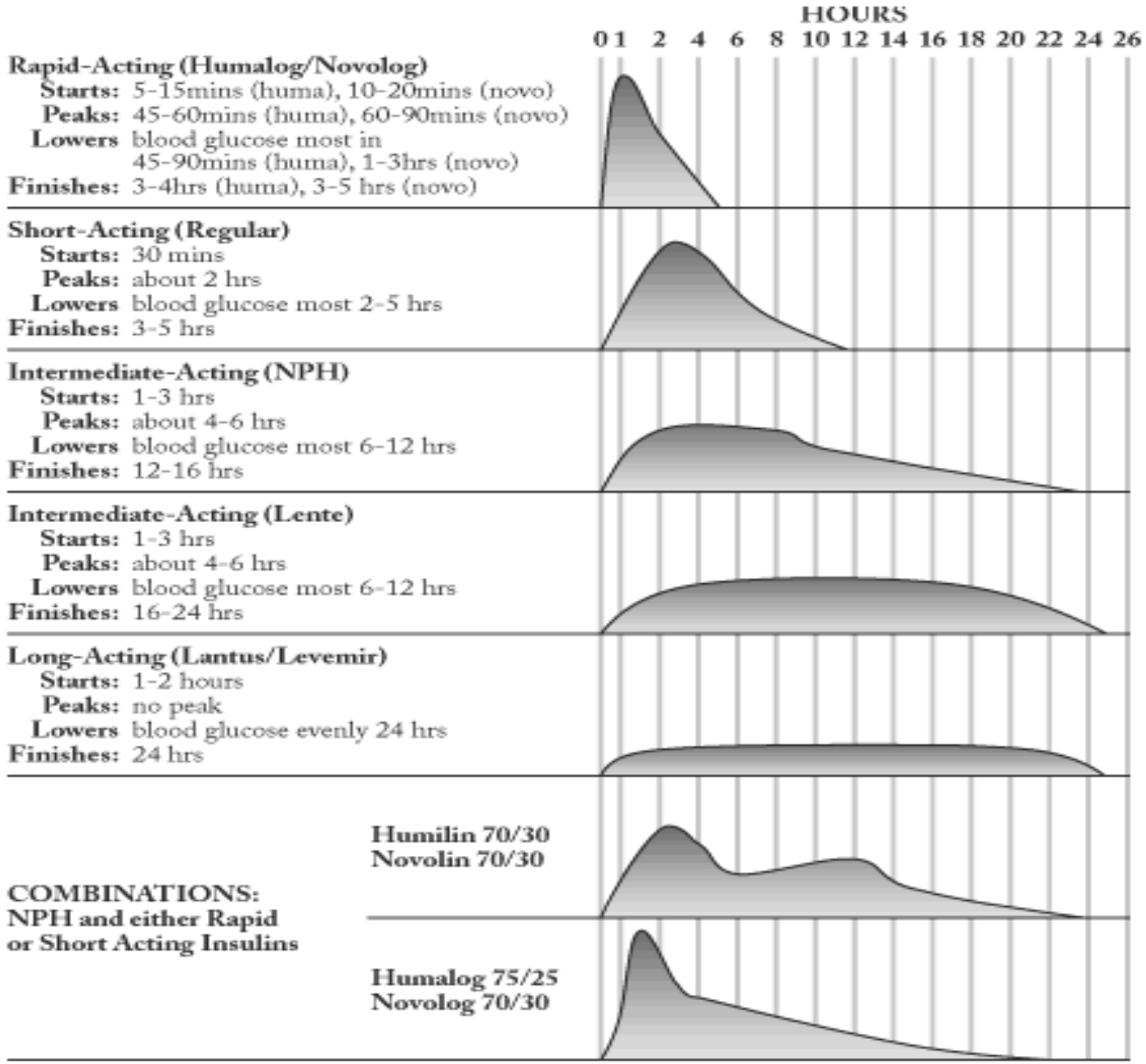
Rapid acting

The rapid acting analogs:

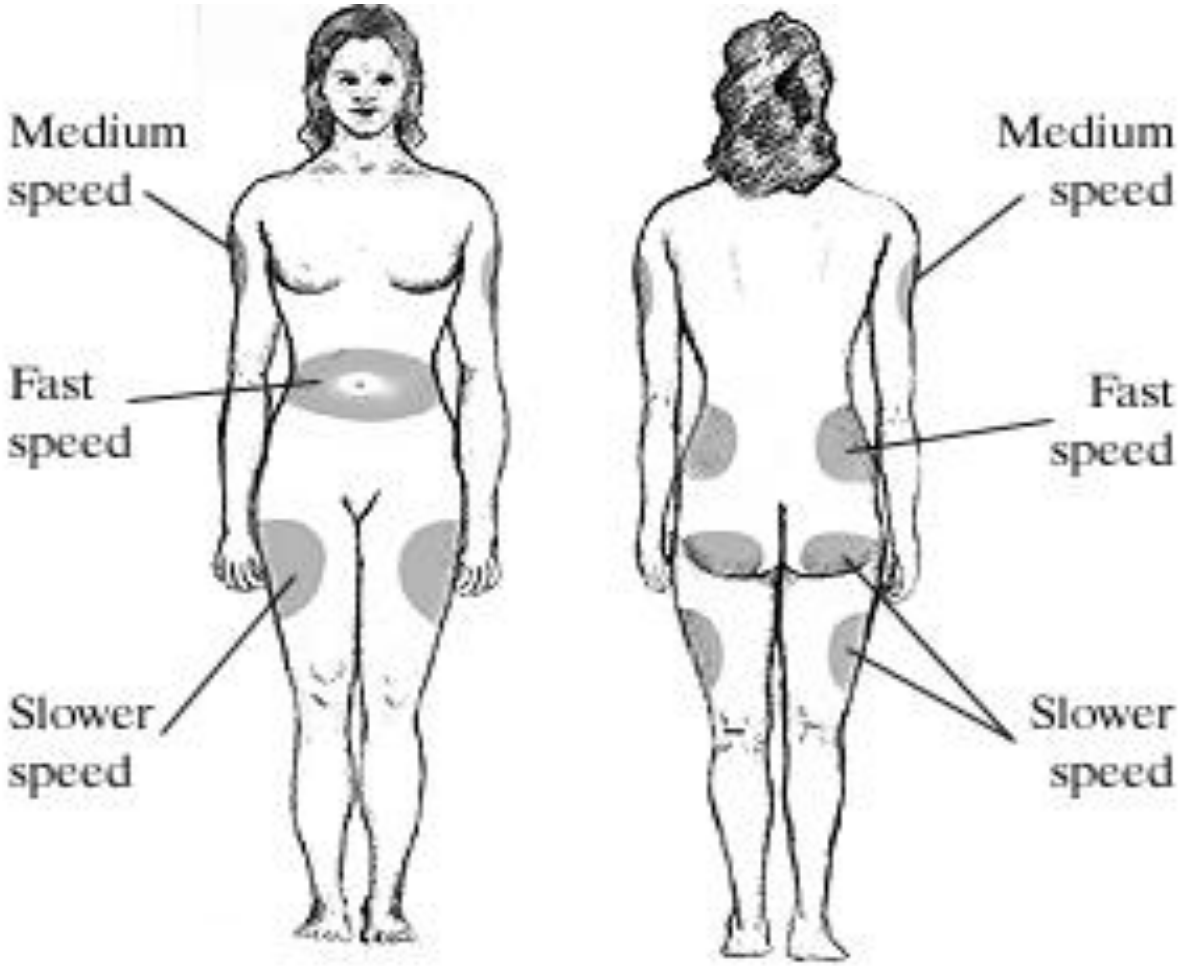
- Can when necessary be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycemia but nocturnal hypoglycemia may also be reduced (33)(34)(35)(36).
- In exceptional cases can be given after food when needed (e.g. infants and toddlers who are reluctant to eat) or prandial doses can be split before and after the meal (42).
- In the face of hyperglycemia, the short acting analog should be given in advance of eating
- Give a quicker effect than regular insulin when treating hyperglycemia, with or without ketosis, including sick days.
- Are most often used as prandial or snack boluses in combination with longer acting insulins (see basal bolus regimens).
- Are most often used in insulin pumps.

Long-acting insulins

A long-acting insulin analog insulins were designed to have a duration of action of more than 24 h to meet basal insulin requirements and therefore could be used in basal-bolus injection regimens.

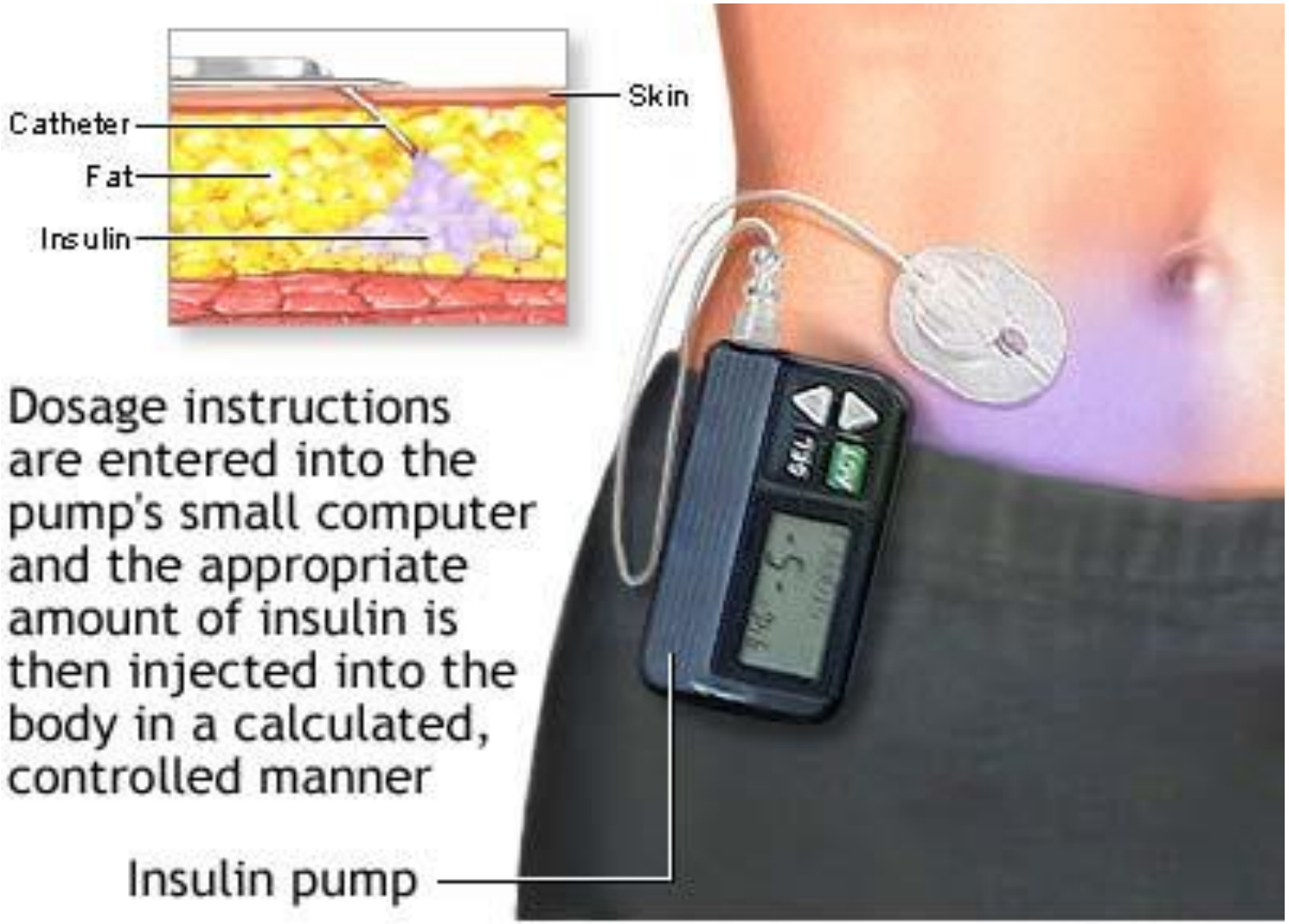

HOURS
0 1 2 4 6 8 10 12 14 16 18 20 22 24 26
Rapid-Acting (Humalog/Novolog)
Starts: 5-15mins (huma), 10-20mins (novo)
Peaks: 45-60mins (huma), 60-90mins (novo)
Lowers blood glucose most in 45-90mins (huma), 1-3hrs (novo)
Finishes: 3-4hrs (huma), 3-5 hrs (novo)
Short-Acting (Regular)
Starts: 30 mins
Peaks: about 2 hrs
Lowers blood glucose most 2-5 hrs
Finishes: 3-5 hrs
Intermediate-Acting (NPH)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 12-16 hrs
Intermediate-Acting (Lente)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 16-24 hrs
Long-Acting (Lantus/Levemir)
Starts: 1-2 hours
Peaks: no peak
Lowers blood glucose evenly 24 hrs
Finishes: 24 hrs
COMBINATIONS:
NPH and either Rapid or Short Acting Insulins
Humilin 70/30
Novolin 70/30
Humalog 75/25
Novolog 70/30

Injection sites



Administration of insulin

- **Injections by syringe**
- **Pen injector technique**
- **Subcutaneous insulin infusion pumps**


Skin
Catheter
Fat
Insulin
Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner
Insulin pump
A.D.A.M.

Daily insulin dosage

Dosage depends on many factors such as

- Age.
- Weight.
- Stage of puberty.
- Duration and phase of diabetes.
- State of injection sites.
- Nutritional intake and distribution.
- Exercise patterns.
- Daily routine.
- Results of blood glucose monitoring and glycated hemoglobin.
- Intercurrent illness.

Guideline on dosage

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/day.
- Prepubertal children (outside the partial remission phase) usually require 0.7 – 1.0 IU/kg/day.
- During puberty, requirements may rise substantially above 1 and even up to 2 IU/kg/day
- It has been observed that an excessive GH secretion in type 1 diabetes during puberty has significant effects on ketogenesis. Rise in beta-hydroxybutyrate and acetoacetate levels, between 2AM and 3AM, observed in puberty can be obliterated with suppression of GH. Hence, adolescent Type 1 Diabetic tends to decompensate very rapidly and develop DKA when the late night insulin dose is omitted

Distribution of insulin dose

- In children on basal-bolus regimens, the basal insulin may represent between 30 (typical for regular insulin) and 50% (typical for rapid-acting insulin) of total daily insulin.
- Approximately 50% as rapid-acting or ~ 70% as regular insulin is divided up between 3 – 4 pre-meal boluses.
- When using rapid-acting insulin for pre-meal boluses, the proportion of basal insulin is usually higher, as short-acting regular insulin also provides some basal effect.
- Glargine is often given once a day, but many children may need to be injected twice a day or combined with NPH to provide full daytime basal insulin coverage

Principles of insulin therapy

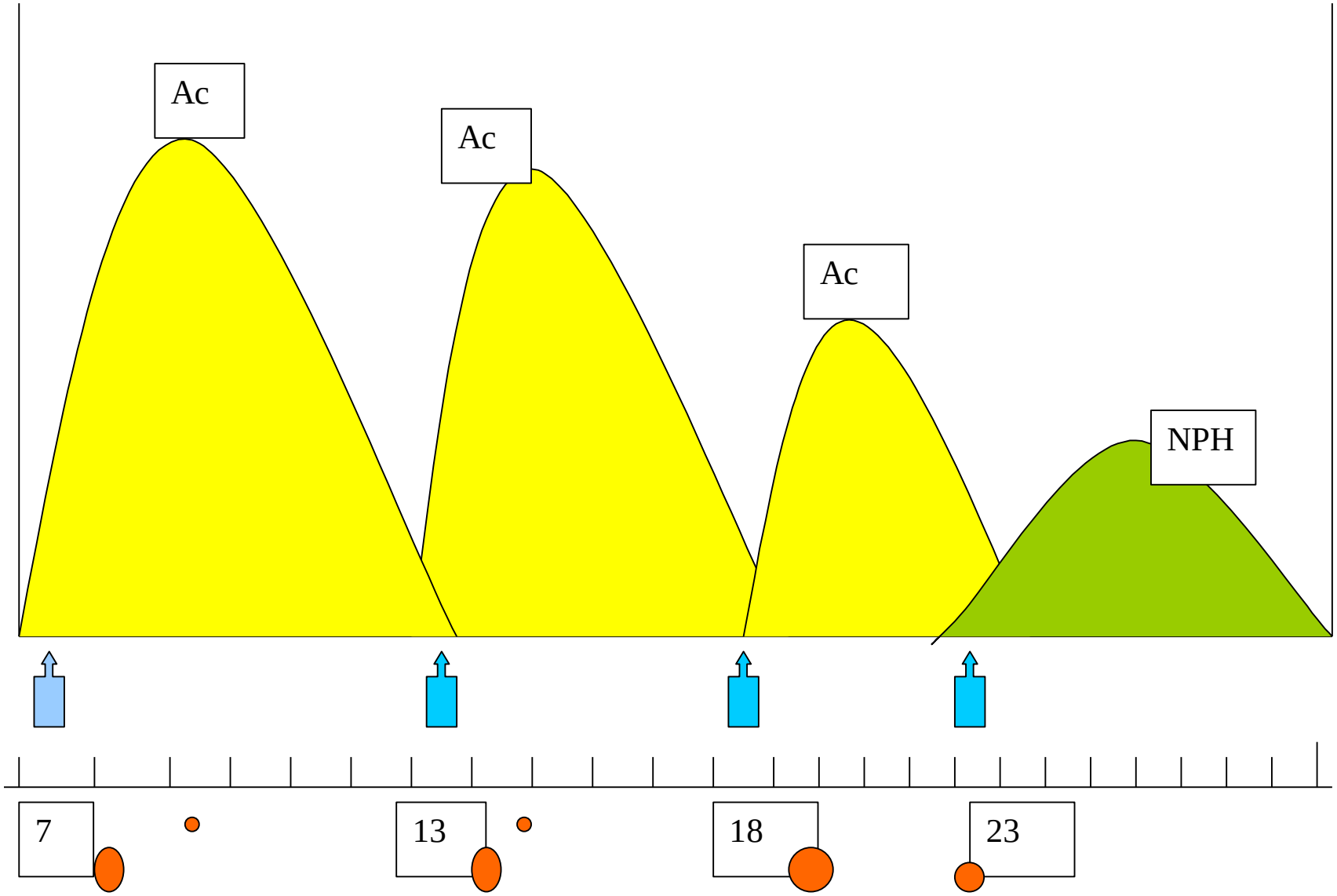
Frequently used regimens

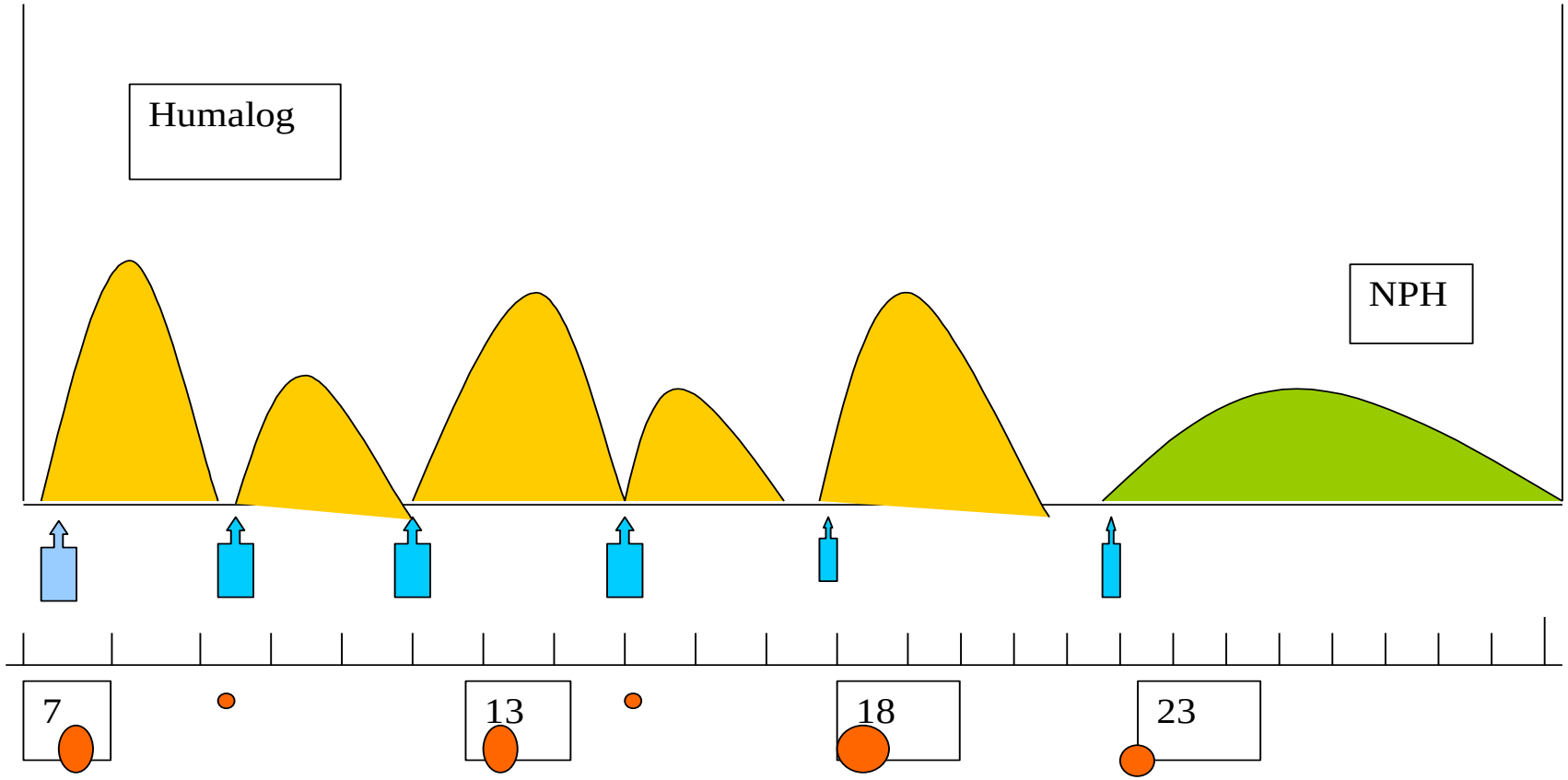
- **Three injections daily** using a mixture of short and intermediate acting insulins before breakfast; short-acting insulin alone before an afternoon snack or main evening meal; intermediate-acting insulin before bed; or variations of this

- **Basal-bolus regimen** of short-acting insulin 20–30 min before main meals (e.g. breakfast, lunch and the main evening meal); intermediate or long-acting insulin at bedtime

- **Basal-bolus regimen** of rapid-acting insulin analog immediately before main meals (e.g. breakfast, lunch and main evening meal); intermediate- or long-acting insulins at bedtime, probably before breakfast and occasionally at lunchtime

- **Insulin pump regimes** are regaining popularity with a fixed or variable basal dose and bolus doses with meals


Ac
Ac
Ac
NPH
7
13
18
23


Humalog
NPH
7
13
18
23

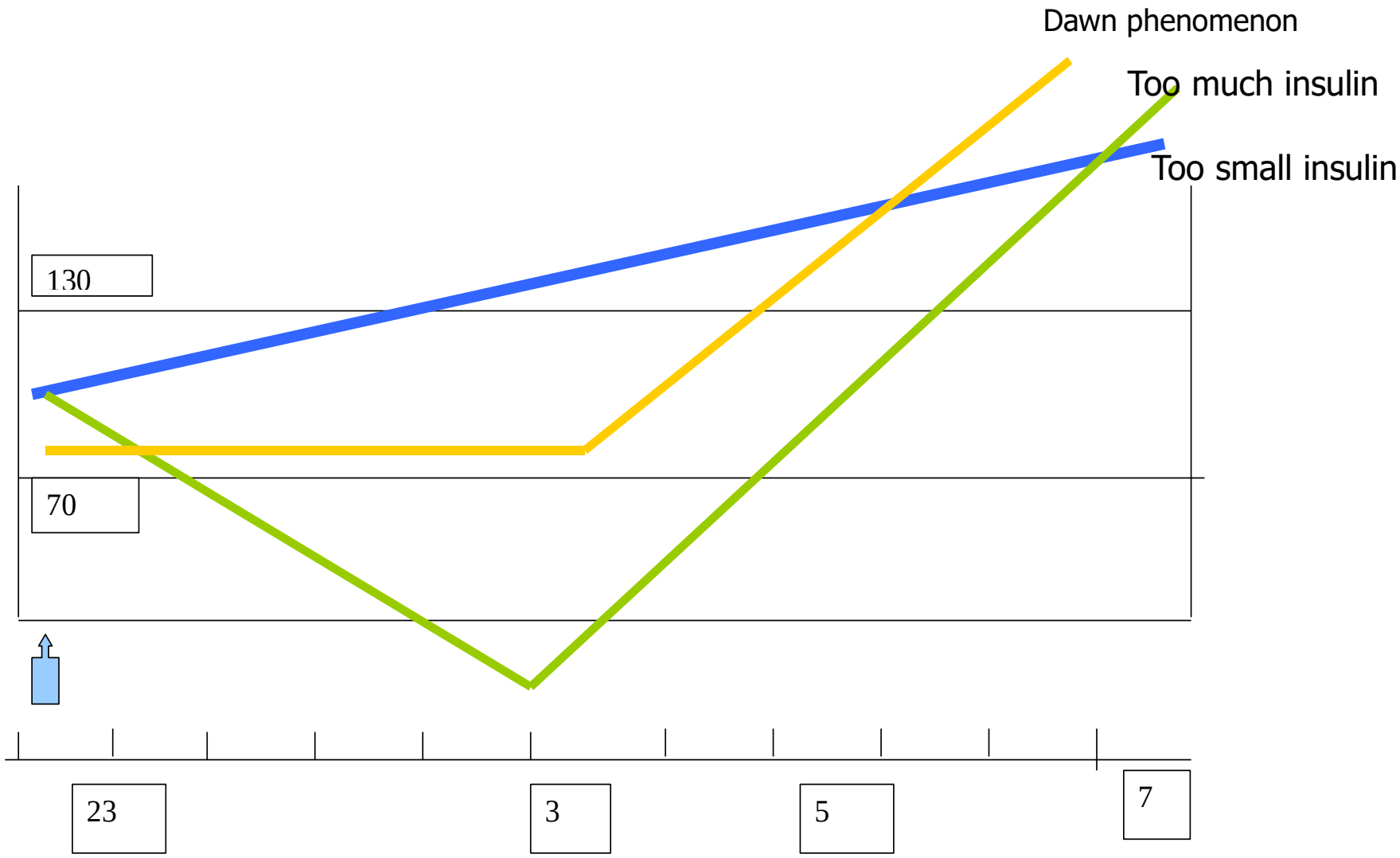
Guideline on dosage

- 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 IU/kg per day

The ‘correct’ dose of insulin is that which achieves the best attainable glycemic control for an individual child or adolescent

Dawn phenomenon

BG levels tend to rise in the hours of the morning (usually after 5.00 am) prior to waking. This is called the dawn phenomenon. 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


Dawn phenomenon
Too much insulin
Too small insulin
130
70
23
3
5
7

Nutritional management

Nutritional management is one of the cornerstones of diabetes care and education

- Achieving a balance between food intake, insulin levels and energy expenditure is an essential prerequisite for achieving glycemic control. Methods for accomplishing this show wide variations and are often complex and controversial
- Nutritional advice must be adapted to cultural, ethnic and family traditions and to the individual requirements of the child
- The psychological significance of feeding patterns, appetite and tastes of the child must not be underestimated