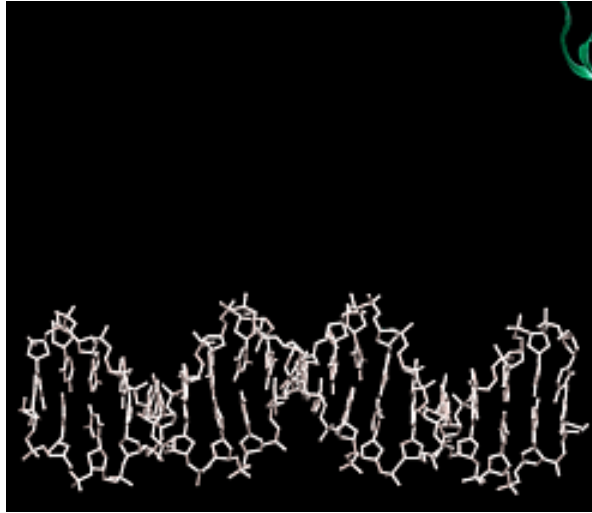




Hiba Abbasi,
MD, Endocrinologist
Department of
Internal Medicine
School of Medicine
University of Jordan

Diabetes mellitus

The History of Diabetes mellitus

- ❑ Approximately 1550BC an Egyptian manuscript mentions a rare disease that causes the patient to lose weight rapidly and **urinate frequently**. This is thought to be the first reference to **diabetes**.
- ❑ Around the 11th Century, Some physicians taste the urine, and diabetes is given its second name **mellitus**, meaning '**sweet as honey**' in Latin.
- ❑ Diabetes mellitus is taken from the Greek word *diabetes*, meaning siphon - to pass through and the Latin word *mellitus* meaning sweet.

- ❑ In 1922 Banting, Best, and Collip purified the hormone insulin from the pancreas of cows at the University of Toronto, leading to the availability of an effective treatment for diabetes in 1922.
- ❑ Over the years, exceptional work has taken place, and multiple discoveries, as well as management strategies, have been created to tackle this growing problem.
- ❑ Unfortunately, even today, diabetes is one of the most common chronic diseases in the country and worldwide.

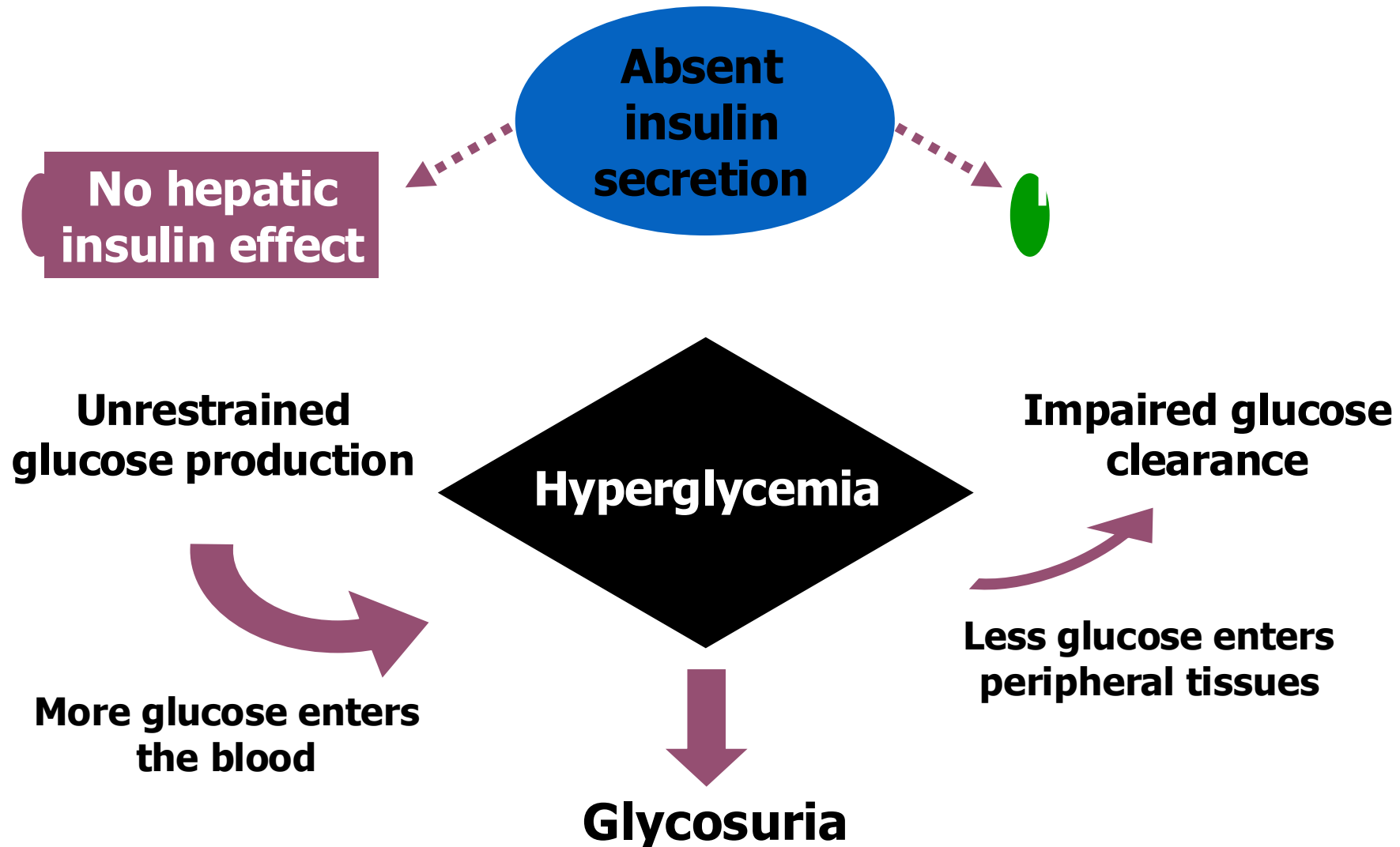
PREVALENCE

- ❑ 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% of the cases.
- ❑ Known monogenic causes of diabetes represent a small fraction of cases.

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 and insulin resistance
- **Gestational** β -cell dysfunction and insulin resistance during pregnancy
- **Other specific types**
 - Pancreatic diabetes.
 - Endocrinopathies
 - Drug- or chemical-induced
 - Other rare forms

Pathogenesis of Type 1 Diabetes : One Defect



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.

- ❑ **Genetic susceptibility** : Polymorphisms of multiple genes are known to influence the risk of type 1A diabetes.
- ❑ **Target autoantigens** : There are a number of autoantigens within the pancreatic beta cells play important roles in the initiation or progression of autoimmune islet injury including: glutamic acid decarboxylase (GAD), insulin, insulinoma-associated protein 2 (IA-2), and zinc transporter ZnT8.
- ❑ **Environmental factors** include pregnancy-related and perinatal influences, viruses, and ingestion of cow's milk and cereals.

Confirmed targets of autoantibodies in type 1 diabetes

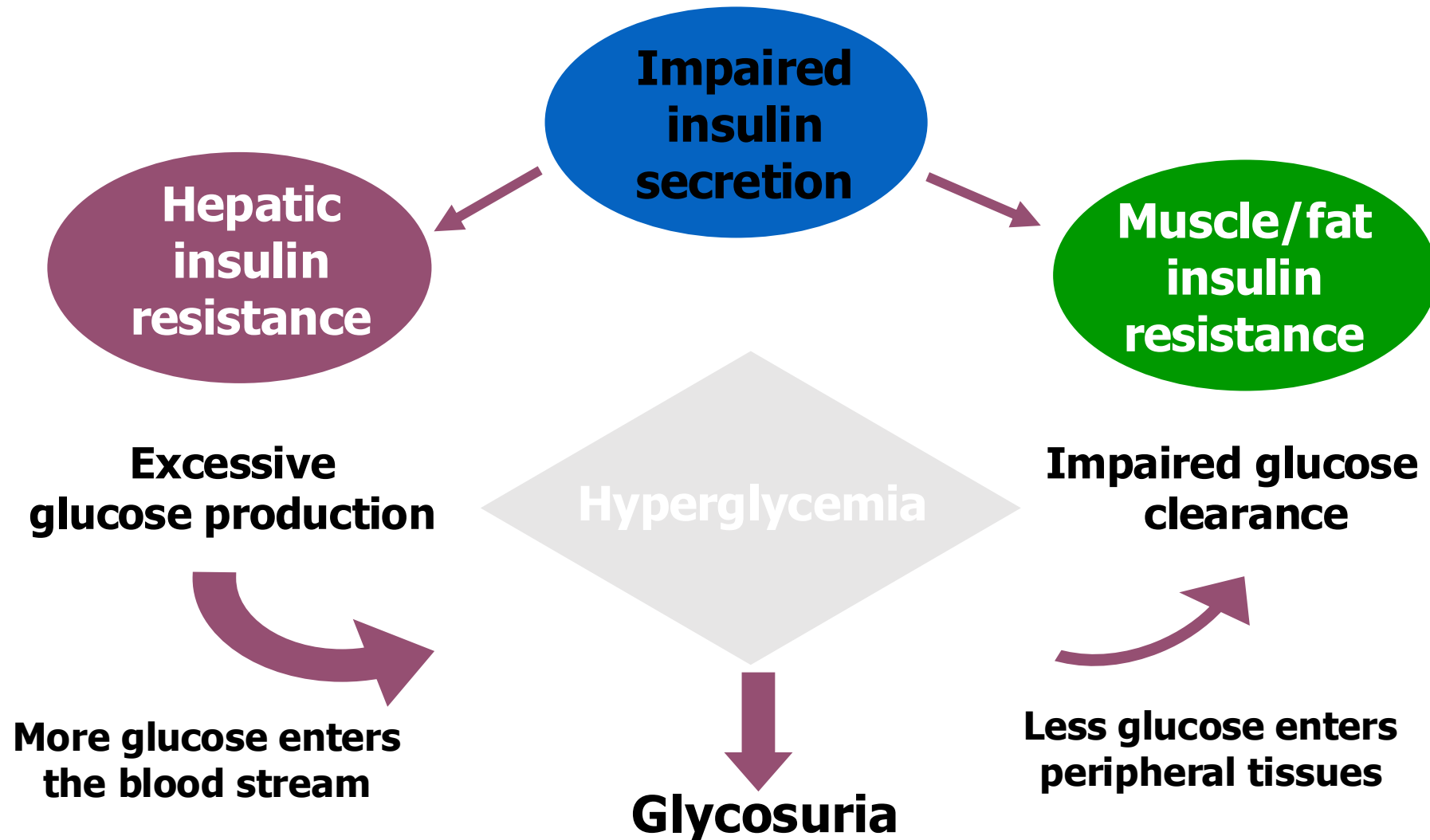
Insulin
Glutamic acid decarboxylase
Insulinoma associated antigens 2 (alpha and beta)
ZnT8 (zinc transporter)

UpToDate

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

Pathogenesis of Type 2 Diabetes : Two Defects



Pathogenesis of type 2 diabetes mellitus

- ❑ Multifactorial

- ❑ Type 2 diabetes is a polygenic disease, with complex interaction between genetic and environmental factors contributing to disease risk.

- ❑ Patients typically present with a combination of varying degrees of insulin resistance and 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.

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

- Diabetes diagnosed at a young age (<25 years)
- Autosomal dominant transmission and lack of autoantibodies.
- MODY is the most common form of monogenic diabetes, accounting for 2 to 5% of diabetes.
- Many patients are misclassified as having either type 1 or 2 diabetes.
- Several different genetic abnormalities have been identified, each leading to a different type of disease.
- The original MODY nomenclature ("MODY1," "MODY2," "MODY3," etc) has been 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 :**
- An adult-onset diabetes 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, body mass index (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.** In genotyping analyses, LADA shares genetic features of both type 1 and type 2 diabetes.

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

Gestational Diabetes

- ❑ 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)*

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.

- ❑ 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.
- ❑ 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.

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.

CLINICAL PRESENTATION

Type 2 DM:

- ☐ The majority of patients are asymptomatic at presentation, with hyperglycemia noted on routine laboratory evaluation.
- ☐ The frequency of symptomatic diabetes has been decreasing in parallel with improved efforts of screening.
- ☐ The classic symptoms of hyperglycemia (including polyuria, polydipsia, nocturia, blurred vision, and weight loss) are often noted only in retrospect after high blood glucose reading.
- ☐ DKA as the presenting symptom of type 2 diabetes is uncommon but may occur under certain circumstances (usually severe infection or other acute illness).
- ☐ Hyperosmolar hyperglycemic state (marked hyperglycemia, severe dehydration, and obtundation, but without ketoacidosis) is rare.

Type 1 DM

- ❑ DKA is the initial presentation in about 25% of adults with newly diagnosed type 1 diabetes.
- ❑ More common in children than in adults with type 1 DM

American Diabetes Association criteria for the diagnosis of diabetes

1. A1C $\geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

2. FPG ≥ 126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*

OR

3. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

Complications of diabetes

- MICROVASCULAR COMPLICATIONS
- Risk factors for the development of these complications include hyperglycemia, hypertension, dyslipidemia,

- **Nephropathy (albuminuria)** — Diabetes-associated nephropathy is a progressive disorder of the microvasculature of the kidney.
- The earliest sign of diabetic nephropathy is moderately increased albuminuria (formerly known as. which can be accompanied by systemic hypertension and impaired glomerular filtration . Some patients with overt proteinuria will progress to end-stage kidney disease.
- Hypertension, chronic hyperglycemia, and smoking are important risk factors for diabetes-associated nephropathy. As a result, intensive monitoring and management for each of these risk factors are essential to reduce the risk for nephropathy

- **Retinopathy** — Diabetes-associated retinopathy is a progressive disorder that affects the microvasculature of the retina. Most patients develop the mildest form of retinopathy (nonproliferative diabetic retinopathy [NPDR]) as duration of diabetes increases, NPDR can progress to proliferative retinopathy, which carries a high risk of visual loss when untreated.
- ● Screening – T2DM should undergo dilated eye examination or retinal imaging to evaluate for retinopathy at the time of diagnosis. If the examination is normal, screening is performed annually.
- Screening allows detection of retinopathy in the nonproliferative stage. At this stage, improving glycemic control can reverse nonproliferative changes and prevent progression. In more severe cases of retinal disease, laser therapy or intravitreal injections can prevent further progression of disease and visual loss.

- **Neuropathy** — Diabetes-associated neuropathy is a progressive disorder that affects both the **autonomic nervous system** (eg, heart rate, postural BP control, pupillary adaption to darkness, and gastroparesis) and **peripheral nerves** (eg, nerve conduction, vibratory threshold, and sensory perception).
- ● Screening – T2DM should undergo annual screening for neuropathy, beginning at diagnosis. Screening consists of a foot examination and testing for pressure sensation and vibration sensation
- If the screening examination is abnormal, we refer to a neurologist for further evaluation, in addition to intensive efforts to improve glycemic control and assess and manage other cardiovascular risk factors such as BP and dyslipidemia.

- **Macrovascular diabetes complications**

- large blood vessel diseases driven by atherosclerosis.
- preventable by : glycemic control, smoking cessation, dyslipidemia control, bp control

- **.Cardiovascular Disease :**

Plaque builds up in the coronary arteries. This restricts blood flow and can lead to chest pain (angina) or a heart attack.

- it is a leading cause of death in DM patients

.Cerebrovascular Disease : cut in the blood supply of the brain causing either Stroke or nutrients. TIA (Transient Ischemic Attack)

- **Peripheral Artery Disease : by 2 mechanisms : Poor Circulation:**

Plaque narrows the arteries carrying blood to the limbs (most often the legs and feet). **Slower Healing:** Reduced blood flow prevents oxygen from reaching wounds, leading to severe foot ulcers (DFU), infections, or even gangrene

Management of diabetes

1. Lifestyle modifications:

- Medical nutrition therapy
- increased physical activity
- weight reduction

2. Oral Drug Therapy/Noninsulin SC therapy

3. Insulin therapy

TREATMENT GOALS

- 1- **Diabetes Education** : instruction on nutrition, physical activity, optimizing metabolic control, and preventing complications.
- 2- Evaluation for micro- and macrovascular complication
- 3- **Attempts to achieve near normoglycemia**
- 4- Minimization of cardiovascular and other long-term risk factors
- 5- Avoidance of drugs that can exacerbate abnormalities of insulin or lipid metabolism.

Diabetes Education

Intensive lifestyle modification

Intensive behavioral modification interventions including weight reduction and increasing activity levels are successful in

- Reducing weight
- Improving glycemic management
- Reducing the need for glucose-lowering medications.

1- Medical nutrition therapy

Aiming for weight reduction or at least weight maintenance.

2- Weight reduction

- By diet control, pharmacological or surgical therapy.
- Improved glycemic state is induced by weight loss through partial correction of the two major metabolic abnormalities in type 2 diabetes: insulin resistance and impaired insulin secretion.
- Weight loss and weight loss maintenance supports all effective type 2 diabetes therapy and reduces the risk of weight gain associated with sulfonylureas and insulin.

3- Exercise

- Regular exercise is beneficial for diabetics independent of weight loss.
- It leads to improved glycemic management due to : increased responsiveness to insulin and so delay the progression of impaired glucose tolerance to overt diabetes.
- These beneficial effects are directly due to exercise.
- Unfortunately, in one study, only 50% of patients with type 2 diabetes were able to maintain a regular exercise regimen.

PHARMACOLOGIC THERAPY

when to start ???

- A reasonable goal of therapy might be an A1C of $\leq 7\%$ for most patients.
- Target A1C goals in patients with type 2 DM should be tailored to the individual, balancing the potential for improvement in microvascular complications with the risk of hypoglycemia,

So there is NO ((ONE SIZE FITS ALL))

- Glycemic targets are generally set somewhat higher for older adult patients and those with comorbidities or a limited life expectancy who may have little likelihood of benefit from intensive therapy.

For most patients with A1C at or above target level (>7.5 to 8%), pharmacologic therapy should be initiated at the time of diagnosis (along with lifestyle modification).

- A 3-6 month trial of lifestyle modification prior to initiation of pharmacologic therapy is reasonable for :

- 1- patients with A1C at or above the target ($7.5 - 8\%$) who have clear and modifiable contributors to hyperglycemia and who are motivated to change them.

- 2- highly motivated patients with A1C near target ($<7.5\%$).

Choice of initial therapy??

Considerations:

1. Patient presentation: presence or absence of symptoms of hyperglycemia
2. Comorbidities
3. Baseline A1C level
4. Individualized treatment goals and preferences
5. The glucose-lowering efficacy of individual drugs, and their adverse effect profile, tolerability, and cost.

Patient presentation:

Asymptomatic, not catabolic:

- The majority of patients with newly diagnosed type 2 diabetes are asymptomatic, without symptoms of catabolism (without polyuria, polydipsia, or unintentional weight loss).
- Hyperglycemia may be noted on routine lab test or detected by screening.
- **Metformin**: In the absence of specific contraindications, it can be used as an initial therapy for those patients.

Advantages of Metformin :

- 1- It is the preferred initial therapy because of **glycemic efficacy (1-2%)**
- 2- Absence of weight gain
- 3- Absence of hypoglycemia (very rare side effect)
- 4- General tolerability, and favorable cost.
- 5- It appears to decrease cardiovascular events and does not have adverse cardiovascular effects.

Symptomatic (catabolic) or severe hyperglycemia:

The frequency of symptomatic or severe diabetes has been decreasing in parallel with improved efforts to diagnose diabetes earlier through screening.

-Ketonuria and/or weight loss present

- Insulin, rather than oral hypoglycemic agents, is often indicated for initial treatment of symptomatic (polyuria or weight loss) or severe hyperglycemia (fasting plasma glucose >250 mg/dl ,RBG >300 mg/dl or A1C >10%)
- Insulin should also be initiated whenever there is a possibility of undiagnosed type 1 diabetes, which should be suspected among those who are **lean** or present with **marked catabolic symptoms**, especially in the presence of a **personal or family history of other autoimmune disease** and/or the **absence of a family history of type 2 diabetes**.

- **Ketonuria and weight loss are absent**
- For patients presenting with severe hyperglycemia but without ketonuria or spontaneous weight loss (i.e type 1 diabetes is not likely) insulin or GLP-1 receptor agonists may be used (with or without metformin, depending on contraindications or intolerance).
- For patients who refuse injections, initial therapy with high-dose sulfonylurea is an alternative option.
- Metformin monotherapy is not helpful in improving symptoms in this setting ,however, it can be started at the same time as the sulfonylurea, slowly titrating the dose upward.

Insulin therapy:

Although historically insulin has been used for type 2 diabetes only when inadequate glycemic management persists despite oral agents and lifestyle intervention, there are **increasing data to support using insulin earlier** and more aggressively in type 2 diabetes.

Benefit ??!!

By inducing near normoglycemia with intensive insulin therapy, both endogenous insulin secretion and insulin sensitivity improve; this results in better glycemic management, which can then be maintained with diet, exercise, and oral hypoglycemics for many months thereafter with less future risk of microvascular complications.

MONITORING

- We obtain A1C at least twice yearly in patients meeting glycemic goals and more frequently (quarterly) in patients whose therapy has changed or who are not meeting goals.
- Self-monitoring of blood glucose (SMBG) is not necessary for most patients with type 2 diabetes who are on a stable regimen of diet or oral agents and who are not experiencing hypoglycemia.
- SMBG may be useful for some type 2 diabetes patients who use the results to modify eating patterns, exercise, or insulin doses on a regular basis.

PERSISTENT HYPERGLYCEMIA

- For patients who are not meeting glycemic targets despite diet, exercise, and metformin, combination therapy is necessary to achieve optimal results.
- The balance among efficacy in lowering A1C, side effects, and costs must be carefully weighed in considering which drugs or combinations to choose.
- Avoiding insulin, the most potent of all hypoglycemic medications, at the expense of poorer glucose management and greater side effects and cost, is not likely to benefit the patient in the long term.

Challenges in management

1- Adherence to Treatment Plans:

Patients may face various barriers to adhering to their treatment plans: lack of motivation, financial constraints, cultural beliefs, and psychological issues.

Strategies to address these challenges:

Engaging in patient education, setting realistic treatment goals, providing support systems, and involving patients in shared decision-making to promote adherence to treatment plans.

2- Glycemic Control:

- ❑ Achieving and maintaining optimal glycemic control needs real effort healthcare providers by regular assessment and adjustment of the treatment plan based on individual patient needs and characteristics.
- ❑ Titrating medications, adjusting insulin doses, and addressing lifestyle factors.
- ❑ Regular monitoring of blood glucose levels, HbA1c levels, and other relevant parameters can provide valuable feedback on the effectiveness of the treatment plan and guide necessary modifications.

3- Patient Education and Self-Management:

Empowering patients to self-manage their diabetes is an essential component of long-term diabetes care.

- ☐ Assess patients' knowledge, skills, and confidence in self-management and provide tailored patient education.
- ☐ Teaching patients about the importance of self-monitoring blood glucose levels, medication adherence, healthy eating, regular physical activity, and self-care practices.
- ☐ Engaging patients in shared decision-making.
- ☐ Setting achievable goals.
- ☐ Providing ongoing support and follow-up.

4- Psychosocial Challenges:

Diabetes is not just a physical condition, but it also has a significant psychosocial impact on patients.

Patients with diabetes may experience emotional distress, depression, anxiety, diabetes-related distress, and other psychosocial challenges that can affect their self-care behaviors and glycemic control.

Healthcare providers need to be aware of the psychosocial challenges associated with diabetes and address them proactively.

Thank you
I thank you