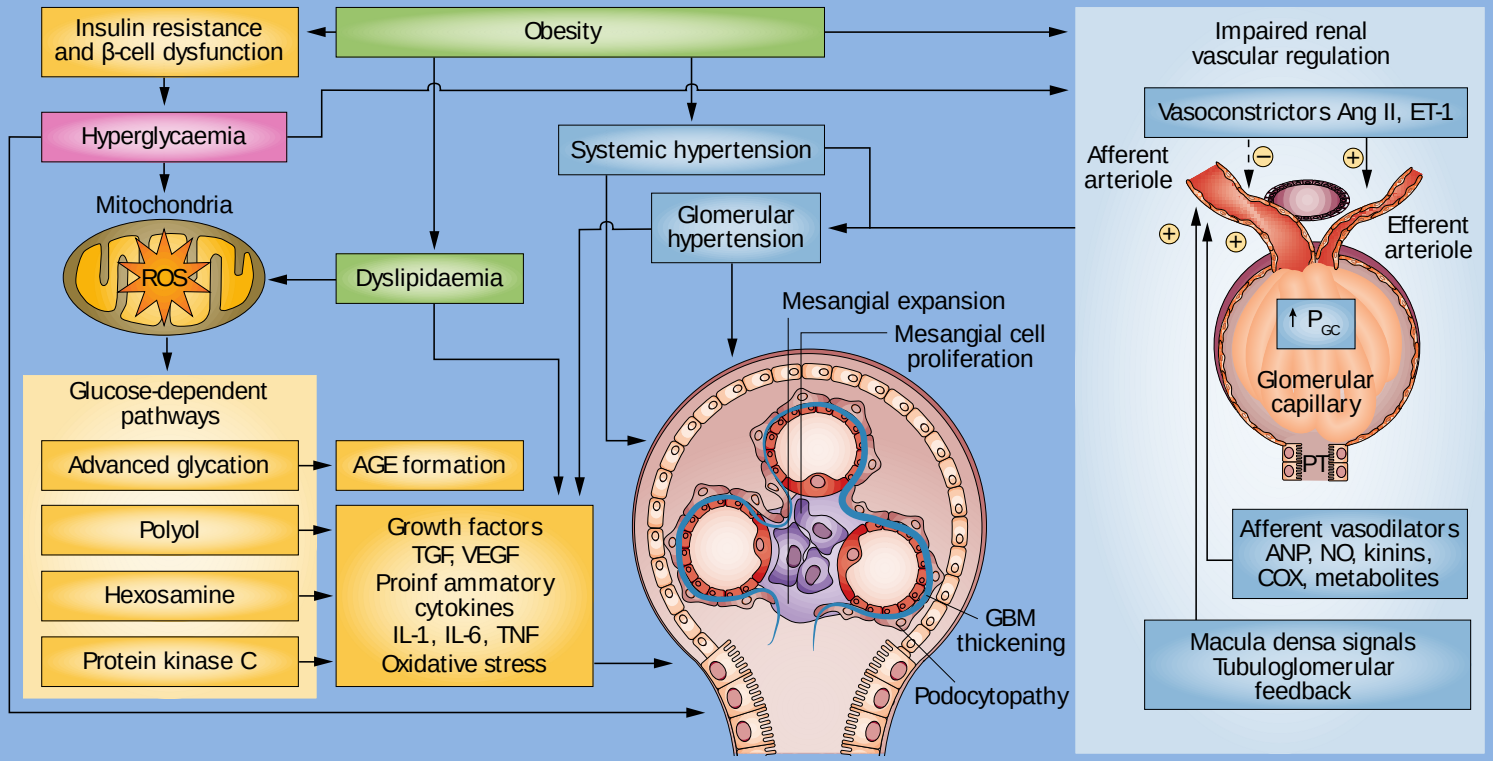
Glucagon-Like Peptide Receptor Agonists in DKD Mechanisms and Outcomes

Ali Ghafari
Associate professor in medicine
Tehran University of medical sciences

Tehran University of Medical Sciences

Pathogenesis of kidney disease in patients with diabetes.



Muskiet, M. H. A. *et al. Nat. Rev. Nephrol.* 10, 88–103 (2014)

Renoprotective strategies for T2DM

- Glucose control
- Blood pressure control
- Multifactorial intervention

Glucose control

- large randomized clinical trials suggest that intensive glucose and blood pressure control might delay the onset and halt the progression of diabetic nephropathy

National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012
update. *Am. J. Kidney Dis.* 60, 850–886 (2012).

The Diabetes Control and Complications Trial Research Group (DCCT). *N. Engl. J. Med.* 329, 977–986 (1993).

- In this randomized controlled trial
- Included 1,441 patients with T1DM

- 6.5 years of intensive diabetes therapy (three or more insulin injections per day or use of an insulin pump) to achieve a target HbA1c level of 7% (versus a target HbA1c level of 9% in the conventional treatment group)

- Reduced the occurrence of microalbuminuria by 39% and that of macroalbuminuria by 54%.

UKPDS

- In the UKPDS, 10 years of intensive glucose therapy

- To achieve a HbA1c level of 7.0%, (versus a target of 7.9% with conventional therapy) conferred beneficial effects on renal end points in 3,867 newly diagnosed patients with T2DM

38.Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352, 837–853 (1998)

- At the 10-year post-trial follow-up
- HbA1c levels were similar in the treatment groups but a sustained reduction in microvascular complications and a significantly reduced risk of myocardial infarction was observed in the patients who had received intensive treatment.
- The findings of the DCCT35 and UKPDS38 suggest that early exposure to hyperglycaemia predisposes individuals to the development of diabetic complications, a phenomenon referred to as ‘metabolic memory’ or the ‘legacy effect’.

Evidence of renoprotection in studies of antihyperglycaemic therapy for T2DM

Study	Duration of T2DM (years)	Number of patients	Primary agent(s)*	Follow-up (years)	Outcome parameters (risk)
UKPDS (1998)[38]	New onset	3,867	Sulphonylurea or insulin	10.0	Microalbuminuria (RR 0.76‡) Macroalbuminuria (RR 0.67‡) Doubling of SCr (RR 0.40‡) ESRD (RR 0.73)
ADVANCE (2008)[43]	8	11,140	Gliclazide (90.5%)	5.0	Microalbuminuria (HR 0.91‡) Macroalbuminuria (HR 0.70‡) Doubling of SCr (HR 1.15) ESRD or death (HR 0.64)
ACCORD (2008 and 2010)[41,42]	10	10,251	Metformin (86.9%) and sulphonylurea (73.8%)	3.5§	Microalbuminuria (HR 0.79‡) Macroalbuminuria (HR 0.69‡) Doubling of SCr (HR 1.07‡) ESRD (HR 0.95)
VADT (2009 and 2011)[44,45]	12	1,791	Rosiglitazone plus metformin (in patients with BMI ≥27 kg/ m^2) or Rosiglitazone plus glimepride (in patients with BMI <27 kg/ m^2)	5.6	Microalbuminuria (RR 0.74) Macroalbuminuria (RR 0.56‡) Doubling of SCr (RR 1.00) ESRD (RR 0.64)

* Numbers in brackets refer to the percentage of patients that used the glucose-lowering drug at the end of follow-up. ‡Indicates significant result. §Study stopped early due to excess mortality in the intensive treatment arm. Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; RR, relative risk; SCr, serum creatinine; T2DM, type 2 diabetes mellitus.

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- A systematic review and meta-analysis, which evaluated seven landmark treatment trials in patients with T2DM

- Concluded that although intensive glycaemic control reduces the risk of microalbuminuria and macroalbuminuria, it does not reduce the risk of important clinical renal end points (such as doubling of serum creatinine levels, ESRD or death from renal disease)

Coca, S. G., Ismail-Beigi, F., Haq, N., Krumholz, H. M. & Parikh, C. R. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch. Intern. Med.* 172, 761–769 (2012).

Evidence of renoprotection in studies of antihypertensive therapy for T2DM

Study	Duration of T2DM (years)	Number of patients	Treatment arms	Follow-up (years)	Outcome parameters (renal risk)
UKPDS (1998)[49]	2.6	1,148	Intensive versus standard	8.4	Microalbuminuria (RR 0.87) Macroalbuminuria (RR 1.06) ESRD and death (RR 0.58)
ADVANCE (2007)[51]	8.0	11,140	Intensive versus standard	4.3	Microalbuminuria (RRR 21%)* Macroalbuminuria (RRR 18%)
ACCORD (2010 and 2012)[52,53]	1.1	4,733	Intensive versus standard	4.7	Microalbuminuria (HR 0.84)* Macroalbuminuria (HR 0.81) ESRD (HR 1.00)
HOPE and MICRO-HOPE (2000)[60]	11.0	3,577	Ramipril versus placebo	4.5‡	Microalbuminuria (RRR 9%) Macroalbuminuria (RRR 24%)* ESRD (RRR −20%)
BENEDICT (2004)[61]	8.0	1,204	Trandolapril versus placebo	3.6	Microalbuminuria (AF 0.47)*
ROADMAP (2011)[62]	6.0	4,447	Olmesartan versus placebo	3.2	Microalbuminuria (HR 0.77)* Doubling of SCr (RR 1.0)
IRMA-2 (2001)[63]	10.0	590	Irbesartan versus placebo	2.0	Restore albuminuria (RRR 34%‖)* Macroalbuminuria (HR 0.30)*
IDNT (2001)[64]	NR	1,715	Irbesartan versus placebo	2.6	Doubling of SCr (RR 0.67)* ESRD (RR 0.77)
RENAAL (2001)[65]	NR	1,513	Losartan versus placebo	3.4§	Composite end point (RRR 16%)* Doubling of SCr (RRR 25%)* ESRD (RRR 28%)*
TRANSCEND (2008)[66]	NR	5,926	Telmisartan versus placebo	4.7	Renal abnormalities (RR 1.86) Cardiorenal end point (HR 0.85)* Doubling of SCr (HR 1.60)* ESRD (HR 0.67)
DIRECT-Protect 2 (2009)[59]	9.0	1,905	Candesartan versus placebo	4.7	Microalbuminuria (HR 1.01¶ and 0.76#) Increase in UAE (HR 0.95¶ and 0.93#)

* Indicates significant result. ‡Study stopped early owing to consistent benefit of ramipril compared with placebo. §Study stopped early because of new evidence suggesting ACE inhibitors might be effective in reducing cardiovascular events in T2DM. ‖Normalization of urinary albumin. ¶Use of antihypertensive medication at baseline. #Normotensive at baseline. Abbreviations: AF, acceleration factor (quantifies the effect of one treatment relative to another treatment in accelerating or slowing the progression of the disease); ESRD, end-stage renal disease; HR, hazard ratio; NR, not reported; RR, relative risk; RRR, relative risk reduction; SCr, serum creatinine; T2DM, type 2 diabetes mellitus; UAE, urinary albumin excretion.

Muskiet, M. H. A. *et al. Nat. Rev. Nephrol.* 10, 88–103 (2014)

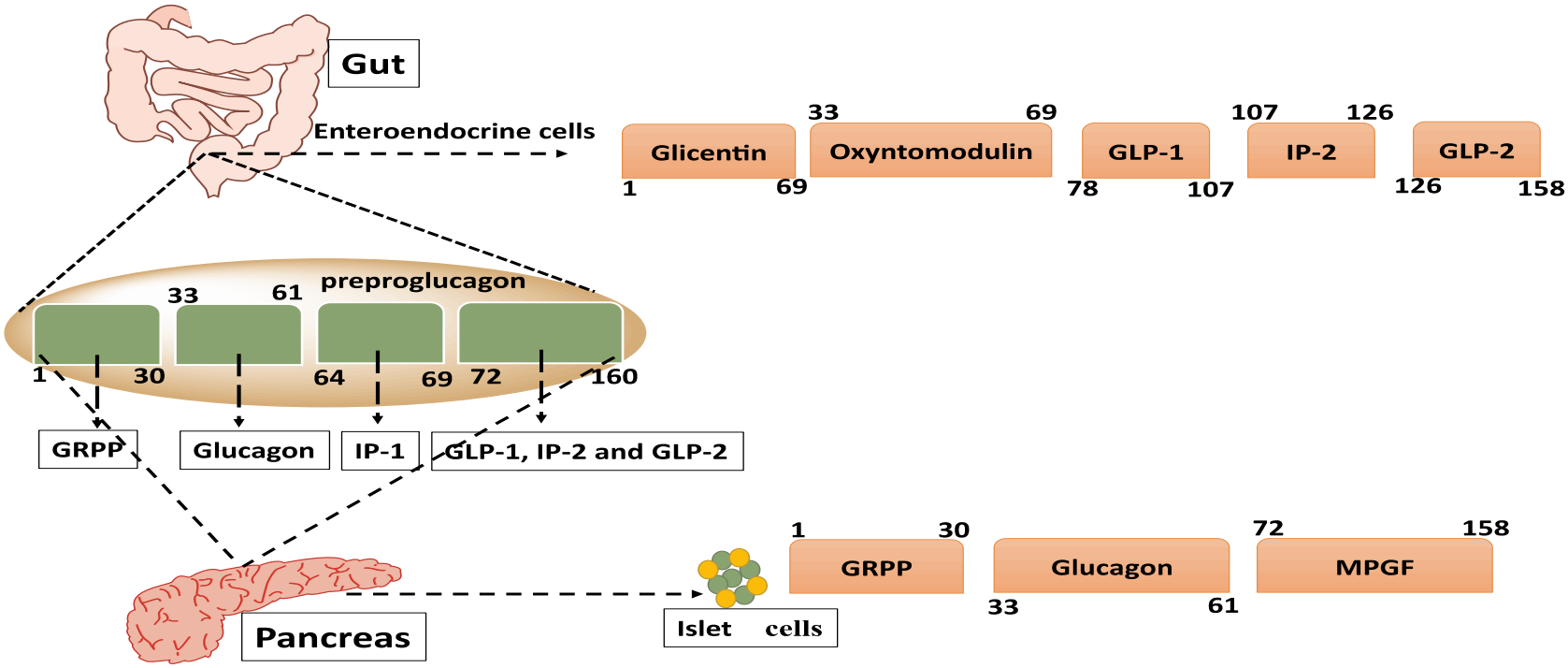
- These results highlight the unmet need for novel strategies to further prevent or delay progression of diabetic nephropathy in patients with T2DM.

The incretin system

- Oral glucose administration elicits a 50–70% greater increase in plasma insulin levels than does glucose given intravenously, despite resulting in similar plasma glucose concentrations.

- The differential response to an oral versus intravenous glucose load is called the ‘incretin effect’, and is mediated by the incretin hormones.

Production of preproglucagon in intestinal enteroendocrine L-cells and Pancreatic α-cells.



GLP-1 peptide drived from Posttranslational processing of preproglucagon by prohormone convertases 1/3 in intestinal L-cells and GLP-2, oxyntomodulin, glicentin, and IP2 also drived in L-cells. In the α-cells of the pancreatic islet, glucagon, glicentin-related pancreatic polypeptide (GRPP) and major proglucagon fragment (MPGF) derived from preproglucagon cleaved by, prohormone convertase 2.

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A sequence alignment of GLP-1, Ex4 and several analogues

```
                    7       15      22              36
                    ¦       ¦       ¦               ¦
GLP-1               HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR
A7-GLP-1            AAEGTFTSDVSSYLEGQAAKEFIAWLVKGR
A10-GLP-1           HAEATFTSDVSSYLEGQAAKEFIAWLVKGR
GLP-1(9-36)           EGTFTSDVSSYLEGQAAKEFIAWLVKGR
GLP-1(15-36)                DVSSYLEGQAAKEFIAWLVKGR

                    1       9       16              30        39
                    ¦       ¦       ¦               ¦         ¦
Ex4                 HGEGTFTSDLSKQMEEEVARLFIEWLKNGGPSSGAPPPS
Ex4(1-30)           HGEGTFTSDLSKQMEEEVARLFIEWLKNGG
Ex4(9-39)                   DLSKQMEEEVARLFIEWLKNGGPSSGAPPPS
Ex4(9-30)                   DLSKQMEEEVARLFIEWLKNGG
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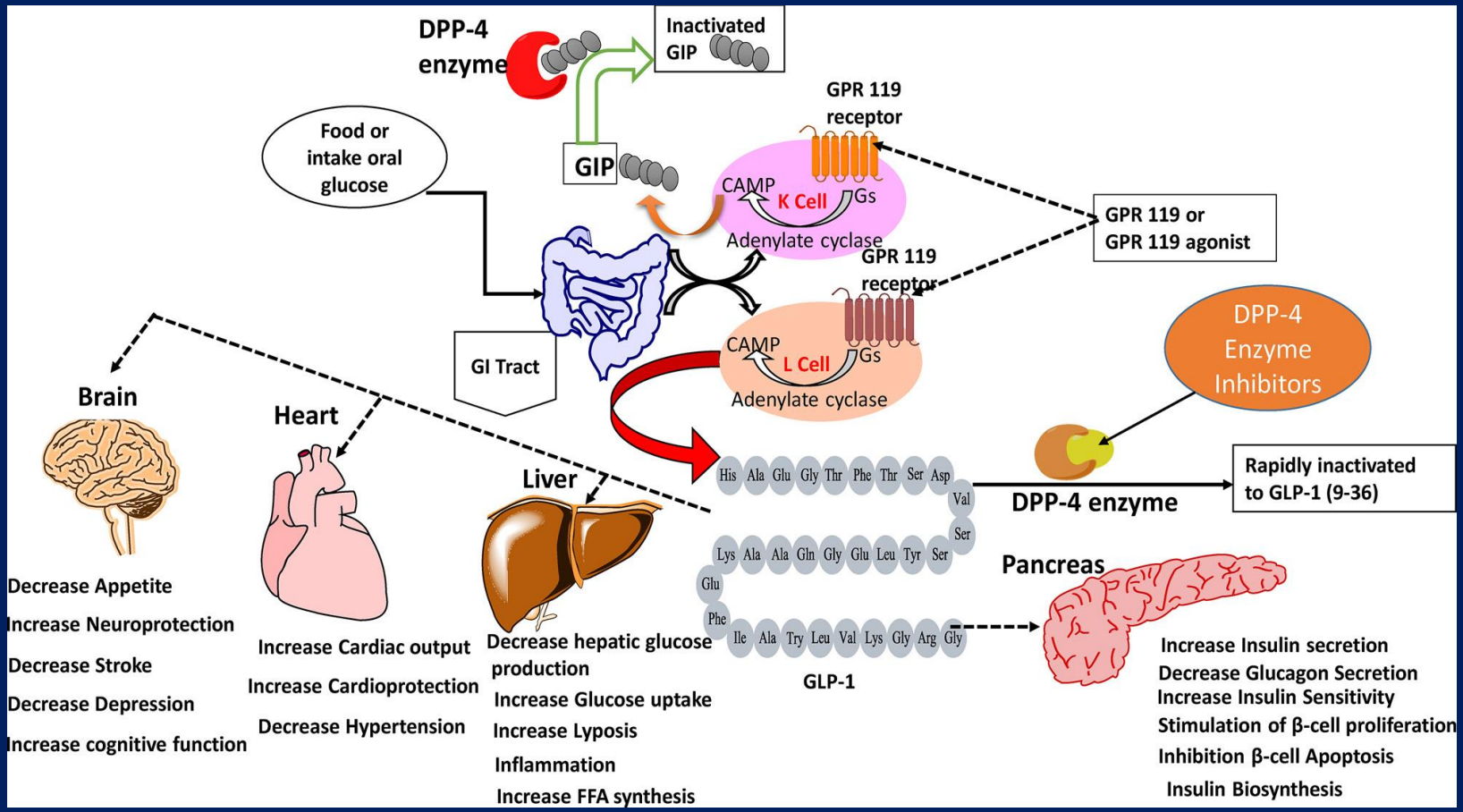
All peptides are C-terminally amidated. Note that the first residue of GLP-1 is His7, while that of Ex4 is His1. Residues changed from the original sequence are underlined.

British Journal of Pharmacology (2012) **166** 27–41

GLP-1 synthesis, release, metabolism and effects of GLP-1 on body organs



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Physiology of GLP-1

- GLP-1 (36 amino acid) is produced in enteroendocrine L-cells of the distal small bowel and colon.
- It is active in two forms, GLP-1(7–36) amide and GLP- 1(7–37), both are equipotent but the earlier one is abundant in nature .
- Their concentrations are low (5–10 pmol/L) during fasting conditions and high (15–50 pmol/L) after meals.
- Alanine, at the second residue of incretins, is the site of cleavage by DPP-4 enzymes, restricting its half-life to only ~2 min by producing inactive GLP-1(9–36) amide or GLP-1(9–37).
- Only 10–15% of secreted GLP-1 finally reaches the systemic circulation.

Regulation of GLP-1 secretion

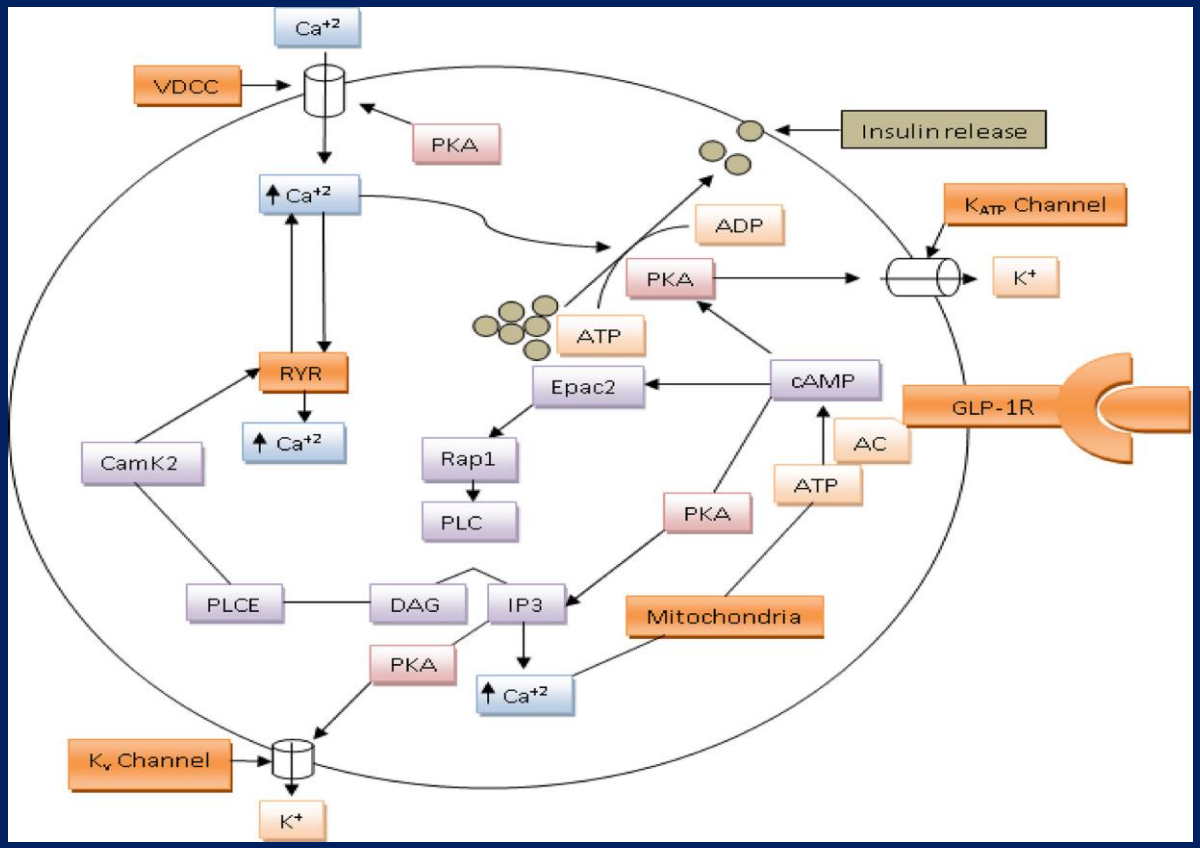
- GLP-1 releases in a biphasic manner
- Rapidly within 15–30 min of nutrient ingestion followed by a second minor peak at 90–120 min.
- The rapid rise of GLP-1 after meals is due to the proximal-distal link regulated by neurotransmitters (Ach), neuropeptide (GRP).
- Subsequent secretion due to the transit of nutrients down the lumen with direct interaction with distal L-cells. The fat, rather than glucose that transits to the lumen, is a more important physiological regulator of GLP-1 release.
- Also, GABA and glycine are reported to secrete GLP-1 from GLUTag cell lines. In rats, GLP-1 is secreted by GIP through a neuronal pathway but in humans the mechanism is different.
- Somatostatin has an inhibitory effect upon GLP- 1 secretion and the inhibition of somatostatin by immunoneutralization leads to increase in GLP-1 secretion up to eight fold

Regulation of insulin secretion by GLP-1

- Binding of GLP-1 to its receptors activates adenylate cyclase, hence, cAMP levels are elevated followed by PKA and cAMP-regulated guanine nucleotide exchange factor 2 (cAMP-GEF2), also known as Epac2.
- PKA causes closure of ATP sensitive K+ (KATP) channels and membrane depolarisation with activation of L-type voltage-dependent calcium channel (VDCC), followed by generation of the action potential and Ca+ influx. PKA-dependent closure of delayed rectifying K+ channels results in prolongation of the duration of the action potential.

- PKA also leads to Ryanodine receptors (RYR) and inositol 1,4,5-tri-sphosphate (IP3) mediated Ca+2 release. Epac2 activates Rap1 with the formation of IP3 and DAG, which further leads to CICR (Calcium-in-duced calcium release), from Ryanodine receptor (RyR) and inositol-3-phosphate receptor (IP3R) respectively. All these pathways ultimately increase cytoplasmic Ca+2 that induce mitochondrial ATP synthesis and exocytotic release of insulin from insulin granules.

Pathway involved in insulin release by GLP-1



: Binding of GLP-1 to its receptor activates adenylate cyclase and cAMP levels are elevated followed by PKA. PKA causes closure of ATP sensitive K (KATP) and activation of L-type VDCC. PKA also leads to RYR and IP3 mediated Ca++ release. All these pathways ultimately increase cytoplasmic Ca which induces mitochondrial ATP synthesis and exocytotic release of insulin from insulin granules.cAMP-GEF2: cAMP-regulated guanine
nucleotide exchange factor 2, VDCC: voltage-dependent calcium channel, RYR: ryanodine receptors, IP3R: iono-cyotol-3-phosphate receptor, EPAC: Epac2 activates Rap1 with formation of IP3 and DAG, CICR: Calcium induced calcium release.

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Glucose-dependent insulinotropic and glucagonostatic actions of GLP1

- Potentiates glucose-induced secretion of insulin
- Increases insulin expression
- Inhibits beta-cell apoptosis
- Promotes beta-cell neogenesis
- Reduces glucagon secretion
- Delays gastric emptying
- Promotes satiety
- Increases peripheral glucose disposal

Other actions of GLP1

- Neuroprotection
- Increased cognitive function
- Cardio-protection
- Decreased hypertension
- Suppression of acid secretion
- Increase in lyposis
- Protection from inflammation.

The mechanisms of action of GLP-1

- Half-life of GLP-1 *in vivo* is short (around 2~min), and it is rapidly degraded to GLP-1(9-36)amide by dipeptidyl peptidase IV (DPPIV)

  - Deacon *etal.*, 1995; Knudsen and Pridal, 1996; Hansen *etal.*, (1999)

The mechanisms of action of GLP-1

To overcome the short half-life of endogenous GLP-1 two approaches are being practiced.

- First is to use DPP-4 inhibitors:
- Sitagliptin
- Vildagliptin
- which prevents the breakdown of native GLP-1.

- Second, is the synthesis of DPP-4 resistant GLP-1 analogs
- Exenatide
- Liraglutide
- Exenatide LAR, Albiglutide
- Dulaglutide
- Lixisenatide

Renal effect of GLP-1 and incretin-based agents

- An incretin effect on sodium handling seems to exist, as dietary intake of sodium induces more marked natriuresis than does intravenously administered sodium.

Renal effect of GLP-1 and incretin-based agents

- GLP-1 promotes natriuresis by acting on the proximal tubule.
- The involvement of NHE-3 (which is bound to a complex that also contains DPP-4) in this process has also been demonstrated.
- Decreased NHE-3 activity augments natriuresis and decreases hydrogen excretion.
- Thus, GLP-1 administration increases urinary pH levels in rats and in humans.

90.Girardi, A. C., Fukuda, L. E., Rossoni, L. V., Malnic, G. & Rebouças, N. A. Dipeptidyl peptidase IV inhibition downregulates Na+-H+ exchanger NHE3 in rat renal proximal tubule. *Am. J. Physiol. Renal Physiol.* 294, F414–F422 (2008).

Renal effect of GLP-1 and incretin-based agents

- Both GLP-1R agonists and DPP-4 inhibitors induce natriuresis.
- An indirect natriuretic or diuretic effect of GLP-1R activation, mediated by secretion of ANP, has been reported in mouse cardiac atria.
- However, GLP-1 infusion in healthy humans did not affect circulating levels of either ANP or its propeptide, despite a marked increase in sodium excretion.

Hirata, K. *et al.* Exendin-4 has an anti-hypertensive effect in salt-sensitive mice model. *Biochem. Biophys. Res. Commun.* 380, 44–49 (2009). Pacheco, B. P. *et al.* Dipeptidyl peptidase IV

Renal effect of GLP-1 and incretin-based agents

- GLP-1-induced proximal natriuresis;
- Increased influx of isotonic tubular fluid into the distal segment of the nephron; distal sodium reabsorption and decreased water permeability of the collecting ducts.
- However, GLP-1-induced changes in RPF might reduce the renal osmotic gradient, owing to washout of solutes, thereby possibly contributing to water impermeability of the collecting duct.
- GLP-1 also reduces water and salt intake in rats, healthy men, and obese individuals.

Rieg, T. *et al.* Natriuretic effect by exendin-4, but not the DPP-4 inhibitor alogliptin, is mediated via the GLP-1 receptor and preserved in obese
type 2 diabetic mice. *Am. J. Physiol. Renal*

Interference with pathways of renal damage

- GLP-1 prevented the development of hypertension, ameliorated histologically verified renal damage and reduced albuminuria.

90.Yu, M. *et al.* Antihypertensive effect of glucagon- like peptide 1 in Dahl salt-sensitive rats. *J. Hypertens.* 21, 1125–1135 (2003).

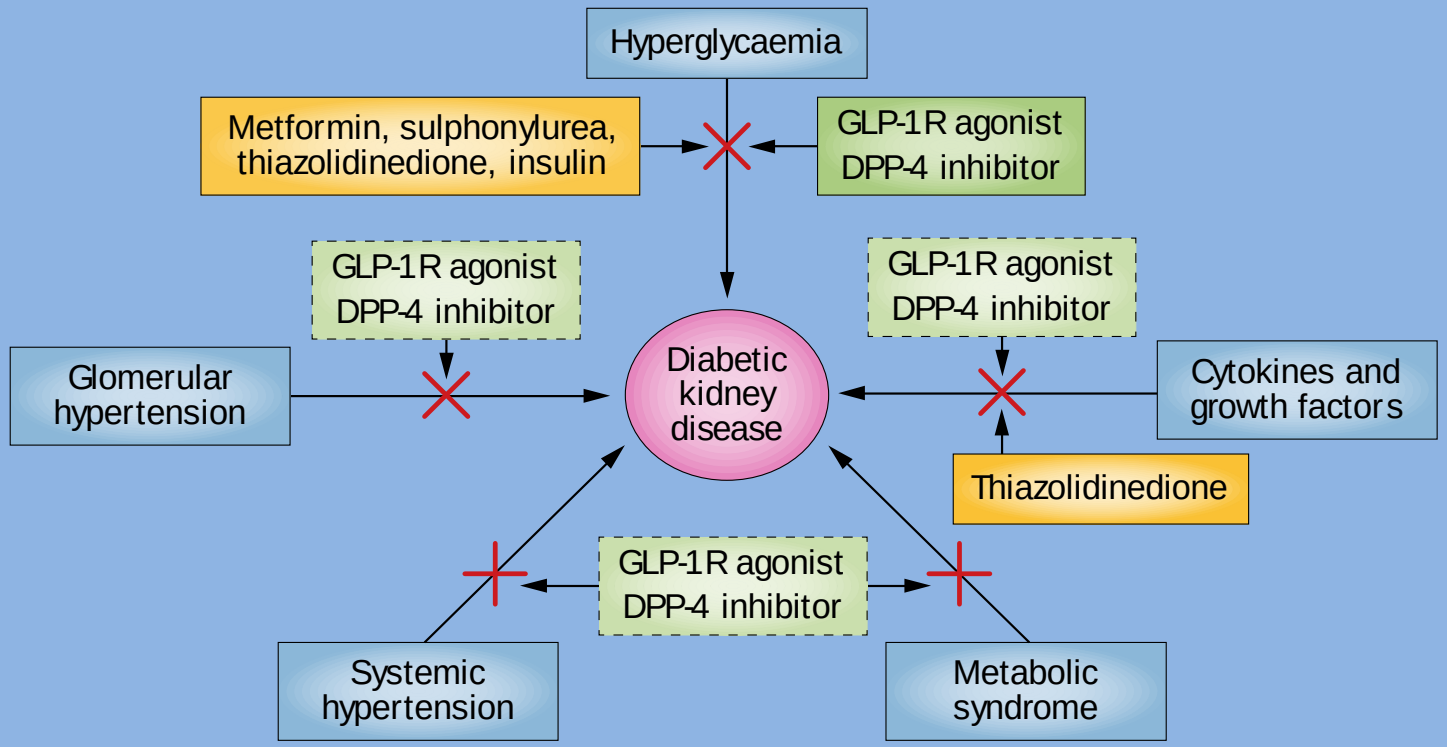
Interference with pathways of renal damage

- in various animal models of diabetes, long-term treatment with GLP-1R agonists and DPP-4 inhibitors gave similar findings.

- Although in most of these studies no control group using other antihyper- glycaemic agents was included to establish effects beyond glucose control, the current evidence suggests that at least some of the renoprotective effects of incretin-based therapies are glucose-independent.

Mega, C. *et al.* Diabetic nephropathy amelioration by a low-dose sitagliptin in an animal model of type 2 diabetes (Zucker diabetic fatty rat). *Exp. Diabetes Res.* 2011, 1–12 (2011).

Effects of incretin-based therapies on renal risk factors in T2DM.



Mechanisms of incretin-based therapies

- *Systemic and renal haemodynamics*
- GLP-1R agonists decreased systolic blood pressure by 2– 5 mmHg, depending on the comparator drug (placebo or an active control, such as insulin, pioglitazone and sulphonylureas).

- The lowering effects of GLP-1R agonists on diastolic blood pressure were more modest, ranging from 0.5–2.0 mmHg, and did not reach statistical significance.

Robinson, L. E., Holt, T. A., Rees, K.,
Randeva, H. S. & O'Hare, J. P. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. *BMJ Open* 3, e001986 (2013).

Mechanisms of incretin-based therapies

- *Systemic and renal haemodynamic*
- Few studies have investigated the antihypertensive effects of DPP-4 inhibitors.

- Although modest reductions in systolic blood pressure were observed in some studies, a meta- analysis failed to show significant effects.

Monami, M., Ahrén, B., Dicembrini, I. & Mannucci, E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes Obes. Metab.* 15, 112–120 (2013).

Mechanisms of incretin-based therapies

- *Systemic and renal haemodynamic*
- The antihypertensive action of GLP-1R agonists might be partly attributable to a combination of GLP-1- mediated natriuresis and diuresis, but could also involve:

- Improved endothelial function

- Increased release of vasoactive factors (such as NO and ANP)

- Decrease in ET-1 levels

- Alteration in the balance of the autonomic nervous system

Mechanisms of incretin-based therapies

- *Systemic and renal haemodynamic*
- GLP-1, GLP-1R agonists and DPP-4 inhibitors also affect renal haemodynamics.

- The GLP-1-related increase in sodium delivery to the macula densa restores disrupted tubuloglomerular feedback associated with diabetes, resulting in relative vasoconstriction of the afferent renal arteriole and, consequently, a decrease in PGC.

140.ensen, E. P. *et al.* Activation of renal GLP-1
141.receptors located in the afferent arteriole causes an increase in renal blood flow. *Diabetologia* 56 (Suppl.), 255 (2013).

Mechanisms of incretin-based therapies

- *Systemic metabolism and inflammation*
- Agonists of GLP-1R and inhibitors of DPP-4, reduce blood glucose and HbA1c levels in patients with T2DM.

- However, GLP-1R agonists have more marked antihyperglycaemic effects than do DPP-4 inhibitors.

Bergenstal, R. M. *et al.* Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 376, 431–439 (2010).

Mechanisms of incretin-based therapies

- *Systemic metabolism and inflammation*
- Exenatide therapy also decreased postprandial markers of oxidative stress (such as serum oxidised-LDL and malondialdehyde) in association with the decrease in postprandial glucose levels, in patients with T2DM.

- Additionally, GLP-1 and DPP-4 inhibitors reduce expression of RAGE, thereby decreasing AGE and other ligand-induced cell death and oxidative stress markers, both *in vitro* and in patients with T2DM.

140.Bunck, M. C. *et al.* One-year treatment with
141.exenatide vs. insulin glargine: effects on postprandial glycemia, lipid profiles, and oxidative stress. *Atherosclerosis* 212, 223–229 (2010).

Mechanisms of incretin-based therapies

- *Systemic metabolism and inflammation*
- In rodents, incretin-based therapies decrease levels of inflammatory and profibrotic markers (such as transforming growth factor [TGF], fibronectin and 8-Oxo-2 -deoxyguanosine) and urinary markers of oxidative stress, as well as reducing glomerular leucocyte infiltration, indicating a decrease in renal inflammation.

- Human studies show that GLP-1R agonists and DPP-4 inhibitors reduce levels of circulating pro- inflammatory factors, both in an acute setting and after long-term treatment.

140.Chaudhuri, A. *et al.* Exenatide exerts a potent antiinflammatory effect. *J. Clin. Endocrinol. Metab.* 97, 198–207 (2012).

Mechanisms of incretin-based therapies

- *Systemic metabolism and inflammation*
- GLP-1R agonists reduce body weight in patients with T2DM and in obese nondiabetic individuals, possibly as a consequence of inducing satiety and reduced caloric intake
- whereas DPP-4 inhibitors are body weight neutral.
- GLP-1R agonists might, therefore, ameliorate kidney disease to a greater extent than do DPP-4 inhibitors, by improving weight-related risk factors,

140.Klonoff, D. C. *et al.* Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr. Med. Res. Opin.* 24, 275–286 (2008).

Mechanisms of incretin-based therapies

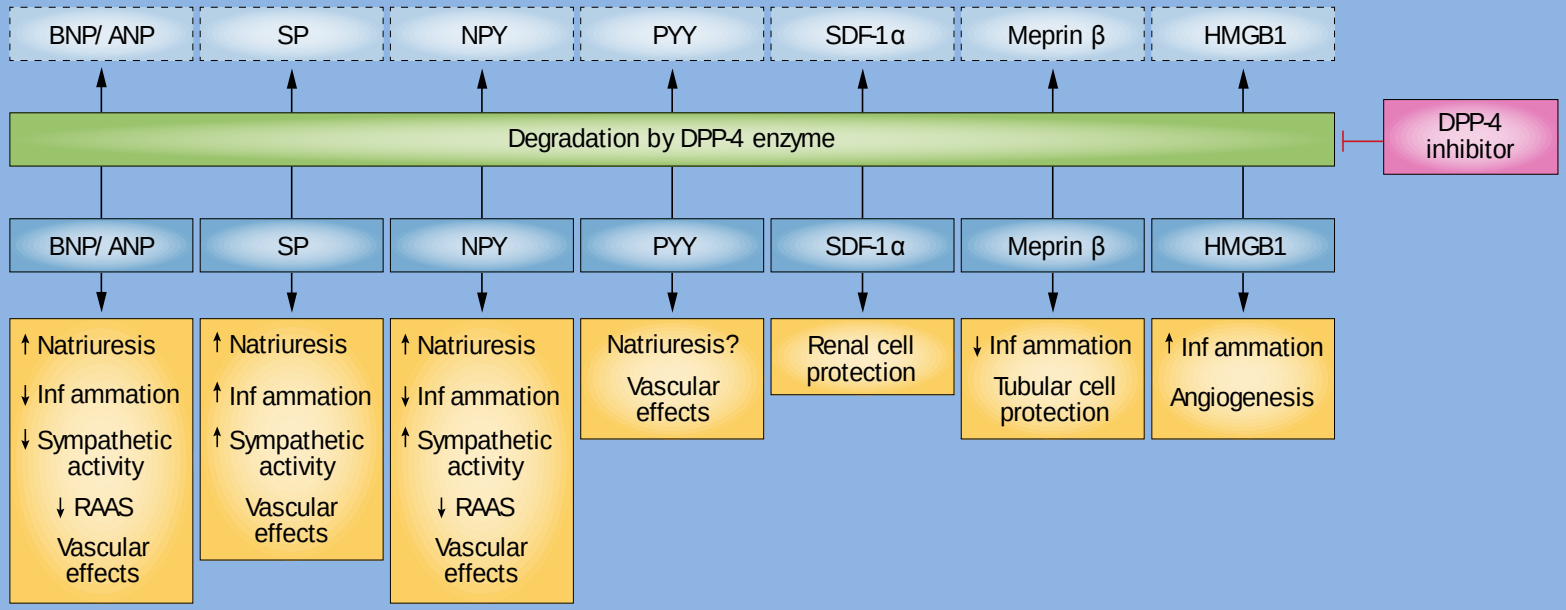
- *GLP-1-independent effects of DPP-4 inhibition*
- Besides GLP-1 and GIP, DPP-4 cleaves multiple substrates, such as brain natriuretic peptide (BNP), ANP, substance P, neuropeptide Y (NPY), peptide YY (PYY), stromal-cell-derived factor 1α (SDF-1α), meprin A subunit β (meprin β) and high mobility group protein B1 (HMGB1) many of which are vasoactive .

- As DPP-4 is also expressed at the apical brush border surface of renal proximal tubular cells, DPP-4-inhibitor-mediated actions on the renal and cardiovascular system might, in part, be GLP-1-independent

Mentlein, R. Dipeptidyl-peptidase IV (CD26)--role in the inactivation of regulatory peptides. *Regul. Pept.* 85, 9–24 (1999).

Mechanisms of incretin-based therapies

GLP-1-independent effects of DPP-4 inhibition



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Mechanisms of incretin-based therapies

- *GLP-1-independent effects of DPP-4 inhibition*
- SDF-1α, a chemokine that is increased in ischaemic tissue and has a major role in attracting stem cells to these sites for the purposes of tissue repair, also seems to be involved in murine kidney repair.

- Preclinical studies in mice and in rats have shown that DPP-4 inhibition decreases infarct size after myocardial ischaemia by preventing the degradation of SDF-1α.

- Sitagliptin also prevented SDF-1α degradation and increased circulating endothelial progenitor cells in patients with T2DM without ischaemia.

Tögel, F., Isaac, J., Hu, Z., Weiss, K. & Westenfelder, C. Renal SDF-1 signals mobilization and homing of CXCR4-positive cells to the kidney after ischemic injury. *Kidney Int.* 67, 1772–1784 (2005).

Mechanisms of incretin-based therapies

- *GLP-1-independent effects of DPP-4 inhibition*
- Increased levels of DPP-4 substrates resulting from the action of DPP-4 inhibitors might be harmful
- In terms of increased activation of the sympathetic nervous system or inflammation.
- HMGB1, a known ligand for Toll-like receptors and RAGE, is cleaved by DPP-4 *in vitro,* and affects angiogenesis in mouse vascular cells.
- Additionally, HMGB1 leads to the production and secretion of proinflammatory cytokines, and contributes to renal injury in mice and rats with streptozotocin- induced diabetes.

. The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: possible role of stromal-derived factor-1α. *Diabetes Care* 33, 1607–1609 (2010).

Mechanisms of incretin-based therapies

- *Renal effects in T2DM*
- Currently, the results of only a few studies suggest that incretin-based therapies can provide renoprotection in humans.

- In phase III trials, GLP-1R agonist use was associated with a reduction in albuminuria in patients with T2DM;

- However, this effect was not statistically significant compared to that of the other agents used, sitagliptin and pioglitazone.

Mechanisms of incretin-based therapies

- *Renal effects in T2DM*
- In small, uncontrolled studies, 6 months of treatment with sitagliptin, or 12 weeks of treatment with alogliptin reduced albuminuria in patients with T2DM.

- These data were confirmed and expanded in a pooled analysis of phase III trials of linagliptin, which showed a significant reduction in albuminuria after a mean of 24 weeks of treatment.

- Interestingly, 16 weeks of treatment with exenatide reduced both albuminuria and urinary levels of TGF and type IV collagen (versus glimepiride) in patients with T2DM.

Zhang, H., Zhang, X., Hu, C. & Lu, W. Exenatide reduces urinary transforming growth factor-β1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. *Kidney Blood Press. Res.* 35, 483–488 (2012).

Mechanisms of incretin-based therapies

- *Renal effects in T2DM*
- Two trials for DPP-4 inhibitors have been published.

- These placebo-controlled studies, involving a median 2 years of treatment with alogliptin and saxagliptin, demonstrated no cardiovascular harm and a modest reduction in albuminuria progression in high- risk patients with T2DM.

Scirica, B. M. *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N. Engl. J. Med.* 369, 1317–1326 (2013).

Tolerability and safety

- Use of GLP-1R agonists, but not DPP-4 inhibitors, is associated with (usually transient)
- Nausea, and occasionally vomiting.
- Other adverse effects, only reported after introduction to the market, include
- sporadic cases of acute renal failure.
- All affected patients had T2DM and used RAAS-inhibiting agents and diuretics, which, together with nausea, might have caused dehydration leading to renal failure.
- However, a retrospective analysis of insurance claim data did not find any association between incretin-based therapy and renal failure

Pendergrass, M., Fenton, C., Haffner, S. M. & Chen, W. Exenatide and sitagliptin are not associated with increased risk of acute renal failure: a retrospective claims analysis. *Diabetes Obes. Metab.* 14, 596–600 (2012)

Tolerability and safety

- Exogenous GLP-1 reduced circulating angiotensin II levels in healthy human. Although renin and aldosterone concentrations remained unchanged.

- In addition, GLP-1R agonists inhibited angiotensin II-induced hypertension in salt-sensitive mice. Specifically, GLP-1R-mediated increases in intracellular cAMP in the glomerular endothelium inhibit phosphorylation and subsequent (post-receptor) actions of the intracellular mediators of angiotensin II, mitogen-activated protein kinase (MAPK) 3 and MAPK1 (also known as ERK1 and ERK2, respectively).

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Tolerability and safety

- Additionally, GLP-1R agonist and DPP-4 inhibitor use is associated with the occurrence of pancreatitis and pancreatic cancer, although no causal relationship has yet been demonstrated in animal studies or published outcome trials.

Pharmacokinetics and pharmacodynamics of incretin-based therapies

Agent	Dose	Half-life (h)	DPP-4 inhibition	Elimination	Use in patients with renal insufficiency	
					Moderate (eGFR 30–60 ml/ min)	Severe (eGFR <30 ml/ min)
GLP-1R agonists						
Exenatide	5-10 µg twice daily	2.4	NA	Glomerular f ltration, proteolytic degradation	Caution	Not recommended
Exenatide	2 mg once weekly	2.4*	NA	Glomerular f ltration, proteolytic degradation*	Not recommended	Not recommended
Liraglutide	1.2–1.8 mg daily	13.0	NA	Generalized proteolysis, Elimination: renal (6%); faecal (5%)	Not recommended	Not recommended
Lixisenatide	20 µg daily	3.0	NA	Glomerular f ltration, tubular reabsorption and metabolic degradation	Caution	Not recommended
DPP-4 inhibitors						
Sitagliptin	100 mg daily	8.0–24.0	Max. ~97% (>80% 24 h post-dose)	Renal excretion (80% unchanged)	Dose reduction	Dose reduction
Vildagliptin	50 mg twice daily or 50 mg once daily (plus sulphonylurea)	1.5–4.5	Max. ~95% (>80% 24 h post-dose)	Metabolized to inactive metabolite, renal excretion (22% unchanged)	Dose reduction	Dose reduction
Linagliptin	5 mg daily	10.0–40.0	Max. ~80% (~70% 24 h post-dose)	Elimination: renal (5%); faecal (85%)	No adjustment	No adjustment
Saxagliptin	5 mg daily	2.2–3.8	Max. ~80% (~70% 24 h post-dose)	Metabolized to active metabolite, Elimination: renal (12–29% unchanged, 21–52% metabolite)	Dose reduction	Dose reduction
Alogliptin	25 mg daily	12.5–21.1	Max. ~90% (~75% 24 h post-dose)	Elimination: renal (>70% unchanged)	Dose reduction	Dose reduction

Muskiet, M. H. A. *et al. Nat. Rev. Nephrol.* 10, 88–103 (2014)

conclusion

- In preclinical studies, GLP-1 and GLP-1R agonists improve metabolic parameters and have beneficial effects on systemic and renal haemodynamics, as well as on the prevention and progression of renal dysfunction and kidney damage.

- Interestingly, GLP-1R agonists in particular interfere with multiple metabolic, haemodynamic and proinflammatory pathways, most of which have a role in the development of diabetic nephropathy.

- The DPP-4 inhibitors, besides blocking the degradation of GLP-1, also modify levels of other (vasoactive) peptides that might act on the kidney. Initial findings in healthy humans and in patients with T2DM have confirmed some of the potentially beneficial effects of both incretin classes.

- However, the added value and true benefit of incretin-based therapies on renal and cardiovascular end points, as well as their long-term safety and tolerability, can only be established by the results of ongoing large, prospective, long-term outcome trials.

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