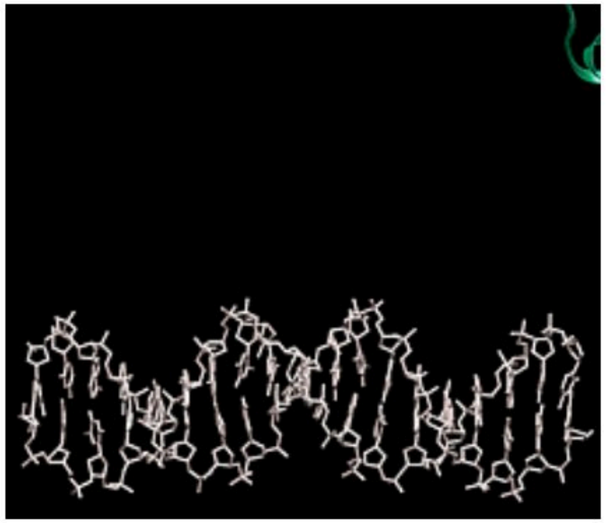

Important note about this modified:
*** The labeled slides with a star ✯ and the highlighted points in slides are mentioned and explained by the doctor.**

*** Slide no.43 is the last required slide.**

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Diabetes mellitus

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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.

PREVALENCE

Common

- Diabetes is estimated to affect > 500 millions adults worldwide, with a global prevalence of 10.5% among adults.
- The most common type:
- 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.
- The 2nd most common type:
- Type 1 diabetes accounts for another 5 to 10% diabetes in adults.
- Less common types
- Known monogenic causes of diabetes represent a small fraction of cases.

Classification of Diabetes Mellitus by Etiology

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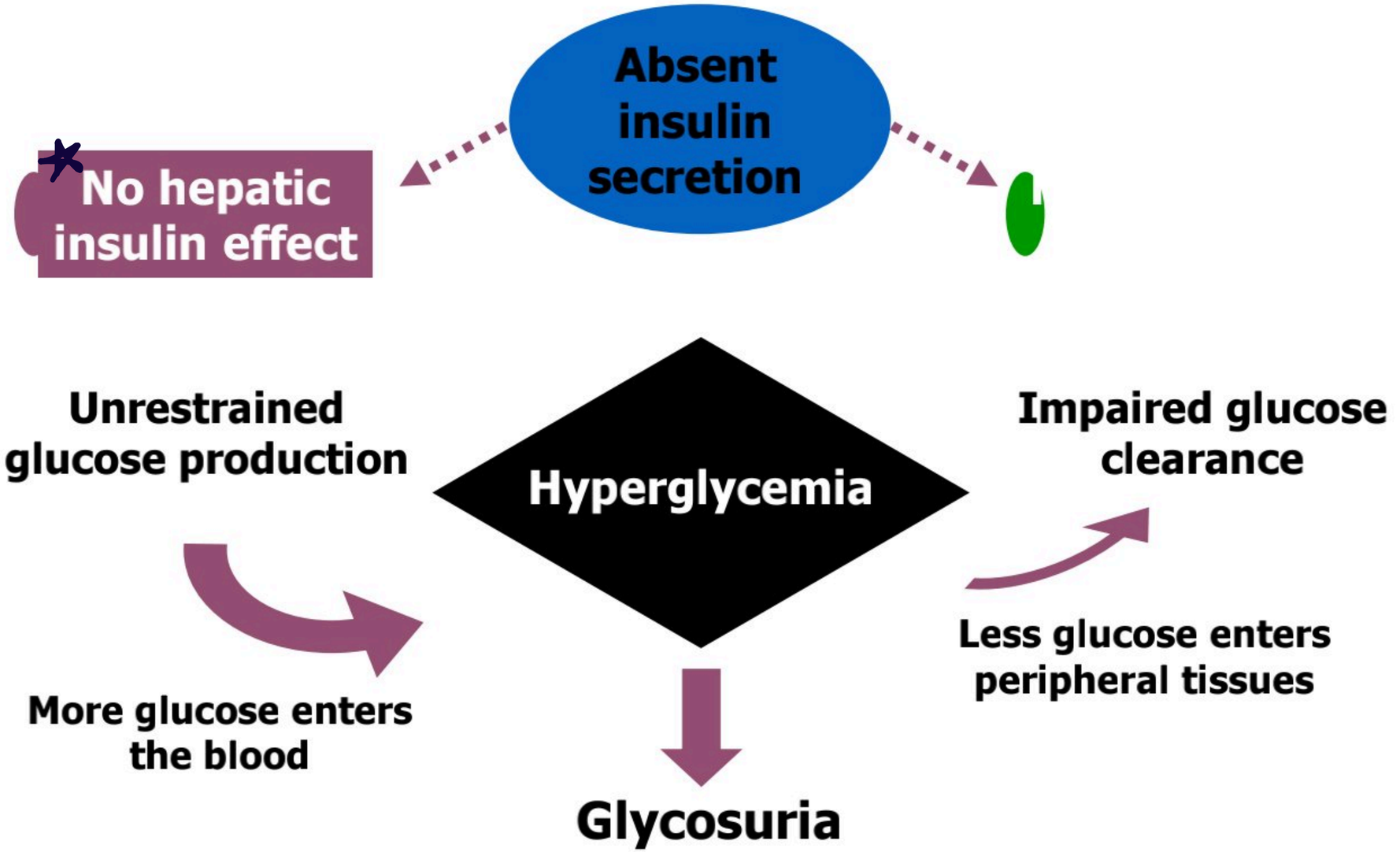
الدكتورة

- **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.
- Family history: Up to 10% of patients with T1DM have an affected close relative.

❑**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

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

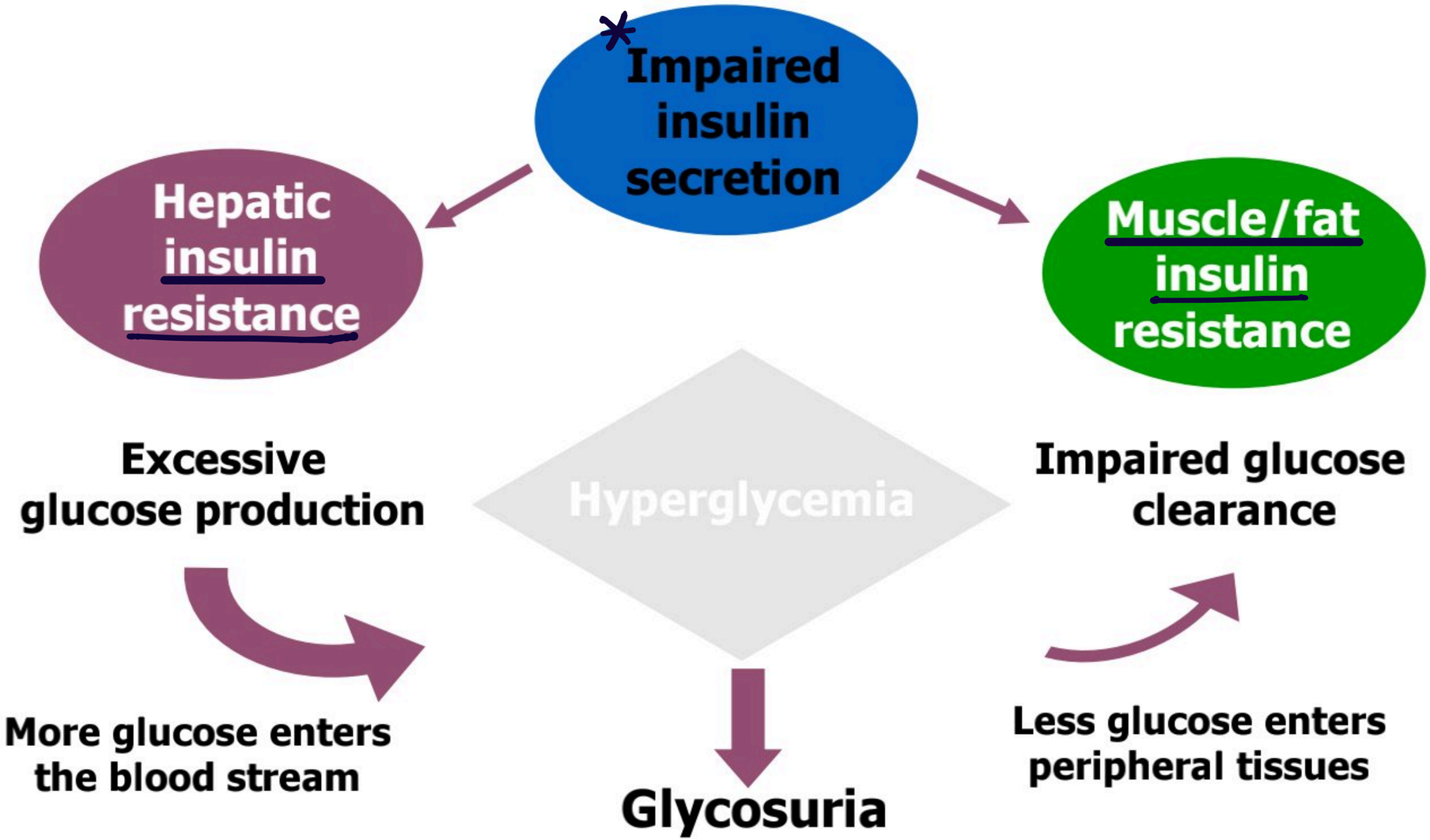
read and understand this slide..

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 :

  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.

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

- 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 rare 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.

Known gene caused that type of diabetes.

- 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.**

The most common

- 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.

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.
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)

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.

Summary:-

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.
- 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

هون الدكتورة قالت إنه حكينا عن هالموضوع بختبر وعملت سكيب

- 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 → have direct effect on glucose control

- 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

type of food important, Not just No. of calori.

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.

3P → polyuria
→ polydipsia
→ polyphagia (weight loss)

→ Diabetic Keto acidosis

- 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.

less common

Type 1 DM

- DKA is the initial presentation in about 25% of adults with newly diagnosed type 1 diabetes.
- DKA is more common in children than in adults with type 1 DM.
- Up to 12% of adults, the clinical presentation is similar to that of type 2 diabetes (older-age onset and not initially insulin dependent), with autoimmune-mediated insulin deficiency developing later in the course of disease (This is sometimes referred to as LADA).

↳ that's why it's most common in children

- Adults with type 1 diabetes (with a longer estimated period prior to diagnosis) are likely to have more prolonged symptoms of hyperglycemia (polyuria, polydipsia, fatigue) than children as the loss of insulin secretory capacity usually is less rapid over time in adults with type 1 diabetes.

Diagnostic Criteria

- **Symptomatic hyperglycemia**

The diagnosis of diabetes mellitus is established when a patient presents with classic symptoms of hyperglycemia (thirst, polyuria, weight loss) with a RBG of 200 mg/dL .

↳ Random Blood glucose

(Most patients with type 1 diabetes and some patients with type 2 diabetes are symptomatic and have plasma glucose concentrations well above ≥200 mg/dL)

- **Asymptomatic hyperglycemia**

The diagnosis of diabetes in an asymptomatic individual (generally type 2 diabetes) can be established with any of the following criteria:

- FPG values ≥126 mg/dL.
- Two-hour plasma glucose values of ≥200 mg/dL during a 75 g OGTT.
- A1C values ≥6.5%

- In the absence of unequivocal symptomatic hyperglycemia, the diagnosis of diabetes must be confirmed on a subsequent day by repeating the same test for confirmation.
- If two different tests are available and are concordant for the diagnosis of diabetes, additional testing is not needed . If two different tests are discordant, the test that is diagnostic of diabetes should be repeated to confirm the diagnosis.

Important

American Diabetes Association criteria for the diagnosis of diabetes

glycosylated Hemoglobin

1. A1C ≥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).

fasting blood glucose

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 ≤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.

End of the lecture

Questions are guaranteed in life; Answers aren't.