Iranian Pediatric Endocrine

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Growth and Development Research Center

SGLT2i and GLP-1 ra therapy in type 1 diabetes ,adjuvant therapy

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Properties of ideal therapy in T2DM

GLP1ra SGL2i

- Improved HbA1c ,TIR and variability
- No increase in hypoglycemia
- Weight reduction
- Improved cardiovascular and renal outcome
- Acceptable risk/side effect

Properties of ideal therapy in T1DM

GLP1ra SGL2i

- Improved HbA1c ,TIR and variability
- No increase in hypoglycemia
- Weight reduction
- Improved cardiovascular and renal outcome
- Acceptable risk/side effect

Weight is an issue for people with T1DM

Overweight and obesity

Insulin-intense therapy

Hypoglycemia-defensive snaking

hormonal change

Alterations to GH-IGF1

Other factors:

Age

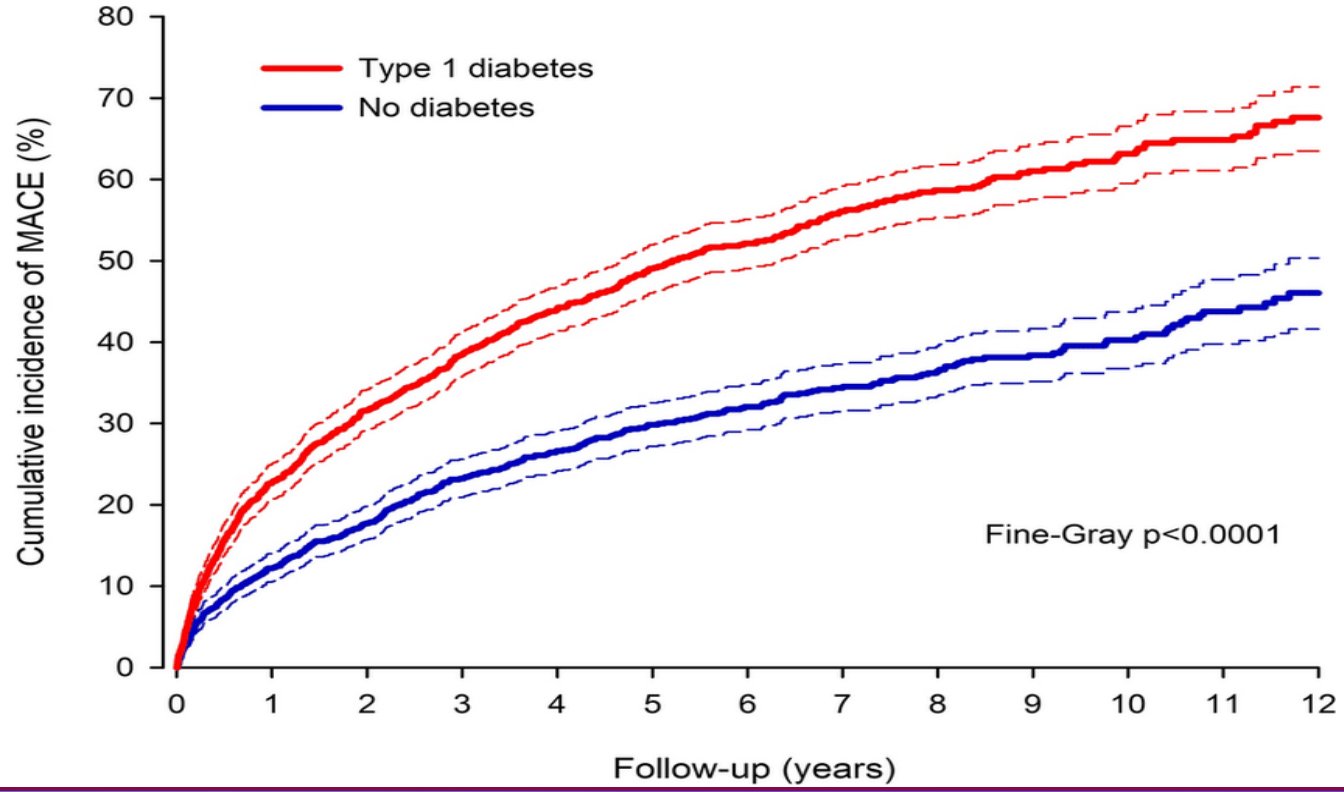
Duration of T1D

Genetic predisportion

Cardiovascular morbidity & mortality in T1DM

- the risk for those with **very poor glycemic control** (HbA1c ≥ 9.7%) is 10 times higher.
- CVD is much higher in patients with T1D onset at a younger age **(<10 years of age**).
- CV risk remains **high in well-controlled** T1D without CV risk factors, suggesting additional factors potentially involved.

Cardiovascular Disease in Type 1 Diabetes Mellitus: Epidemiology and Management of Cardiovascular Risk. J Clin Med. 2021 Apr


Type 1 diabetes
No diabetes
Cumulative incidence of MACE (%)
Follow-up (years)
Fine-Gray p<0.0001
0
10
20
30
40
50
60
70
80
0
1
2
3
4
5
6
7
8
9
10
11
12

Cardiovascular diseases in T1DM

Increased CVD in T1D

Increased CVD morbidity (vs. control population)

- x 2.4 to 3.6 in men
- x 3.0 to 7.7 in women

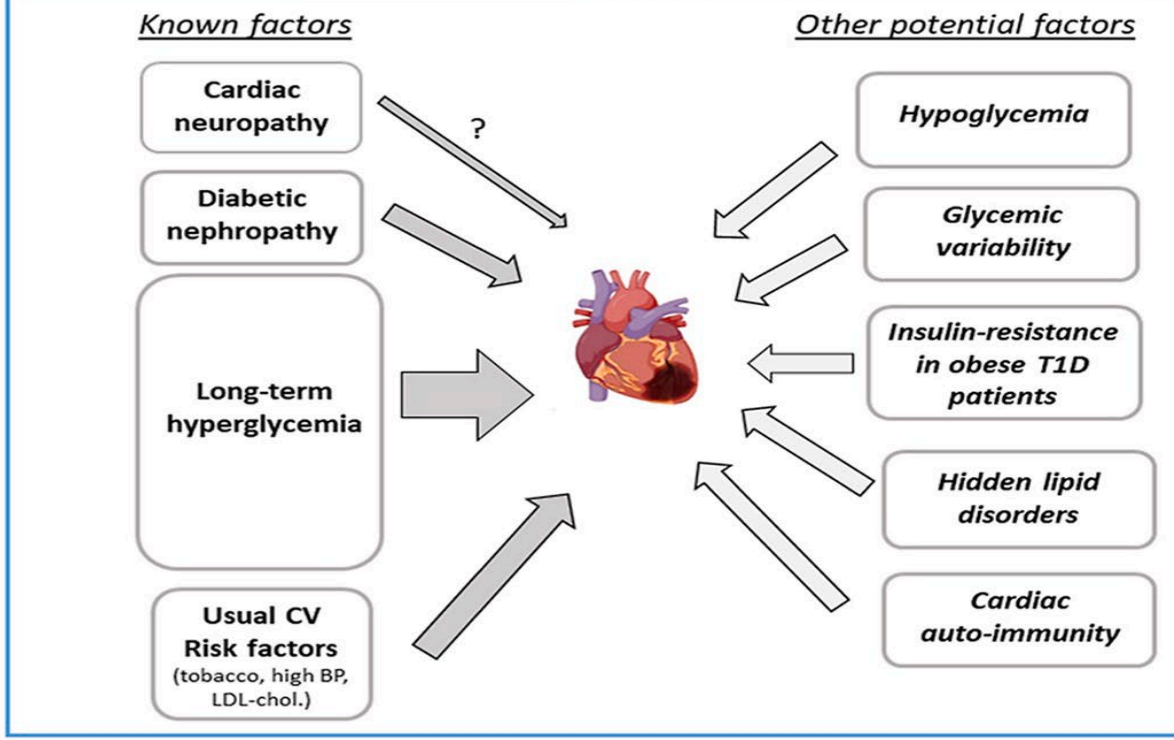
Increased CVD mortality (vs. control population)

- x 2.6 to 8.8 in men
- x 2.7 to 24.7 in women

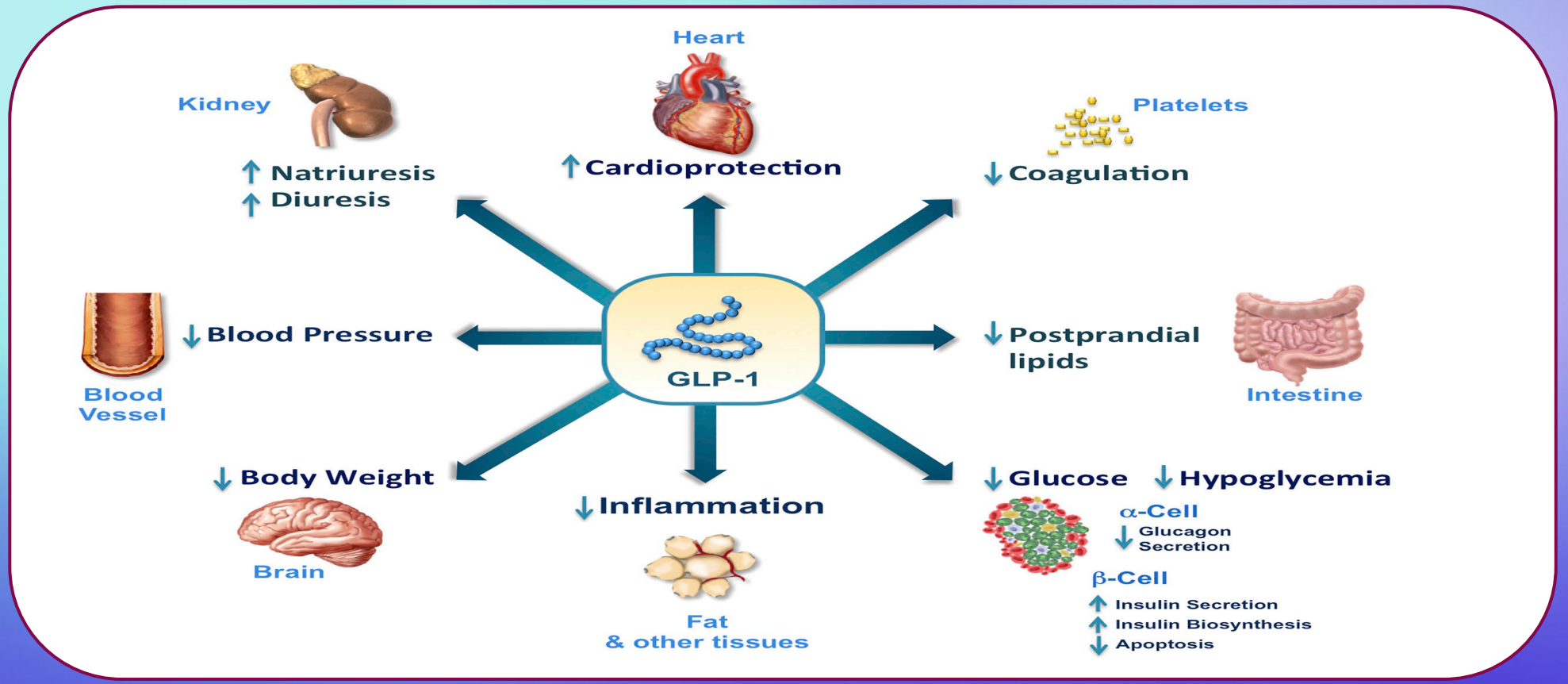
Higher CVD risk in T1D with early onset

- CVD morbidity (vs. control population):
  - x 11.4 if T1D onset< 10 yrs
  - x 3.8 if T1D onset > 26 yrs
- CVD mortality (vs. control population):
  - x 7.4 if T1D onset< 10 yrs
  - x 3.6 if T1D onset > 26 yrs

Pathophysiological mechanisms promoting CVD in T1D



Majority GLP1ra effects are beta-cell independent



Protective effect of GLP1ra

- GLP-1RA is a new type of **hypoglycemic** drug which potently lowers blood glucose and **body weight** , with overt beneficial effects on **cardiovascular diseases**.
- However, GLP-1 RAs' effects on the microvasculature are controversial.
- GLP-1RAs exert anti-oxidative, anti-inflammatory, anti-apoptotic, and anti-remodeling effects on cardiac and vascular cells.

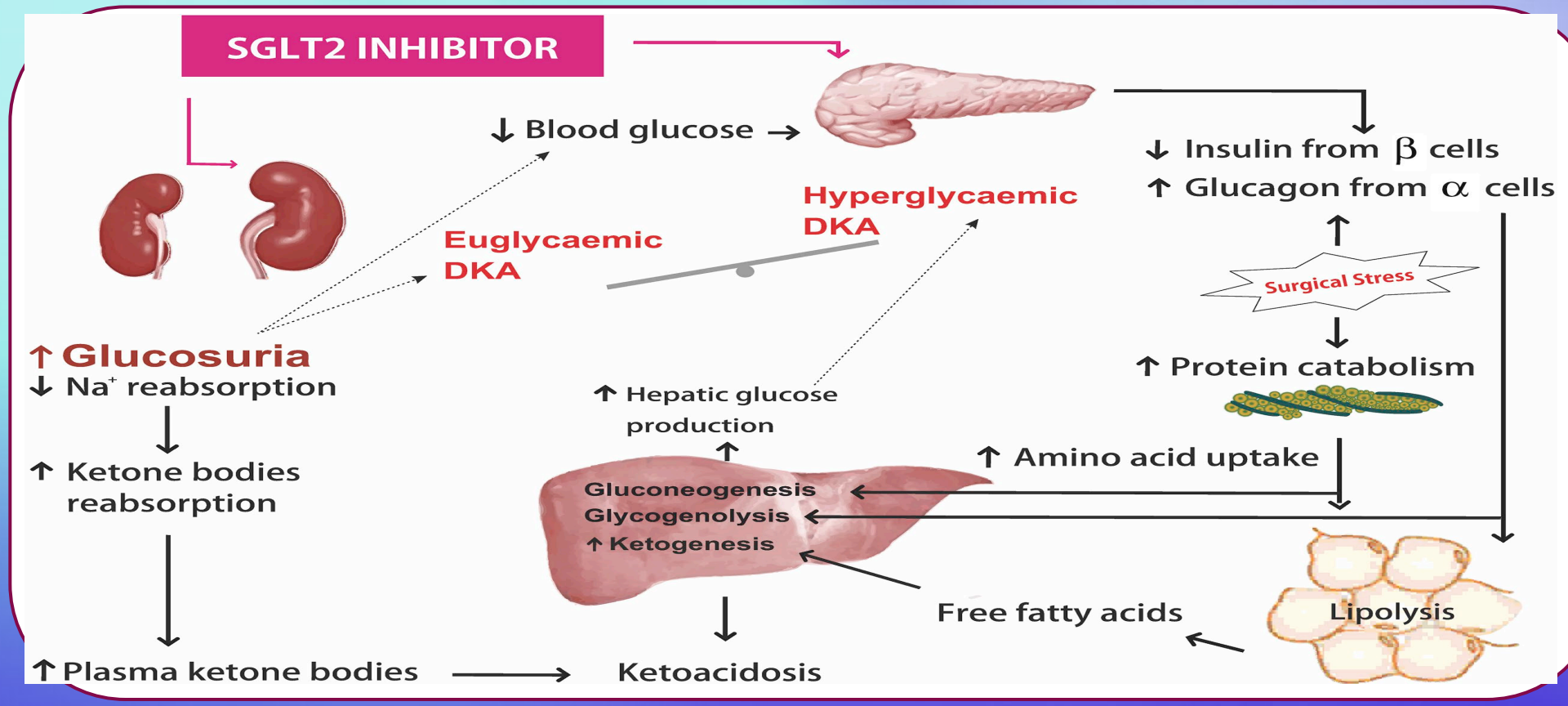
Properties of ideal therapy in T1DM

	GLP1ra	SGL2i
Improved HbA1c ,TIR and variability	ok	
No increase in hypoglycemia	ok (insulin dose adjutement)	
Weight reduction	ok	
Improved cardiovascular and renal outcome	likely	
Acceptable risk/side effect	ok (GLP1 dose adjutement)	

SGLT2 inhibitor

- **dapagliflozin** (5 mg) and **sotagliflozin** (200 and 400 mg) have been temporarily licensed for use by the **European Medical Agency (EMA)** as an adjunct to insulin therapy in adults with **T1D** with a body mass index (BMI) of **27 kg/m2** or higher.

SGLT2 i mechanism



Protective effect of SGLT2i

- pharmacological agents that act by inhibiting the SGLT2, by reducing the renal plasma glucose **threshold** and inducing glycosuria, resulting in a blood glucose lowering effect
- SGLT2 inhibitors are beneficial in the treatment of blood glucose in patients with TIDM, but their use has been controversial due to their serious and life-threatening adverse effects **DKA.**
- both **cardiovascular and renal outcomes** have been established to improve with SGLT2i

SGLT2 in adult T1DM

- Reduction of HBA1c 0.5-0.8% **(TIR +9.7%)**
- 20-40% increased of hypoglycemic risk , reduction of insulin dose **11-49%**(total daily dose),reduced betta cell apoptosis.
- Improvement of **microalbuminuria 32%** and **macroalbuminuria 41%** and inhibitor of renal fibrosis.
- Gross weight loss (4.9kg in 20 weeks
- Increased of **euglycemic DKA** in T1DM.
- Antiatherosclerosis effect

Properties of ideal therapy in T1DM

	GLP1ra	SGL2i
Improved HbA1c ,TIR and variability	ok	ok
No increase in hypoglycemia	ok (insulin dose adjutement)	ok
Weight reduction	ok	ok
Improved cardiovascular and renal outcome	likely	very likly
Acceptable risk/side effect	ok (GLP1 dose adjutement)	DKA

General **conclusion**

- Data show that GLP1ra and SGL2i have benefits in people with T1D, improving **glycemic control** and **weight management.**
- Real-world studies suggest also **cardiorenal benefits** in T1DM , especially for SGL2i.
- Extra care should be taken when combining SGL2i with HCL system since **excesive** insulin dose reduction might provoke DKA.
- Inequality in access to GLP1 ra and SGL2i is a major issue.
- Due to the likely but major impact on CV and renal outcomes, studies should focus on data needed to obtain access to GLP1ra and SGL2i for T1DM.