Classification of Diabetes Mellitus by Etiology

- **Type 1:** β-cell destruction–complete lack of insulin
- **Type 2:** β-cell dysfunction & insulin resistance → mc (>90%)
- **Gestational:** β-cell dysfunction & insulin resistance during pregnancy
- **Other specific types:** Pancreatic diabetes. (ex: chronic pancreatitis, pancreatic malignancy, cystic fibrosis)
  Endocrinopathies (ex: Cushing syndrome) - Somatostatinoma - acromegaly - glucagonoma
  Drug-or chemical-induced (ex: steroids)
  Other rare forms
  Chromosomal syndromes (Turner syndrome - Down sydrome - Klinefelter's syndrome)
  45 XO\XX

ISLET CELLS ANTIBODIES:

- A heterogeneous group of AB against a variety of cytoplasmic islet cell antigens
- Not exclusively against Beta cells. Other islet cells are also targets.
- Highly positive esp. in the pre- diabetic phase
- More positive at onset than later.
- Positivity decreases rapidly with duration of diabetes.

ex →

ANTI GLUTAMIC ACID DECAROXYLASE (GAD) Antibodies

- Present in 75- 84 % of recent onset DM type1.

D.M. Type 1

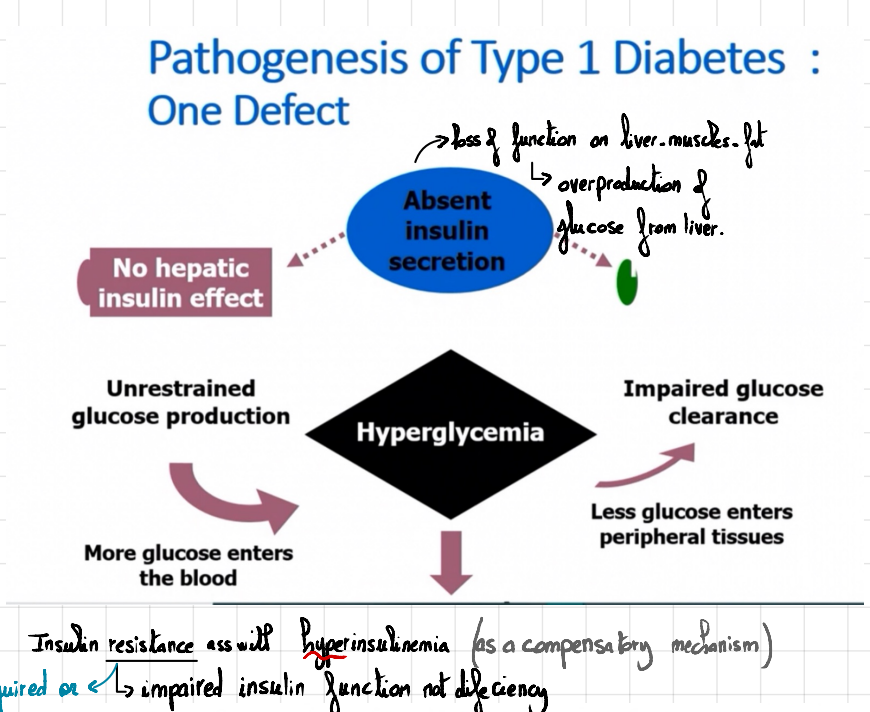
- The combination of genetic ,environmental & autoimmune factors ultimately leads to B- cell destruction, which is an insidious process that may take up to 10 yrs before completion; once the B- cell mass is <5-10% of its original amount, symptoms of diabetes become manifest.

ROLE OF DIET, OBESITY, & INFLAMMATION

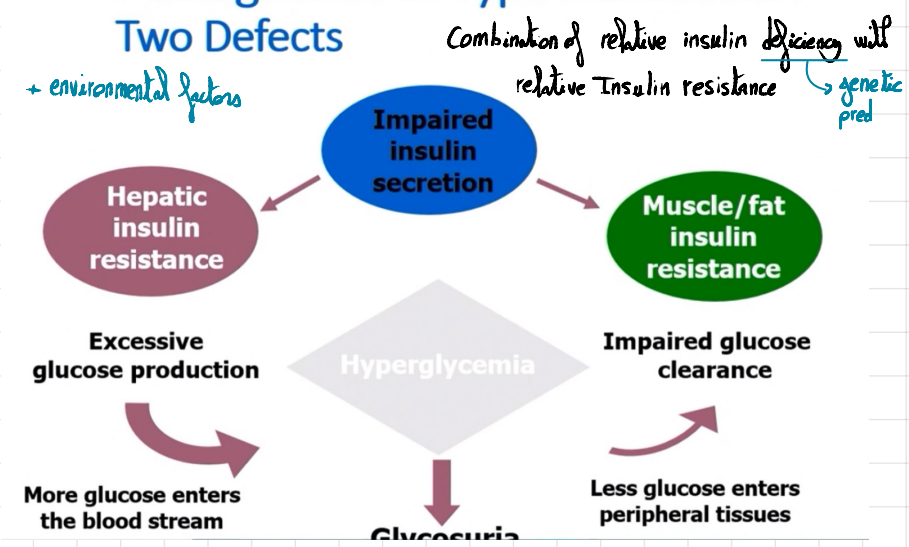
- Increasing weight & less exercise
- Obesity epidemic
- Increasing T2DM in children & adolescents

MAJOR RISK FACTORS (Type2 DM)

- FHx of DM
- Overweight (BMI > 25 kg/m2) → causes Insulin resistance (visceral adiposity)
- Physical inactivity
- Race/ethnicity (African-Americans, Hispanic-Americans)
- Hx of Impaired Fasting Glucose or Impaired Glucose Tolerance
- Hx of Gestational DM or delivery of a baby weighing >4.5 kg
- Signs of insulin resistance or conditions associated with insulin resistance: (1) [metabolic syndrome]
  (2) *Hypertension (140/90 mmHg in adults)
  (3) *HDL cholesterol 35 mg/dl and/or a triglyceride level 250 mg/dl.
  (4) *Polycystic ovary syndrome
  *acanthosis nigricans [hyperpigmentation on the back of neck]
  (5) * waist circumference
  (6) * Non alcoholic fatty liver



Insulin resistance ass with hyperinsulinemia (as a compensatory mechanism)
↳ impaired insulin function not deficiency
acquired or genetic



Type 1 VS type 2 diabetes

	T1 DM	T2 DM
1) Body habitus	lean (mostly)	Overweight
2) Age	4-6 Yo & 10-14 Yo	after puberty - >50
3) Insulin resistance	×	acanthosis nigricans - HTN - PCOS - dyslipidemia
4) FH	⊕	⊕ ⊕
5) Tests	⊕ GAD - Tyrosine phosphate (IA2) - Abs	up to 30% → ⊕ Abs

LADA

latent autoimmune DM of adults
- young adult <50
- lean / wt loss
- require insulin
- No FHx of T2 DM
- FHx of autoimmune disease

MODY

- MODY is non-insulin requiring form of diabetes, occurring in children & young adults,resulting from genetic defect in beta- cell function,& inherited in AD trait.
- **MATURITY ONSET DIABETES OF THE YOUNG** (MODY)
  - Clinical presentation partly similar to type 2 DM but occurring in young age group-mostly adolescents
  - AD inheritance; 5 different gene defects described
  - All relatively rare.

Gestational diabetes

(after 5th month → some have genetic predisposition so they develop it; >25 age)
[Pregnancy is a state of Insulin resistance]

- Hyperglycemia during pregnancy,that usually resolves after birth
- High risk of perinatal morbidity & mortality
- High risk of later T2 DM in both mother & baby
- Dx by specific glucose test methods (GTT. at 0 h <92 - at 1 h <180 - at 2 h <153)
- Requires intensive dietary & glycemic management

	Obesity	Insulin resistance	Autoimmunity
Type 1	No	No	Yes
Type 2	Yes	Yes	No
MODY	No	No	No

Criteria for the diagnosis of diabetes

1. A1C >= 6.5 %. (pre: 6.17 - 6.49)
2. FPG >= 126 mg/dL. Fasting is defined as no caloric intake for at least 8 hr. (fasting plasma glucose; pre (100-125))
3. Two-hour plasma glucose >= 200 mg/dL during an OGTT. 75 g anhydrous glucose dissolved in water. (pre (140-199))
4. In a pt with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >= 200 mg/dL .

* In the absence of unequivocal symptomatic hyperglycemia, criteria 1- 3 should be confirmed by repeat testing.

Symptoms

- Polyuria, increased frequency of urination, nocturia.
- Increased thirst, & dry mouth
- Polyphagia ,& Weight loss (in catabolic state>> absolute insulin deficiency)
- Blurred vision
- Numbness in fingers & toes (neuropathy)
- Fatigue Impotence (in some men)

Signs

- Muscle weakness
- Decreases sensation
- Loss of tendon reflexes
- Foot Inter-digital fungal infections
- Retinal changes by fundoscopy

Management of diabetes

1. Lifestyle modifications:

 # Medical nutrition therapy Aiming for weight reduction or at least weight maintenance.

 # Weight reduction → ↑ Insulin sensitivity & secretion + ↓ need of medications

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

 # Exercise

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

2. Oral Drug Therapy/Non insulin SC therapy

3. Insulin therapy

TREATMENT GOALS

1- Diabetes Education : physical activity ↔ nutrition

Intensive lifestyle modification → intensive behavioral modification , instruction on nutrition, optimizing metabolic control, & increasing physical activity levels are successful in

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

2- Evaluation for micro- & macrovascular complications

3- Attempts to achieve near normoglycemia

4- Minimization of cardiovascular & other long-term risk factors

5- Avoidance of drugs that can exacerbate abnormalities of insulin or lipid metabolism.

PHARMACOLOGIC THERAPY

- A reasonable goal of therapy might be an A1C of =<7% (7 - 7.5%) for most patients.
- Target A1C goals in pts 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 pts & those with comorbidities or a limited life expectancy who may have little likelihood of benefit from intensive therapy.
- For most pts 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- pts with A1C at or above the target (7.5 - 8%) who have clear & modifiable contributors to hyperglycemia & who are motivated to change them.
  2- highly motivated pts with A1C near target (<7.5%).

Choice of initial therapy

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

we always start with a low dose then ↑ gradually, to ↓ SE.

Metformin: In the absence of specific contraindications, it can be used as initial therapy for asymptomatic , not catabolic pts.

Dosing: We begin with 500 mg/day with the evening meal &, if tolerated, add a second 500 mg dose with breakfast.
The dose can be increased slowly (1 tablet every 1-2 weeks) as necessary to reach a total dose of 2000 mg/day.

Advantages: 1- It is the preferred initial therapy because of glycemic efficacy (1-2%)
2- Absence of weight gain (it's wt neutral)
3- Absence of hypoglycemia (very rare SE for metformin)
4- General tolerability, & favorable cost.
5- It appears to decrease cardiovascular events & does not have adverse cardiovascular effects.

Adverse effects: 1- GI → mc SE including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, & soft bowel movements or diarrhea.
→ Usually mild, transient, & reversible after dose reduction or discontinuation of drug.
→ They are minimized by taking the medication with food & gradually .
2- Vit B12 deficiency → Due to reduced intestinal absorption of vit B12 by metformin.
(very rare, most serious) → In some patients, vitamin B12 deficiency may present as peripheral neuropathy.
3- lactic acidosis : very low incidence but high mortality rate

Patient presentation: (no wt loss)

- **Asymptomatic, not catabolic:**
  - The majority of pts with newly diagnosed T2 DM 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 can be used

(polyurea, polydipsia, wt loss)

- **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 sereening.

 # Ketonuria &/or weight loss present

(we need to start it) Insulin is often indicated for initial Tx of symptomatic or severe hyperglycemia (fasting plasma glucose >250 mg/dl ,RBG >300 mg/dl or A1C >10%)

- Insulin should be initiated whenever there is a possibility of undiagnosed T1 DM, which should be suspected among those who are lean or present with marked catabolic symptoms, especially in the presence of a personal or family Hx of other autoimmune disease &/or the absence of a family Hx of T2 DM.

 # Ketonuria & weight loss absent

- For pts with severe hyperglycemia but without ketonuria or spontaneous wt loss (i.e T1 DM) Insulin or GLP-1 receptor agonists may be used (with or without metformin, depending on contraindications or intolerance).
- For pts 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 with sulfonylurea, slowly titrating the dose upward.

Comorbidities:

 # Pts with established cardiovascular or kidney disease

- Pts with cardiorenal comorbidities should be treated with glucose- lowering medications that have evidence of cardiorenal benefit such as GLP-1 receptor agonists & SGLT2 inhibitors.
- The cardiorenal benefits of GLP-1 receptor agonists & SGLT2 inhibitors have not been demonstrated in drug-naïve pts without established CVD (or at low cardiovascular risk) or without severely increased albuminuria.

 # Pts without established CVD or kidney disease

↗ Insulin secretagogues → ↑ Insulin secretion regardless of glucose level → can cause hypoglycemia

—> who can take metformin & their A1C =< 9% >> insulin, GLP-1 receptor agonists, sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, Repaglinide, or Pioglitazone.

↳ Incretin based therapy, ↑ glucose stimulated Insulin secretion ↳ So they do not cause hypoglycemia

—> who cannot take metformin & their A1C > 9-10% >> Insulin or GLP-1 receptor agonist for initial Tx

Insulin may cause wt gain & hypoglycemia

If wt loss is a priority >> GLP-1 receptor agonist

Considerations in drug selection:

- If wt loss is a priority &/or avoidance of hypoglycemia is a priority (ie, cuz of potentially dangerous work or an elderly pt with inability to self-manage himself at all times) >> GLP-1 receptor agonists , SGLT2 inhibitors , DPP-4 inhibitors (weight neutral).
  ↳ anti obesity medication, might be given to non DM pts
- If cost is a concern >> short- or intermediate-acting **Sulfonylurea**.
  —> The choice of sulfonylurea balances glucose-lowering efficacy, universal availability, & low cost with risk of hypoglycemia & wt gain.
- Pioglitazone >> relatively low-cost oral agent, may also be considered in pts with specific contraindications to metformin & sulfonylureas.
  —> **SE** : wt gain, HF, fractures, & increased risk of bladder cancer.

Insulin therapy:

- Although historically insulin has been used for T2 DM only when inadequate glycemic management persists despite oral agents & lifestyle intervention, there are increasing data to support using insulin earlier & more aggressively in T2 DM.
  —> By inducing near normoglycemia with intensive insulin therapy, both endogenous insulin secretion & insulin sensitivity improve; this results in better glycemic management, which can then be maintained with diet, exercise, & oral hypoglycemics for many months thereafter with less future risk of microvascular complications. → on long term ; it'll ↓ risk of retinopathy, microvascular & other complications + make it easier to achieve normoglycemia

Cardiovascular outcomes

- Virtually all trials evaluating the safety & efficacy of all anti diabetes drugs have recruited pts who were already had preexisting CVD or were at very high risk for CVD. So the long-term benefits & risks of using one agent over another in the absence of diagnosed CVD are unknown.
- CV benefit has been demonstrated for many of these medications, but benefit has not been investigated in drug-naïve ps without established CVD or at low CV risk.

Microvascular outcomes

- In trials designed to evaluate renal outcomes in pts with CKD & severely increased albuminuria , SGLT2 inhibitors reduced the risk of kidney disease progression & death from renal disease.
- In trials of pts with T2 DM with & without CKD , GLP-1 receptor agonists slowed the rate of decline in eGFR & prevented worsening of albuminuria.

MONITORING

↗ every 2-3 months

- We obtain A1C at least twice yearly in pts meeting glycemic goals & more frequently (4/y) in pts whose therapy has changed or who are not meeting goals.
- Self-monitoring of blood glucose (SMBG) is not necessary for most pts with T2 DM who are on a stable regimen of diet or oral agents & who are not experiencing hypoglycemia.
- SMBG may be useful for some T 2 DM pts who use the results to modify eating patterns, exercise, or insulin doses on a regular basis.

PERSISTENT HYPERGLYCEMIA

- For pts who are not meeting glycemic targets despite diet, exercise, & metformin, combination therapy is necessary to achieve optimal results.
- The balance among efficacy in lowering A1C, SE, & 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 & greater SE & cost, is not likely to benefit the pt in the long term.