Diabetes Mellitus Masterclass
Chapter 1

WHAT IS DIABETES?

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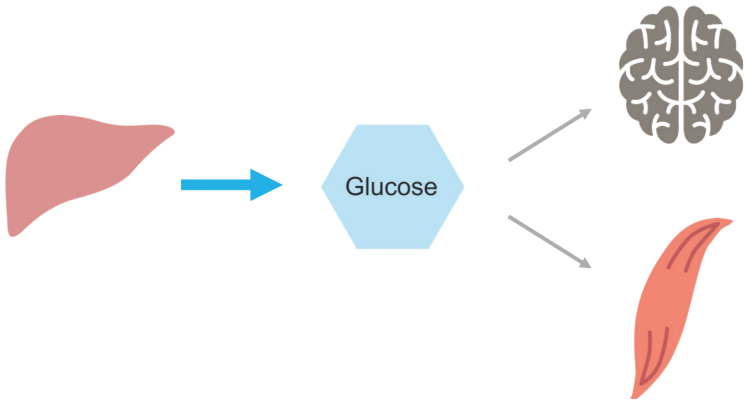
BASICS OF GLUCOSE REGULATION

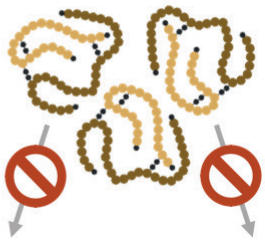
In the fasting state, the majority of glucose is produced by the liver. This glucose is used by the brain for fuel, and by other tissues, including the gut and muscle.



Glucose production and uptake are balanced, maintaining fasting blood glucose levels between 70–90 mg / dL (3.9–5.0 mmol / L).

Impairments in insulin production (insulin deficiency) or insulin action (insulin resistance) can cause diabetes, a disorder characterized by high blood sugars. Increased glucose production from the liver leads to fasting hyperglycemia. Impaired insulin response with meals leads to post-meal hyperglycemia.

Insulin deficiency



Insulin resistance

Hyperglycemia

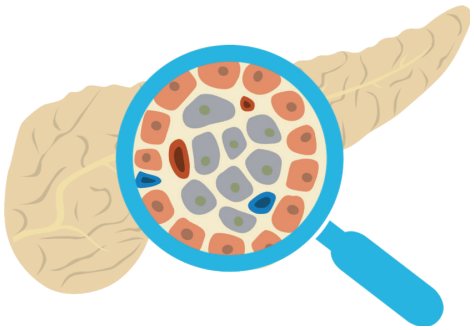
High blood sugars can cause multiple symptoms

- **Polyuria** due to osmotic diuresis
- **Polydipsia** also due to osmotic diuresis and volume depletion
- **Blurred vision** due to changes in lens shape
- Genital yeast **infections** due to high glucose levels in urine

Treatment of diabetes is initially aimed at decreasing the **immediate** symptoms of hyperglycemia, but the ultimate goal is to limit the **long-term** complications related to diabetes.

TYPE 1 DIABETETS

Type 1 diabetes is also known as autoimmune diabetes, and results from destruction of the beta cells in the pancreas, which leads to absolute insulin deficiency.

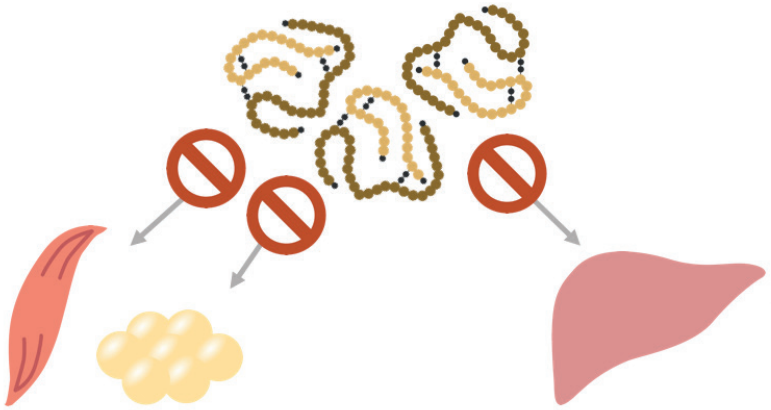


Features of type 1 diabetes

- Patients tend to be thinner, with normal BMI
- Symptoms present abruptly
- Presence of insulin autoantibodies (GAD65, IA-2, anti-insulin Ab and ZnT8 zinc finger Ab)
- Low insulin, as measured by C-peptide
- Can present at **any age**, with at least 25% of patients diagnosed as adults
- Requires insulin for therapy from time of diagnosis

TYPE 2 DIABETES

Type 2 diabetes occurs as a result of insulin resistance. These patients often have high insulin levels, but suffer from insulin resistance, meaning the target organs are unable to *see* the insulin—resulting in a relative insulin deficiency.



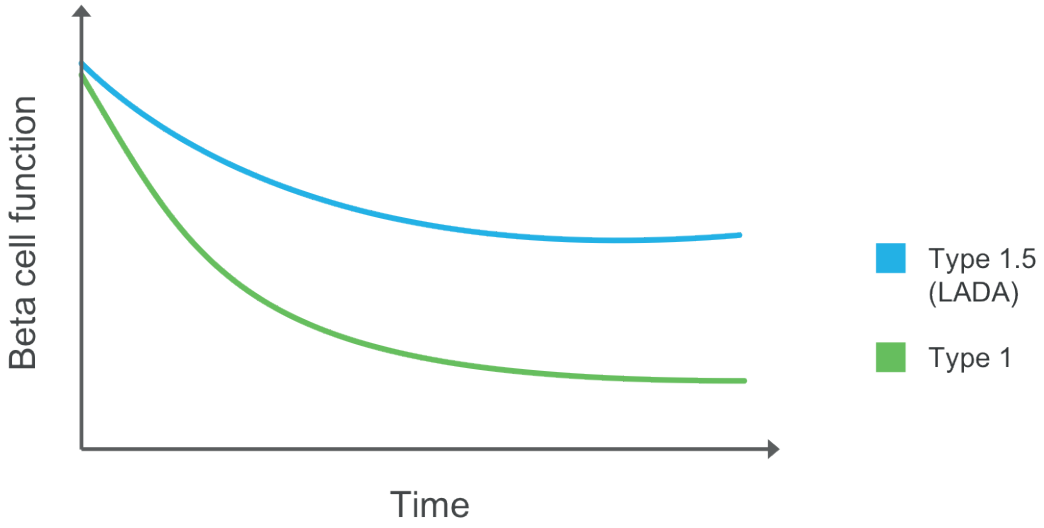
Features of type 2 diabetes

- Patients are typically overweight adults
- Strong genetic component
- Insidious onset
- May be initially controlled with diet and exercise
- As disease progresses, additional medications are often needed

OTHER FORMS OF DIABETES

Latent autoimmune diabetes of adults (LADA)

This is a variation of autoimmune, or type 1 diabetes, that progresses more slowly than typical type 1 diabetes. It is sometimes referred to as type 1.5 diabetes.



Clinical features

- Presents in adulthood
- Can be managed without insulin for more than six months
- Patients lack clinical features of type 2 diabetes (e.g., obesity, metabolic syndrome, family history)
- Positive insulin autoantibodies on labs
- Will ultimately need insulin treatment

Maturity onset diabetes of the young (MODY)

MODY is an inherited form of diabetes that results from a single gene mutation that leads to impaired insulin release from beta cells.

Clinical features

- Diagnosed in late teens or early 20s
- May be misdiagnosed as either type 1 or type 2 diabetes

- Patients lack clinical features of type 2 diabetes
- Negative insulin autoantibodies
- Strong multigenerational history of similar diabetes presentations

Most common mutations involve

- Glucokinase gene
  - patients present with mild fasting hyperglycemia
  - does not require treatment
- HNF-1A and HNF-4A genes
  - requires treatment
  - responds very well to sulfonylureas

Gestational diabetes (GDM)

GDM is diabetes that develops during pregnancy, and is usually detected during screening for diabetes between 24–28 weeks gestation. These glucose abnormalities will often resolve following delivery, but it is important to recognize and appropriately treat GDM to prevent complications for both mother and baby. This will be covered in more detail in a later chapter.

Post-transplant diabetes

Patients who have had solid organ transplants are at risk of developing what is known as post-transplant diabetes. This is often due to medications required to prevent rejection of the transplanted organ.

- Prednisone
  - can cause insulin resistance
- Tacrolimus
  - inhibits insulin release and is directly toxic to beta cells, causing insulin deficiency
- Sirolimus
  - causes insulin resistance

Patients should be screened for the development of post-transplant diabetes 90 days following transplant and often require insulin therapy to control blood sugars if diagnosed.

READING LIST

An overview of the different classifications of diabetes:
American Diabetes Association. 2011. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* **34**: S62–S69.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3006051/

Review of LADA:
Stenström, G, Gottsäter, A, Bakhtadze, E, et al. 2005. Latent autoimmune diabetes in adults: definition, prevalence, beta-cell function, and treatment. *Diabetes.* **54**: S68–S72.
https://www.ncbi.nlm.nih.gov/pubmed/16306343

Review of MODY:
Fajans, SS, Bell, GI, and Polonksy, KS. 2001. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Eng J Med.* **345**: 971–980.
https://www.ncbi.nlm.nih.gov/pubmed/11575290

A more detailed article discussing the discovery of MODY and the underlying pathophysiology:
Fajans, SS and Bell, GI. 2011. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care.* **34**: 1878–1884.
https://www.ncbi.nlm.nih.gov/pubmed/21788644