Definition

- The term DIABETES MELLITUS refer to a state of HYPERGLYCEMIA resulting usually from progressive loss of insulin secretion from the beta cell (–/+) superimposed on a background of insulin resistance, resulting in relative insulin deficiency.

Combination : insulin resistance (Variable degrees) → Type 2
+ relative or absolute insulin deficiency
type 2 — type 1 + type 2 ← في مراحل متأخرة

PREVALENCE

- Diabetes is estimated to affect > 500 millions adults worldwide, with a global prevalence of 10.5% among adults.
- Type 2 diabetes accounts for 90-95% of cases of diabetes worldwide.
- The prevalence of type 2 diabetes has risen alarmingly in the past decade, linked to the trends in obesity and sedentary lifestyle.
- Given the marked increase in childhood obesity, there is concern that the prevalence of diabetes will continue to increase substantially.
- Type 1 diabetes accounts for another 5 to 10% diabetes in adults .
- Known monogenic causes of diabetes represent a small fraction of cases.

- Common - Top 10

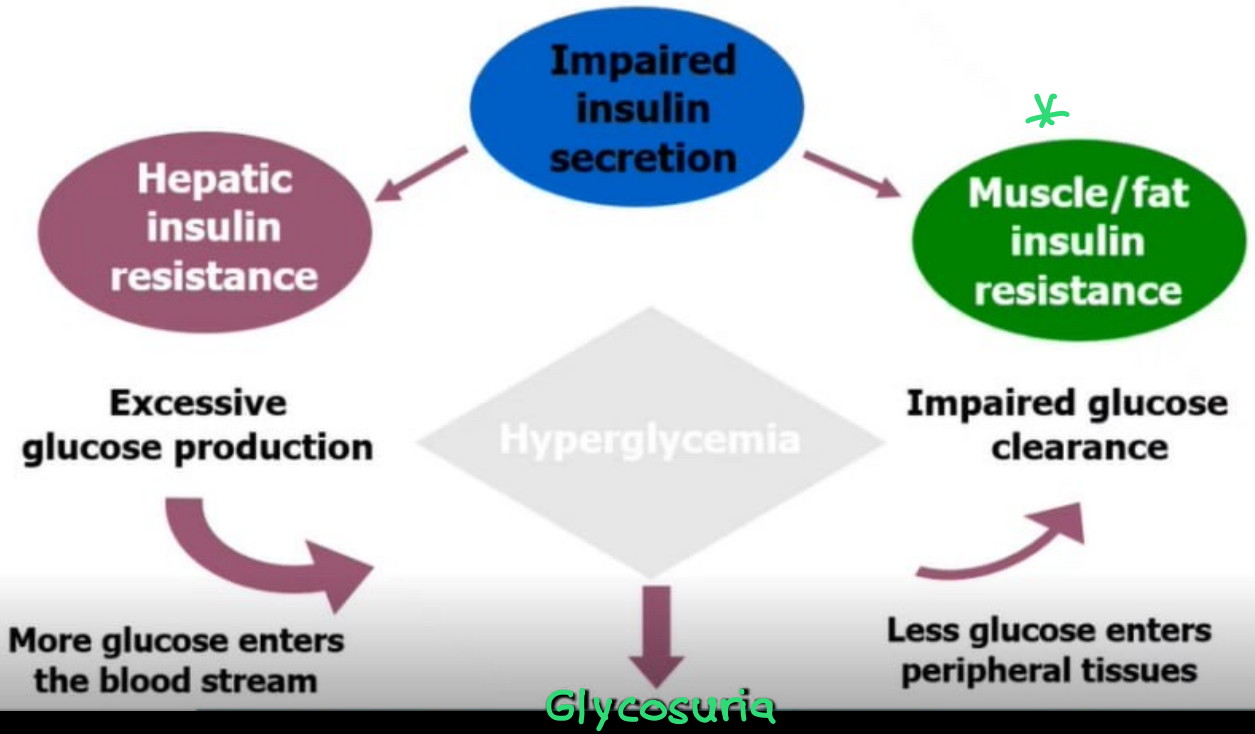
* Jordan: 25% → Diabetic / prediabetic
: 11-13% → أغلب الأرقام

Classification of Diabetes Mellitus by Etiology

- **Type 1** — autoimmune destruction of the beta cells (type 1A)
  nonautoimmune islet destruction (type 1B)
- **Type 2** — β-cell dysfunction (1) and insulin resistance (2)
  - β-cell dysfunction: Variable degrees
  - insulin resistance: impaired insulin function
- **Gestational** — β-cell dysfunction and insulin resistance during pregnancy
- **Other specific types**
  - Pancreatic diabetes.
  - Endocrinopathies
  - Drug- or chemical-induced
  - Other rare forms

* Main problem in Both: inadequate control of Blood Glucose by endogenous insulin.
* Natural History of Type 2: progressive decline in the endogenous secretion of insulin.

Pathogenesis of Type 2 Diabetes : Two Defects



Pathogenesis of type 2 diabetes mellitus

- Multifactorial => more complicated
- Type 2 diabetes is a polygenic disease, with complex interaction between genetic and environmental factors contributing to disease risk.

Cause Decrease of B cell function

- Patients typically present with a combination of :
  1- Varying degrees of peripheral insulin resistance
  2- Relative or absolute defective insulin secretion (beta cell dysfunction).

- **Insulin resistance :**

Attributed to predominantly "environmental" factors related to overeating, sedentary lifestyle, and resulting overweight and obesity, with less prominent contributions from aging and genetics.

- **Impaired insulin secretion:**

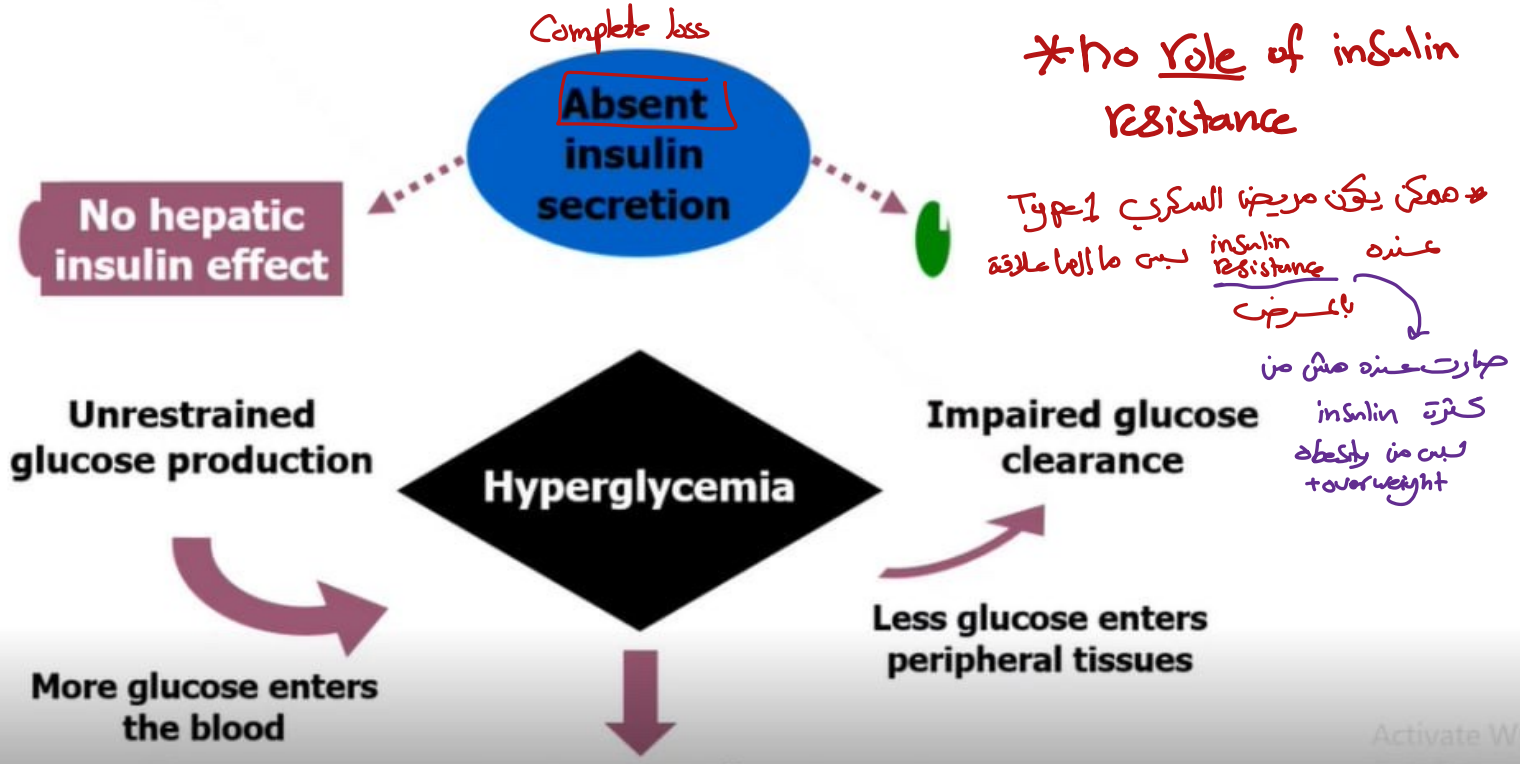
Resulting from genetic influences and the programming of the beta cell mass and function in utero.

- Hyperglycemia itself can impair pancreatic beta cell function and exacerbate insulin resistance ("glucotoxicity"), leading to a vicious cycle of hyperglycemia causing a worsening metabolic state.

* إذا الشخص عنده Genetic predisposition to Diabetes راح يصير عنده السكري حتى لو كان ببيأكل صحي ومحافظ على وزنه بس هاي العوامل بتقلل من progression of diabetes

* إذا اجى المريض أول مرة وعنده Hyperglycemia بنسميه Transient Shutdown
↳ can improve with treatment + exercise to improve endogenous insulin secretion

Pathogenesis of Type 1 Diabetes : One Defect



*no role of insulin resistance

*ممكن يكون مريض السكري Type1 عنده insulin resistance بس ما الها علاقة باعراض

صارت عنده هيش من insulin كثرة obesity بس من overweight

Has 2 peaks ↗ 4-6 ↘ 12-15

Type 1A diabetes:

- Autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans leading to **absolute** insulin deficiency.

- Occurs in **genetically susceptible** subjects, triggered by one or more **environmental agents**, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. This long latent period is a reflection of the large number of functioning beta cells that must be lost before hyperglycemia occurs.

* Autoantibodies directed against Autoantigens within pancreatic B cells
* How to confirm the presence of Autoimmune destruction?
  Autoimmune marker test

Confirmed targets of autoantibodies in type 1 diabetes

* Insulin
* Glutamic acid decarboxylase (GAD) important in Glucose homeostasis
Insulinoma associated antigens 2 (alpha and beta)
ZnT8 (zinc transporter)

Type 1B or "idiopathic" diabetes:

- Some patients with absolute insulin deficiency have no evidence of autoimmunity and have no other known cause for beta cell destruction.

-ve titer

- Presence of nonautoimmune pathophysiologic processes leading to near-complete loss of beta cell function.

* Management of Type 1A is the same as Type 1B

Monogenic diabetes (formerly called maturity onset diabetes of the young)

Known gene

Rare

* Multigenerational family History

- Diabetes diagnosed at a young age (<25 years)
- Autosomal dominant transmission with lack of autoantibodies.
- MODY is the most common form of monogenic diabetes, accounting for 1-2 % of diabetes.
- Many patients are misclassified as having either type 1 or 2 diabetes.
- The original MODY nomenclature ("MODY1," "MODY2," "MODY3," etc) has bee replaced by the term "monogenic diabetes" with the name of the gene associated with the trait.

- The genes involved control pancreatic beta cell development, function, and regulation, and the mutations in these genes cause **impaired glucose sensing and insulin secretion with minimal or no defect in insulin action.**
- Mutations in hepatocyte nuclear factor-1-alpha (*HNF1A,50-65%*) and the glucokinase(*GCK,15-30%*) genes are the most commonly identified.
- Mutations in hepatocyte nuclear factor-4-alpha (*HNF4A*) account for approximately 10% of MODY cases.
- Some members of a family have the genetic defect but do not develop diabetes; the reason for this is unclear. Other patients may have the MODY phenotype but do not have an identifiable mutation in any of the known MODY genes.

Latent autoimmune diabetes in adults (LADA)

❑ **Diagnosis** :

- In an adult who are positive for at least one islet autoantibody with prolonged preservation of insulin secretion.
- LADA may be considered a slowly progressive **variant of type 1 diabetes**. Patients with LADA are a heterogeneous group with variable titers of antibodies, BMI, and rate of progression to insulin dependence.
- Adults with LADA may not require insulin treatment at diagnosis but typically progress to insulin dependence after several months to years.
- The clinical utility of the diagnosis lies in the identification of patients with a clinical course that will differ from that in patients with type 2 diabetes. The presence and degree of elevation of anti-GAD or anti-ICA antibodies can help predict accelerated disease progression, an earlier requirement for insulin therapy, subtherapeutic responses to oral hypoglycemic medications, and greater risk of ketoacidosis.
- **Genetics**:

LADA shares genetic features of both type 1 and type 2 diabetes.

✓ autoimmune destruction ⇒ +ve for at least 1 of the antibody in type 1A

Age
20-30

* degree of hyperglycemia * rate of progression as type 1 diabetes

- **When to perform islet autoantibody testing**

1. We measure autoantibodies when the diagnosis of type 1 or type 2 diabetes is uncertain by clinical presentation.
2. Patients who have a sub-therapeutic response to initial therapy with sulfonylureas or metformin
3. Those without overweight or obesity. => lean body habitus
4. Individuals with a personal or family history of autoimmune disease.
5. Young adults (age <35 years)
6. Adults age ≥35 years who present with unintentional weight loss or ketoacidosis at the time of diagnosis.
7. Absence of family history of type 2 DM.
8. Catabolic presentation (eg, weight loss, ketonuria)

Family History is more Significant in Type 2

- 5-10% of the patients with Type 1 have first degree family history
- 75-90% of ~ ~ ~ Type 2 ~ ~ ~ ~ ~

Gestational Diabetes

- Occurs when a woman's pancreatic function is insufficient to overcome the insulin resistance associated with the pregnancy state (placental secretion of diabetogenic hormones)
- Develops in the second or third trimester and usually resolves after birth.
- High risk of perinatal morbidity and mortality
- High risk of later type 2 diabetes in both mother and baby.
- Diagnosed by specific glucose tolerance test methods.
- Requires intensive dietary and glycemic management.

Clinical features distinguishing type 1 diabetes, type 2 diabetes, and monogenic diabetes*

Clinical features	Type 1 diabetes mellitus	Type 2 diabetes mellitus	Monogenic diabetes
Age of diagnosis (years)	Majority <25, but may occur at any age	Typically >25 but incidence is increasing in adolescents, paralleling increasing rates of obesity in children and adolescents¶	<25
Weight	Usually thin, but with obesity epidemic overweight and obesity at diagnosis becoming more common	>90% at least overweight	Similar to general population
Autoantibodies	Present	Absent	Absent
Insulin dependent	Yes	No	No
Insulin sensitivity	Normal when controlled	Decreased	Normal (may be decreased if obese)
Family history of diabetes	Infrequent (5 to 10%)	Frequent (75 to 90%)	Multigenerational, ie, ≥3 generations
Risk of diabetic ketoacidosis	High	Low	Low

Major Risk Factors (Type2 DM)

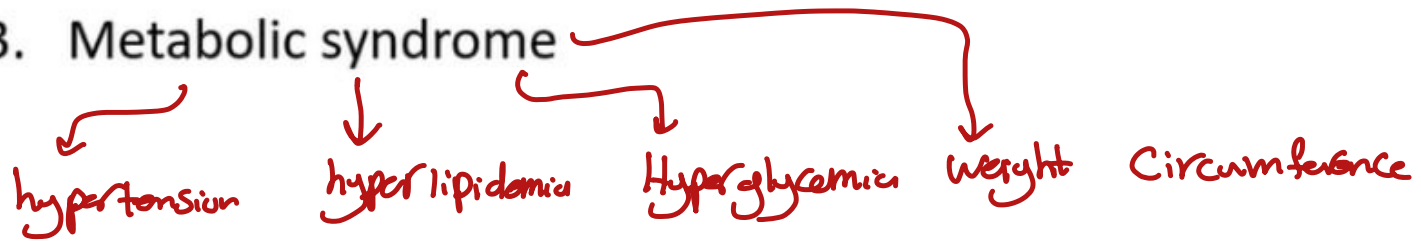
Categories of increased risk for diabetes (prediabetes)*

annual screening

FPG 100 to 125 mg/dL (5.6 to 6.9 mmol/L) – IFG
2-hour post-load glucose on the 75 g OGTT 140 to 199 mg/dL (7.8 to 11.0 mmol/L) – IGT
A1C 5.7 to 6.4% (39 to 46 mmol/mol)

Medical conditions associated with an increased risk of type 2 diabetes including:

1. Gestational diabetes
2. Polycystic ovary syndrome
3. Metabolic syndrome



Obesity

- Obesity is the most important modifiable risk factor for type 2 diabetes.
- Inducing resistance to insulin-mediated peripheral glucose uptake.
- The mechanism by which obesity induces insulin resistance is poorly understood.
- Reversal of obesity decreases the risk of developing type 2 diabetes and improves glycemic management and can lead to remission in diabetic patients.

1) Changing life Style → ما زبط → 2) pharmacological treatment

3) Bariatric Surgery → آخر حل

- The degree of insulin resistance and the incidence of type 2 diabetes are highest in those with central or abdominal obesity, as measured by waist circumference.

- Intra-abdominal (visceral) fat rather than subcutaneous or retroperitoneal fat appears to be of primary importance.

- Why the pattern of fat distribution is important and the relative roles of genetic and environmental factors in its development are not known!

Family history/Genetic susceptibility

- The risk is likely mediated through genetic, anthropometric (BMI and waist circumference), and lifestyle (diet, physical activity, smoking) factors.
- Family history: Up to 75 to 90% of those with T2DM have an affected close relative.
- Any first degree relative ..... 2X-3X increase risk of developing DM.
- With both a maternal and paternal history of type 2 diabetes...5X-6X increase risk of DM .
- Insulin resistance and impaired insulin secretion in type 2 diabetes have a substantial genetic component.

Lifestyle factors

- Insulin resistance and impaired insulin secretion in type 2 diabetes have a substantial genetic component, and can be influenced, both positively and negatively, by behavioral factors, such as **physical activity**, **diet**, **smoking**, alcohol consumption, body weight, and sleep duration. Improving these lifestyle factors can reduce the risk of diabetes mellitus.

Exercise

- A sedentary lifestyle lowers energy expenditure, promotes weight gain, and increases the risk of type 2 diabetes .
- Among sedentary behaviors, prolonged television watching is consistently associated with the development of obesity and diabetes.
- Physical inactivity, even without weight gain, appears to increase the risk of type 2 diabetes.
- Physical activity of moderate intensity reduces the incidence of new cases of type 2 diabetes, regardless of the presence or absence of IGT.

* physical activity has direct effect on glucose control even without weight reduction

Smoking

- Several large prospective studies have raised the possibility that cigarette smoking increases the risk of type 2 diabetes.
- Secondhand smoke also increases the risk.
- While a definitive causal association has not been established, a relationship between cigarette smoking and diabetes mellitus is biologically possible based upon a number of observations:

1. Smoking increases the blood glucose concentration after an oral glucose challenge.
2. Smoking may impair insulin sensitivity.
3. Cigarette smoking has been linked to increased abdominal fat distribution.

Dietary patterns

Adherence to a diet high in fruits, vegetables, nuts, whole grains, and olive oil is associated with a lower risk of type 2 diabetes.