Physiopathology of Diabetes & Diagnosis

Contents

- Normal physiology of glucose control
- Classification of diabetes
- Type 2 diabetes
- Type 1 diabetes
- Diagnosis of diabetes
Insulin and Glucagon Regulate Normal Glucose Homeostasis

Glucagon (alpha cell)

Fasting state

Release of gut hormones — Incretins\(^1,2\) (GLP-1 & GIP)

Insulin (beta cell)

Fed state

Glucose output

Blood glucose

Liver

Muscle

Adipose tissue

Insulin Action in Muscle and Fat Cells
Mobilization of GLUT4 to the Cell Surface

- Insulin receptor
- Intracellular signaling cascades
- GLUT4 vesicle mobilization to plasma membrane
- GLUT4 vesicle integration into plasma membrane
- Glucose entry into cell via GLUT4

GLUT4 = glucose transporter 4
## Classification of Diabetes Mellitus by Etiology

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td><strong>β</strong>-cell destruction—complete lack of insulin</td>
</tr>
<tr>
<td>Type 2</td>
<td><strong>β</strong>-cell dysfunction and insulin resistance</td>
</tr>
<tr>
<td>Gestational</td>
<td><strong>β</strong>-cell dysfunction and insulin resistance during pregnancy</td>
</tr>
<tr>
<td>Other specific types</td>
<td>• Genetic defects of <strong>β</strong>-cell function</td>
</tr>
<tr>
<td></td>
<td>• Exocrine pancreatic diseases</td>
</tr>
<tr>
<td></td>
<td>• Endocrinopathies</td>
</tr>
<tr>
<td></td>
<td>• Drug- or chemical-induced</td>
</tr>
<tr>
<td></td>
<td>• Other rare forms</td>
</tr>
</tbody>
</table>
Etiology of Type 2 Diabetes
Impaired Insulin Secretion and Insulin Resistance

Genes and environment

- Impaired insulin secretion
- Insulin resistance

Impaired glucose tolerance

Type 2 diabetes
Natural History of Type 2 Diabetes Progression

- Insulin resistance increases over time.
- Insulin secretion decreases.

Pre-diabetes, Macrovascular complications, Type 2 diabetes (T2DM)

Onset, Diagnosis
Pathogenesis of Type 1 Diabetes
One Defect

- No hepatic insulin effect
  - Unrestrained glucose production
  - More glucose enters the blood

- Absent insulin secretion
  - Hyperglycemia

- No muscle/fat insulin effect
  - Impaired glucose clearance
  - Less glucose enters peripheral tissues

Glycosuria
Natural History Of “Pre”–Type 1 Diabetes

- Putative trigger
- Cellular autoimmunity
  - Circulating autoantibodies (ICA, GAD65)
  - Loss of first-phase insulin response (IVGTT)
- Glucose intolerance (OGTT)
- Clinical onset— only 10% of β-cells remain

β-Cell mass 100%

- Genetic predisposition
- Insulitis
- β-Cell injury
- “Pre”-diabetes
- Diabetes

Time

Glucose Tolerance Categories

**FPG**
- **Diabetes Mellitus**
- **IFG**
- **Normal**

**2-h PPG (OGTT)**
- **Diabetes Mellitus**
- **IGT**
- **Normal**

Plasma glucose (mg/dL)
- 240
- 220
- 200
- 180
- 160
- 140
- 126
- 120
- 100
- 80
- 60

Plasma glucose (mmol/L)
- 11.1
- 7.0
- 5.5

American Diabetes Association. *Diabetes Care*. 2007;30(suppl 1)
Criteria for the Diagnosis of Diabetes Mellitus

• Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL)

  or

• Fasting plasma glucose 7.0 mmol/L (126 mg/dL)

  or

• Two-hour plasma glucose 11.1 mmol/L (140 mg/dL) during an oral glucose tolerance test
Acute Complications of DM

- Diabetic Ketoacidosis (DKA)
- Hyperglycemic Hyperosmolar State (HHS)

Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities.
Hyperglycemia
The Defining Feature of Diabetes

Excessive glucose production

Impaired glucose clearance

Tissue injury
Two Mechanisms of Tissue Injury by Hyperglycemia

- **Glycation pathway**
  - Glycated proteins (eg, A1C)
  - Advanced glycation end products (AGEs)
  - Altered function or turnover
  - Receptor-mediated cytokine effects

- **Sorbitol pathway**
  - Sorbitol and fructose
  - Oxidative effects
  - Osmotic effects

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Chronic Complications of DM

- Microvascular
- Macrovascular
- Other
  - Gastrointestinal
  - Genitourinary
  - Dermatologic
  - Infectious
  - Cataracts
  - Glaucoma
What are the Microvascular Complications?

Hyperglycemia

- Eye
  - Retinopathy
  - Macular edema
  - Blindness

- Kidney
  - Nephropathy
    - Microalbuminuria
    - Gross albuminuria
  - Kidney failure
  - Death and/or disability

- Nerves
  - Neuropathy
    - Peripheral
    - Autonomic
  - Amputation
Retinopathy

Normal retina

Proliferative retinopathy
What are the Macrovascular Complications?

Metabolic injury to large vessels

Heart
- Coronary artery disease
  - Coronary syndrome
  - MI
  - CHF
- Coronary artery disease

Brain
- Cerebrovascular disease
  - TIA
  - CVA
  - Cognitive impairment
- Cerebrovascular disease

Extremities
- Peripheral vascular disease
  - Ulceration
  - Gangrene
  - Amputation
- Peripheral vascular disease
Macrovascular disease at diagnosis in Type 2 diabetes

- Cerebrovascular disease: 1%
- Abnormal ECG: 18%
- Hypertension: 35%
- Absent foot pulses: 13%
- Intermittent claudication: 3%

5% of all deaths in people with Type 2 diabetes are due to cardiovascular disease.

Risk of Microvascular Complications vs. A1C in Type 1 Diabetes

Results From the DCCT

Risk of Microvascular Events vs. A1C in Type 2 Diabetes

37% change per 1% change in A1C

Stratton IM et al. *BMJ*. 2000;321:405-412
A1C Predicts Myocardial Infarction in Type 2 Diabetes

UKPDS

4585 Patients Followed for 10 Years*

Relative risk

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>1</td>
</tr>
<tr>
<td>6 to &lt;7</td>
<td>1.3</td>
</tr>
<tr>
<td>7 to &lt;8</td>
<td>1.8</td>
</tr>
<tr>
<td>8 to &lt;9</td>
<td>1.9</td>
</tr>
<tr>
<td>9 to &lt;10</td>
<td>2.5</td>
</tr>
<tr>
<td>≥10</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and duration of diabetes

Stratton IM et al. *BMJ.* 2000;321:405-412
TREATMENT
Guidelines: Limitations

- Despite many current guidelines for glycaemic control there is still a lack of consensus on ‘ideal’ target and intervention values.
- Incorporation of guidelines into clinical practice can be difficult:
  - large-scale studies have shown the need for improved glycaemic control, but many patients fail to reach goals for glycaemic control.
  - the complexity of the individual’s characteristics, risk factors, needs and personal goals still need to be taken into account.
Current guidelines recommend targets for HbA1c, FPG and PPBG levels

<table>
<thead>
<tr>
<th>Glucose control</th>
<th>Healthy</th>
<th>ADA (^1)</th>
<th>AACE (^3)</th>
<th>IDF (^4)</th>
<th>ADA/EASD (^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA(_{1c}) * (%)*</td>
<td>&lt;6.0(^1)</td>
<td>&lt;7.0</td>
<td>≤6.5</td>
<td>&lt;6.5</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>FBG, mmol/L (mg/dL)</td>
<td>&lt;5.6(^2) (≤100)</td>
<td>5.0–7.2</td>
<td>≤6.0</td>
<td>&lt;6.0</td>
<td>3.89–7.22</td>
</tr>
<tr>
<td>PPBG, mmol/L (mg/dL)</td>
<td>&lt;7.8(^*\ast) (≤140)</td>
<td>&lt;10.0(*) (≤180)</td>
<td>≤7.8(*) (≤140)</td>
<td>&lt;8.0(*) (≤145)</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

\*DCCT aligned; **1-2 hours postprandial

Insulin and Glucagon Regulate Normal Glucose Homeostasis

Glucagon (alpha cell)

Fasting state

Release of gut hormones — Incretins¹,² (GLP-1 & GIP)

Insulin (beta cell)

Fed state

Blood glucose

Glucose output

Liver

Glucose uptake

Muscle Adipose tissue

Treatment of Diabetes

- Non-pharmacologic
- Oral agents
- Insulin
Non-pharmacologic

- Nutrition
- Exercise
- Life-style Change
Treatment of T2DM Is Accomplished by Different Agents via Different Modes of Action

- Insulin secretagogues
  - Insulin secretion

- Inhibitors of gluconeogenesis
  - Insulin
  - Inhibitors of glucose absorption

- Insulin sensitizers
  - Insulin resistance

- Liver/gut glucose delivery

- Glucose toxicity

- Blood glucose
Oral Anti-Diabetes Agents

**OADs**

- **INSULIN SENSITIZERS**
  - acarbose
  - GLUCOBAY (Bayer)

- **OTHERS**
  - α-Glucosidase Inhibitor
    - Biguanides
      - metformin
      - GLUCOPHAGE (Merck)
    - Thiazolidinediones / Glitazone (TZD)
      - rosiglitazone
      - AVANDIA (GSK)
      - pioglitazone
      - ACTOS (Eli Lilly)

- **INSULIN SECRETAGOGUES**
  - Sulphonylureas
    - chlorpropamide
    - DIABENESE (Pfizer)
    - glibenclamide
    - DAONIL (Aventis)
    - gliclazide
    - DIAMICRON (Servier)
    - glipizide
    - MINIDIAB (Pfizer)
    - glimepiride
    - AMARYL (Aventis)
  - Non-Sulphonylureas
    - repaglinide
    - NOVONORM (Novo)
    - nateglinide
    - STARLIX (Novartis)
How Different Agents Regulate Hyperglycemia in Diabetes

Pancreatic beta cells
- Sulfonylureas
- Meglitinides
  Stimulate insulin release

Liver
- PPARs (TZDs or glitazones)
- Biguanides
- Insulin
  Inhibit glucose production

Muscle
- PPARs (TZDs or glitazones)
- Biguanides
- Insulin
  Stimulate glucose uptake

Gut
- Alpha-glucosidase inhibitors
  Retard glucose reflux into circulation

PPAR=peroxisome proliferator-activated receptor agonist.

## Therapeutic Effects and Limitations

<table>
<thead>
<tr>
<th>Class</th>
<th>Primary Effect</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>↓ HbA1c</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>↓ PPG</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>↓ HbA1c</td>
<td>GI adverse effects, lactic acidosis (rare)</td>
</tr>
<tr>
<td>PPARs</td>
<td>↓ HbA1c</td>
<td>Weight gain, edema, anemia, potential for liver toxicity</td>
</tr>
<tr>
<td>Alpha-glucosidase</td>
<td>↓ PPG</td>
<td>GI adverse effects</td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>↓ HbA1c</td>
<td>Injectable route, hypoglycemia, weight gain</td>
</tr>
</tbody>
</table>

PPG = postprandial glucose; GI = gastrointestinal.

Insulin Deficiency and Resistance

**Type 2 DM**

- Insulin resistance
- Relative function (%)
- Insulin level
- \( \beta \)-cell failure
- Duration of Diabetes (years)

The Number of Medications Taken Usually Increases With Duration of Disease

IGT=impaired glucose tolerance.
## Oral Monotherapy: Failure Is Inevitable

### Type 2 DM

Failure rates for oral monotherapy in type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>3 Years</th>
<th>6 Years</th>
<th>9 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 49</td>
<td>&gt;45%</td>
<td>NS</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>(N=4075)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS 24</td>
<td>NS</td>
<td>52%</td>
<td>NS</td>
</tr>
<tr>
<td>(N=458)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Failure rates defined as A1C concentration >7% in UKPDS 49 and >8% in UKPDS 24.
NS, not studied; UKPDS, United Kingdom Prospective Diabetes Study.

Insulin Therapy
Action of Insulin

Graph showing the levels of Glucose and Insulin over time with breakfast, lunch, and dinner indicated.

Bolli et al., 1999
Normal Insulin Secretion: The Basal-Bolus Insulin Concept

Endogenous Insulin
Bolus Insulin
Basal Insulin

Time of Administration
B, breakfast; L, lunch; D, dinner; HS, bedtime.

Adapted from:
## Comparison of Human Insulins and Analogues

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
<th>Onset of Action</th>
<th>Peak of Action (h)</th>
<th>Duration of Action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human</td>
<td>30-60 min</td>
<td>2-4</td>
<td>6-8</td>
</tr>
<tr>
<td>Rapid Acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro/Aspart/Glulisine</td>
<td>5-15 min</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-3 h</td>
<td>5-7</td>
<td>13-16</td>
</tr>
<tr>
<td>Lente</td>
<td>1-3 h</td>
<td>4-8</td>
<td>13-20</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2 h</td>
<td>Peakless</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Ultralente</td>
<td>2-4 h</td>
<td>8-14</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

Time course of action of any insulin can vary in different people or at different times in the same person; thus, time periods indicated here should only be considered general guidelines.

Insulin Time Action Curves

- Rapid (Lispro, Aspart/Glulisine)
- Short (Regular)
- Intermediate (NPH)
- Prolonged Intermediate (Ultralente)
- Long (Glargine, Detemir)

Time (Hours): 0 2 4 6 8 10 12 14 16 18 20

Relative Insulin Effect
Twice-daily pre-mixed insulins

Breakfast
Dinner
Lunch
Snack

Regular insulin
NPH insulin
Normal endogenous insulin
Both insulins combined
Risk of hyperglycaemia
Risk of hypoglycaemia

NPH=neutral protamine Hagedorn.
Insulin Treatment Regimens

- OAD + Basal
- OAD + Bolus
- Premix
- Basal + Bolus
## Basal insulins: The choices

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin analogues</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus®</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>Levemir®</td>
</tr>
<tr>
<td>NPH [Neutral Protamine Hagedorn] insulin</td>
<td>Insulatard®, Novolin® N, Protaphane®</td>
</tr>
<tr>
<td><strong>Human insulin</strong></td>
<td></td>
</tr>
<tr>
<td>Lente insulin (zinc suspension)</td>
<td>Iletin Lente, Insulin Lente Pork (Humulin® L*, Novolin® L*)</td>
</tr>
<tr>
<td>Ultralente insulin (extended zinc suspension)</td>
<td>(Humulin® U*, Ultratard®*)</td>
</tr>
</tbody>
</table>

*Discontinued*
Basal Insulin

Long acting (e.g. glargine)
- Provides optimal basal insulin coverage with a once daily dosing
- Lower risk of hypoglycemia
- Flat release profile

Intermediate acting (e.g. NPH, lente)
- Less optimal as a basal insulin, because it doesn’t have a flat insulin release profile
- More hypoglycemic episodes
**Prandial insulin – promotes total flexibility in meal timing**

<table>
<thead>
<tr>
<th>Ultra short/rapid acting insulin analogues (lispro)</th>
<th>Short acting insulin (regular insulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Rapid onset of action</td>
<td>- Less optimal profile as compared to rapid acting analogues</td>
</tr>
<tr>
<td>- Forms monomers and thus is absorbed rapidly</td>
<td>- Forms hexamers and has slower absorption</td>
</tr>
<tr>
<td>- Duration of action lasts for 4 hours regardless of the dose given</td>
<td>- Sustained duration of action may lead to post-prandial hypoglycemia</td>
</tr>
<tr>
<td>- Less hypoglycemia</td>
<td></td>
</tr>
</tbody>
</table>
Limitations of Intermediate Insulins: NPH

- Does not mimick basal insulin profile\textsuperscript{1,2}
  - Variable absorption
  - Pronounced peak
  - 13-16–hour duration
  - Requires twice-daily administration to provide 24-hour basal insulin coverage

- Fear of hypoglycaemia\textsuperscript{3}
  - Major factor limiting insulin adjustments

The Ideal Basal Insulin

- 1 injection daily covers 24 hours
- No peaks
- Low incidence of hypoglycaemia
- Good glycaemic control
- Less weight gain
- Safe
- Predictable
- Easy handling
  - Injection at different sites
  - Injection at different times
  - No mixing necessary/clear solution
- High treatment satisfaction and acceptance
Characteristics of Insulin Glargine

- Recombinant human insulin analogue\(^1\)
- Basal (long-acting) insulin\(^1\)
- Relatively constant peakless concentration over 24 hours\(^1,2\)
- Once-daily SC administration\(^1\)
- For adult and paediatric (aged ≥6 years) patients with type 1 diabetes and adults with type 2 diabetes\(^1,2\)
- Lower risk of hypoglycaemia than with traditional basal insulins\(^1\)
- Flexible dosing\(^1\)

1. Lantus\(^\circledast\) (insulin glargine) EMEA Summary of Product Characteristics. 2002.
ADA/EASD consensus algorithm for type 2 diabetes mellitus (2006)

Diagnosis

Lifestyle intervention and metformin

HbA\(_1c\) \(\geq 7\%\)

No

Add basal insulin\(^c\) – most effective

HbA\(_1c\) \(\geq 7\%\)

No

Intensify insulin\(^c\)

Yes\(^a\)

Add glitazone\(^b\)

HbA\(_1c\) \(\geq 7\%\)

No

Add sulfonylurea

Yes\(^a\)

Add basal insulin

HbA\(_1c\) \(\geq 7\%\)

No

Add glitazone – no hypoglycemia

Yes\(^a\)

Add basal or intensify insulin\(^c\)

Add sulfonylurea\(^b\)

HbA\(_1c\) \(\geq 7\%\)

No

Intensive insulin + metformin +/- glitazone

---

\(a\) Check HbA\(_1c\) every 3 months until HbA\(_1c\) is <7%, and then at least every 6 months.

\(b\) Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

\(c\) See Nathan et al for initiation and adjustment of insulin.

Nathan D, et al.
ADA/EASD consensus algorithm

for type 2 diabetes mellitus (2008)

Tier 1: well-validated therapies

At diagnosis:
Lifestyle + Metformin

Lifestyle + Metformin + Basal insulin

Lifestyle + Metformin + Sulfonylureas

Lifestyle + Metformin + Intensive insulin

Tier 2: Less well validated therapies

STEP 1

Lifestyle + Metformin + Pioglitazone
No hypoglycaemia
Oedema/CHF
Bone loss

Lifestyle + metformin + GLP-1 agonist
No hypoglycaemia
Weight loss
Nausea/vomiting

STEP 2

Lifestyle + metformin + Pioglitazone + Sulfonylurea

Lifestyle + metformin + Pioglitazone + Basal insulin

STEP 3