
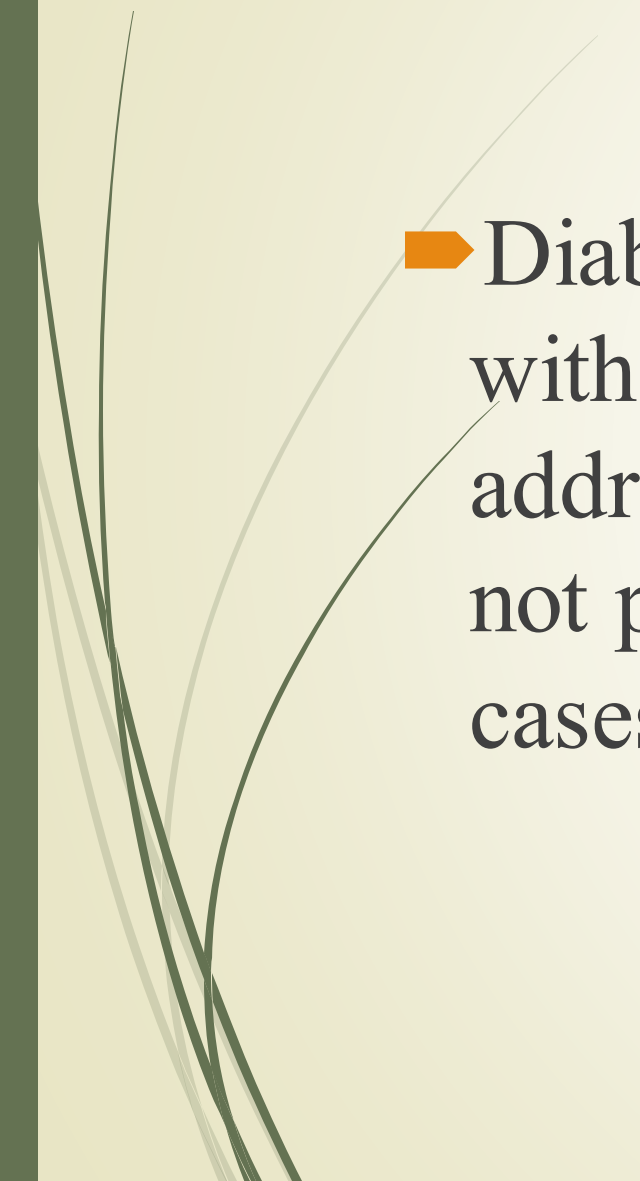




Combination therapy in modern treatments

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- Diabetes is a progressive condition and treatment with a single glucose lowering agent can only address limited pathophysiologic targets and does not provide adequate glycemic control in many cases




Pathophysiology of type 2 DM

- ▶ **Insulin resistance** : in prediabetes and early type 2 DM
- ▶ **Relative insulin deficiency** : late in natural course of type 2 DM
- ▶ **Increase in liver gluconeogenesis**




What is combination therapy ?

- ▶ Combination therapy is a treatment that uses two or more medication to address various health conditions, such as type 2 diabetes
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Monotherapy vs Combination therapy

- Many monotherapy options is lack of glycemic durability
- There is often a delay in titrating monotherapy or in initiating combination therapy (clinical inertia)
- Increase in adverse effects in maximum effective dose of monotherapy
- In monotherapy (stepwise approach) evaluation of a drug efficacy and of any possible adverse effects is possible




Important considerations in combination therapy in type 2 DM

- ▶ should use the lowest number of agents to combat the highest number of pathophysiologic mechanisms causing hyperglycemia
 - ▶ Agents should have an additive effect
 - ▶ Correct established pathophysiologic defects
 - ▶ Preserve or improve pancreatic beta-cell function to ensure durable glycemic control
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What factors are important in finding the right combination therapy?

- Presence of ASCVD ,CKD or HF
 - History of hypoglycemia
 - Side effects of treatment
 - Treatment priorities
 - Treatment goals
 - Treatment cost
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Oral combination therapy in type 2DM

- ▶ As multiple pills : higher cost over single pill fixed dose combinations(FDCs)
- ▶ As single pill fixed-dose combination(FDCs)

Benefits of FDCs:

- ▶ Convenience
- ▶ Ease of administration
- ▶ Reduction in medication burden
- ▶ Improve patients treatment adherence
- ▶ Optimize achievement and maintenance of glycemic targets



Metformin-based combination therapy



Metformin plus :

- DPP-4 inhibitors
- SGLT2 inhibitors
- Sulfonylurea
- TZDs
- GLP-1 RA
- Basal insulin



Non-metformin-based combination therapies

- ▶ In patients unable to tolerate metformin or metformin is contraindicated
- ▶ SU plus TZDs
- ▶ TZDs plus DPP-4 inhibitors
- ▶ SGLT2 inhibitors plus DPP-4 inhibitors
- ▶ SGLT2 inhibitors plus SU
- ▶ SGLT2 inhibitors plus TZDs



No adequate control with
combination of two oral agents

Third oral agent

Add GLP-1 RA

Add basal insulin



Triple combination of oral therapies

- ▶ SGLT2 inhibitors **plus** DPP-4 inhibitors **plus** Metformin:
- ▶ Empagliflozin plus linagliptin plus metformin (Glotrio® ,
Avanomet ER®)

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graph TD; A["Random BS ≥ 300 mg/dl or FBS > 250 mg/dl"] --> D((Add Insulin)); B["A1C > 10%"] --> D; C["Symptomatic hyperglycemia and unexplained weight loss (catabolic state)"] --> D;
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Random BS \geq 300 mg/dl or FBS $>$ 250 mg/dl

A1C $>$ 10%

Symptomatic hyperglycemia and unexplained weight loss (catabolic state)


Add Insulin





Type 2 DM with established CVD

or

type 2 DM high risk for CVD

- ▶ SGLT2 Inhibitors
 - ▶ GLP-1 receptor agonists
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- ▶ Heart failure or CKD (eGFR < 60 , Albuminuria $> 300\text{mg/day}$) : Low dose of SGLT2 inhibitors (empa- , cana- and dapagliflozin)
 - ▶ ASCVD , high A1c, high BMI : GLP-1 RAs (lira- , sema- or dulaglutide)

Injectable combination therapy

- ▶ **iGlarLixi** (2 u,1 μ Max: 40 u ,20 μ) , (3 u , 1 μ Max: 60 u, 20 μ)
- ▶ **iDegLira** (Max: 50 u, 1.8 mg)
- ▶ Basal insulin : improves FPG
- ▶ GLP-1 RA : reduces PPG

Advantages of injectable FDCs:

- ▶ Lower risk for hypoglycemia compared with insulin alone
- ▶ High percentage of patients achieving A1c target
- ▶ Weight loss vs weight gain with insulin
- ▶ Reduced frequency of GI side effects due to slow titration with low initial dose of GLP-1 RA

Thank you for your attention

