GLP1 AGONIST

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INTRODUCTION

- Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both incretin hormones inactivated by dipeptidyl peptidase-4 (DPP-4), stimulate insulin secretion after an oral glucose load via the incretin effect.

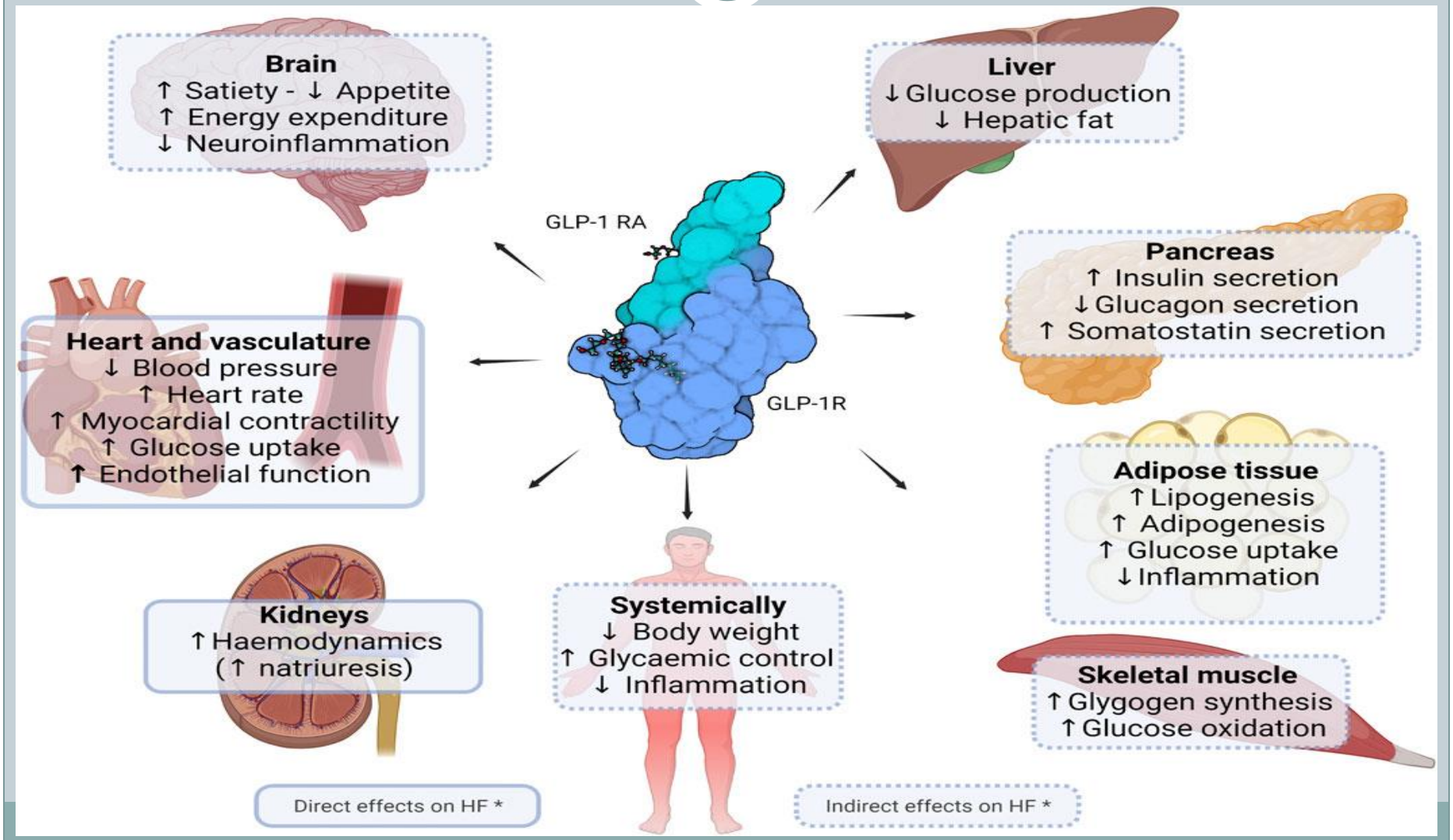
- ADA 2022 approved GLP-1 A as first line therapy for treating DM in patients with atherosclerotic cardiovascular disease and obesity.

- 1980s, Jean-Pierre Raufman of the National Institute of Health investigated the Gila monster and later John Engg isolated Exendin -4 from it.

PHARMACOKINETICS

- **Absorption**: GLP-1 Receptor Agonists (RAs) like Exenatide, Liraglutide, and Semaglutide are administered subcutaneously, ensuring rapid absorption and achieving peak concentrations within hours.
- **Distribution**: Post-absorption, GLP-1 RAs (eg, Exenatide, Liraglutide, and Semaglutide) exhibit a low volume of distribution, predominantly remaining in the bloodstream.
- **Metabolism**: Exenatide undergoes primary metabolism in the kidneys and liver through hydrolysis, yielding smaller, inactive peptides. Liraglutide follows a similar pathway involving proteolytic cleavage.
- **Excretion**: Renal elimination primarily governs the clearance of GLP-1 RAs, including Exenatide, Liraglutide, and Semaglutide.

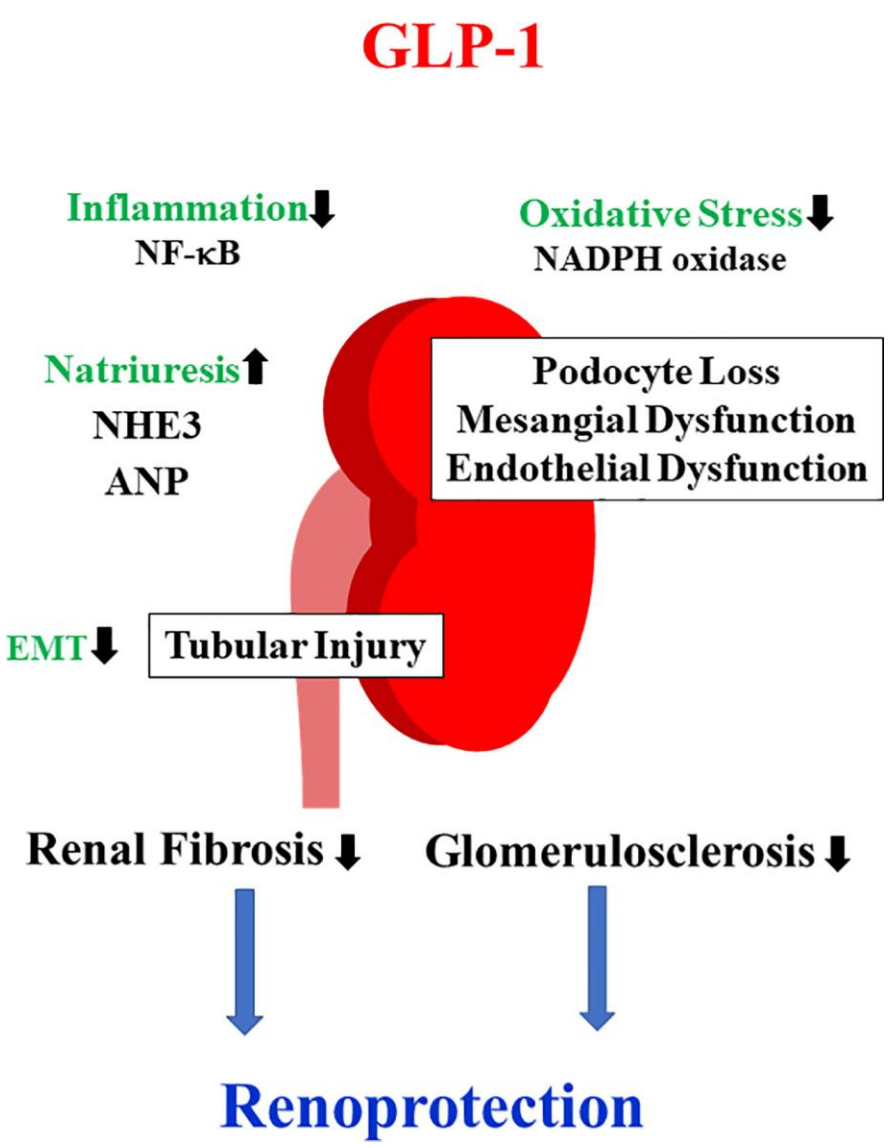
EFFECTS OF GLP1A



DOSE AND SIDE EFFECTS

GLP-1 & GIP Receptor Agonists

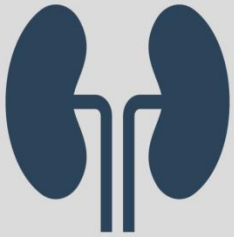
Class/Main Action	Name	Dose Range	Considerations
GLP-1 RA - Glucagon Like Peptide Receptor Agonist **"Incretin Mimetic"** • Increases insulin release with food • Slows gastric emptying • Promotes satiety • Suppresses glucagon	exenatide (Byetta)	5 and 10 mcg BID	**Side effects for all:** Nausea, vomiting, weight loss, injection site reaction. Report signs of acute pancreatitis (severe abdominal pain, vomiting), stop med. Increase dose monthly to acheive targets. **Black box warning:** Thyroid C-cell tumor warning (avoid if family history of medullary thyroid tumor). *Significantly reduces risk of CV death, heart attack, and stroke. †Approved for pediatrics 10-17 yrs Lowers A1c 0.5 – 1.6% Weight loss of 1.6 to 6.0 kgs
	exenatide XR† (Bydureon)	2 mg 1x a week Pen injector - Bydureon BCise	
	liraglutide (Victoza)*†	0.6, 1.2 and 1.8 mg daily	
	dulaglutide* (Trulicity)	0.75, 1.5, 3.0 and 4.5 mg 1x a week pen injector	
	lixisenatide (Adlyxin)	10 mcg 1x a day for 14 days 20 mcg 1x day starting day 15	
	semaglutide* (Ozempic)	0.25, 0.5, 1.0 and 2.0 mg 1x a week pen injector	
	(Rybelsus) Oral tablet	3, 7, and 14 mg daily in a.m. Take on empty stomach w/H2O sip	
GLP-1 & GIP Receptor Agonist Activates receptors for GLP-1 (see above) & Glucose-dependent Insulinotropic Polypeptide (GIP).	Tirzepatide (Mounjaro)	2.5, 5.0, 7.5, 10, 12.5 and 15 mg 1x a week prefilled single dose pen Increase dose by 2.5 mg once monthly to reach targets.	**Side effects include:** Nausea, diarrhea, injection site reactions. Avoid if family history medullary thyroid tumor. Report pancreatitis or acute gallbladder problems. Lowers A1C ~ 1.8 - 2.4% Weight loss of ~ 5.4 – 10 kgs



- GLP-1RAs have been shown to activate PKA and increase the production of cyclic adenosine monophosphate (cAMP).
- NADPH oxidase and NF-κB activity are inhibited, resulting in the attenuation of oxidative stress and inflammation.
- Prevent podocyte loss as well as mesangial and endothelial dysfunction.
- GLP-1RAs inactivate NHE3 and promote atrial natriuretic peptide (ANP) secretion, thereby inducing natriuresis.
- GLP-1RAs inhibit tubular injury and subsequent tubulointerstitial fibrosis.

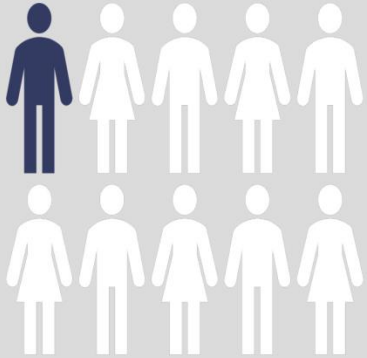
FLOW: the first dedicated kidney outcomes trial with a GLP-1RA

CKD is a common complication of T1D and T2D



46%

536 million affected in 2021, predicted to rise to 783 million by 2045



$39 million in the US alone

85,000 deaths every year

1 in 10 in the general population

A global kidney outcomes trial

Randomized controlled clinical trial

QW SC semaglutide 1 mg + SOC (n=1767)	baseline eGFR: 46.9
Placebo + SOC (n=1766)	baseline eGFR: 47.1

- **3.4**-year follow-up
- **28** countries
- **387** sites
- **3,533** participants
- **Primary outcome:** time to first occurrence of major kidney outcomes

Key findings for semaglutide

24% lower risk of composite primary outcome

Consistent reductions for kidney disease components

1.16 mL/min/1.73m² per year Slower reduction in mean eGFR

Rossing P, Pratley R, Perkovic V, et al. The First Dedicated Kidney Outcome Trial with a GLP-1 Receptor Agonist—Once-Weekly Semaglutide and the FLOW Trial Results. Presented at ADA 2024.