

# The privileged position of glp-1 in diabetic nephropathy

## Abstract

Nowadays worldwide, an estimated 200 million people have chronic kidney disease (CKD). Diabetic nephropathy is a diagnosis that refers to specific pathologic structural and functional changes seen in kidney patients with Type 2 Diabetes Mellitus (T2DM). Incretins such as Glucagon like peptide 1 (GLP-1) control blood glucose level through different metabolic pathways; for example, inhibition of glucagon production, and delay in gastric emptying and satiety induction. Accumulated evidence suggests that long term treatment with GLP-1 receptor agonist is associated with a reduction in measured glomerular filtration rate (GFR), preservation of renal function and/or a decrease in the incidence of cardiovascular events.

**Keywords:** diabetes mellitus, diabetic nephropathy, enterohormones, incretins, GLP-1, renoprotection

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## Introduction

Nowadays worldwide, an estimated 200 million people have chronic kidney disease (CKD). About 40% of patients with T2DM develop CKD. As a result of intensive blood glucose control through pharmacological intervention, it is possible to delay CKD progression with standard therapies for treatment of T2DM. These include metformin, sulfonylureas, meglitinides, thiazolidinediones, and insulin. Up to date therapies such as glucagon like peptide 1 receptor agonist (GLP-1) are increasingly being used in the treatment of T2DM.<sup>1-7</sup>

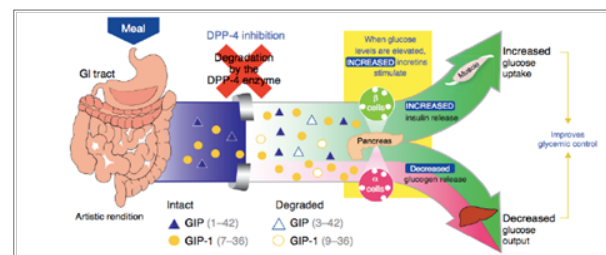
According to the National Kidney Foundation (NKF) Practice Guidelines from Chronic Kidney Disease, it is defined as either kidney damage or decreased kidney function, decreased glomerular filtration rate (GFR) for 3 or more months. Structural or functional abnormalities of kidney damage are shown through pathologic abnormalities of kidney damage, such as abnormal blood tests, urinalysis or renal imaging. In this classification, five stages chronic kidney diseases are defined (KDOQI). Diabetic Kidney disease is over stage 4 and 5 when diagnosed.<sup>8-12</sup>

Diabetic kidney disease occurs in patients with T2DM as a consequence of reduced kidney function, triggered by hypertensive nephrosclerosis and unresolved acute renal failure as the main culminating reasons.<sup>13-19</sup>

Diabetic nephropathy is a diagnosis that refers to specific pathologic structural and functional changes seen in kidneys of patients with T2DM. These changes result in a clinical presentation that is characterized by proteinuria, hypertension, and progressive reductions in kidney function.<sup>20-26</sup>

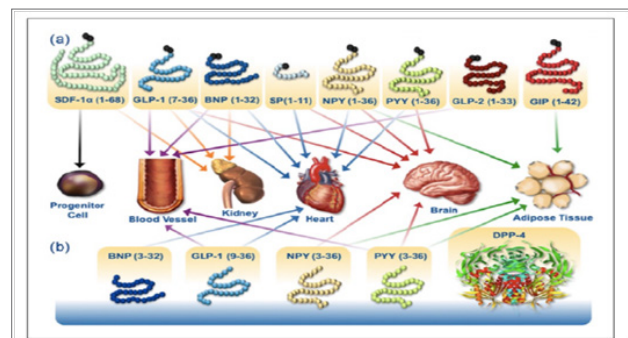
Incretins (GLP-1) and glucose dependent insulinotropic peptide (GIP) are small peptides produced by cells of the small intestine as a response to the ingestion of various nutrients. They participate in the regulation of carbohydrate homeostasis through the increase in the production of insulin in a glucose dependent manner, and suppression of the production of glucagon by pancreatic alpha cells. Furthermore, these molecules also have extrapancreatic mechanisms of action that

contribute to their glucose lowering properties, such as slow gastric emptying and increase satiety (Figure 1).<sup>27-39</sup>



**Figure 1** Current Diabetes Reviews.

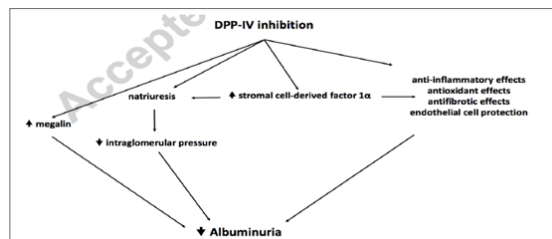
Dipeptidyl peptidase 4 (DPP4) is an enzyme responsible for glucagon like peptide-1 inactivation and plays an important role in glucose metabolism. DPP4 have demonstrated anti hyperglycemic efficacy of DPP4 inhibitors alone or in combination, with mean change in Hb1ac-3 to -19 mmol/mol (-0.3 to -1.7%) without excess risk of hypoglycemia or weight gain (Figure 2).<sup>40-45</sup>



**Figure 2** The effects of GLP-1 analogues, DPP-4 inhibitors and SGLT2 inhibitors on the renal system.

Linagliptin is the only DPP4 inhibitor excreted primarily via non-renal, and no dose adjustment is necessary in patients with CKD. Different pharmacological trials approved DPP4 inhibitors

(Sitagliptin, Saxagliptin and Alogliptin) can be used in patients with CKD or end stage renal disease. The only requirement is an assessment of renal function before initiating therapy, and periodical check-ups thereafter are recommended (Figure 3).<sup>46-54</sup>



**Figure 3** Effects of incretin-based therapies on renal function.

Therefore GLP-1 receptors and DPP4 inhibitors both stimulate insulin secretion and inhibit glucagon secretion in a glucose dependent manner. Among the substrates of DPP4 are peptide hormones such as β type natriuretic peptides,

neuropeptide Y, peptide YY and stromal cell derived factor 1 alpha.<sup>55-63</sup>

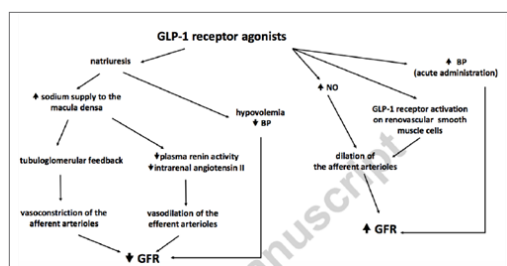
About 40% patients with diabetes mellitus (diagnosed or not) have an advanced stage of kidney disease, often because of serious deficiencies in the management of the disease itself. The main renal dysfunctions are due to the thickening of the glomerular basement membranes, formed of microaneurysms and development of mesangial nodules. The latest estimates show a global prevalence of 415 million adults with diabetes mellitus, of which 90% suffer T2DM. The onset of an initially documented diabetic nephropathy is generally preceded by the appearance of proteinuria greater than 500 mg/day.<sup>64-71</sup>

### How does GLP-1 works?

Incretin-like actions control blood glucose level through different metabolic pathways, such as the stimulation of insulin secretion, the inhibition of the production of glucagon, delay in gastric emptying and induction of satiety.<sup>71-76</sup>

Furthermore, it is able to reduce the levels of HbA1c in the percentage varying between 0.55%-1.9% with extremely low risk of hypoglycemic episodes, enabling rapid gastric emptying.<sup>77-82</sup>

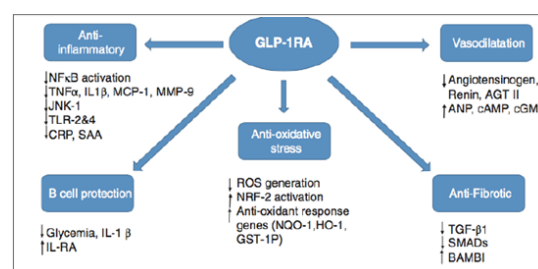
Additionally, studies in healthy humans have shown GLP-1 infusion to increase sodium excretion by kidneys. And in obese insulin resistant, GLP-1 infusion was associated with an increased sodium excretion, a decreased urinary secretion and a decreased GFR. Recent findings indicate that treatment with GLP-1 decelerates the progression of diabetic nephropathy by inhibiting inflammatory actions and by improving endothelial function (Figure 4).<sup>83-87</sup>



**Figure 4** Effects of incretin-based therapies on renal function.

GLP-1 receptor is highly expressed in both the glomeruli and proximal tubules in the kidney. It has been stated by (Park et al. 2007) that GLP-1 agonist has a renoprotective role through increasing this molecule receptor expression in diabetic kidneys.<sup>88-92</sup> Oxidative stress is well known to be a major contributor of the pathophysiology of hypertensive nephropathy. Inhibition of nitric oxide (NO), followed by arterial hypertension lead to the production of excessive reactive oxygen species (eNOS), that results in oxidative stress. GLP-1 is claimed to have antioxidant activity due to activation of Foxo3a signaling after the up-regulation level and its receptor. Activation of Foxo3a leads to increase the activity of the antioxidants enzymes as superoxide dismutase (SOD).

The inhibition of NF-κB (nuclear factor kappa-light chain enhancer of activated β cells) binding was associated with reduction in the expression of 2 key proinflammatory cytokines, TNFα (tumor necrosis factor alpha) and IL-1β (interleukin1 β). There was a reduction in the expression of JNK-1 (C- Jun N- terminal kinases), TLR-2 (Toll- like receptor 2) and TLR-4 at mRNA (messenger ribonucleic acid) and protein level. As Fig. 5 shows, in addition there was a reduction in plasma concentration of MCP1 (Monocyte chemoattractant protein 1), the chemokine MMP-9 (metalloproteinase 9) and somatic afferents fibers. GLP-1 induces a marked increase in plasma concentrations of interleukin 1 receptor antagonist.<sup>3</sup> This would interfere with the damaging effect of IL-1β on the β-cell, thus potentially increasing insulinogenesis and possibly prolonging β-cell life. Furthermore, exenatide suppressed plasma concentrations of GFβ (Transforming growth factor), the cytokine contributed to the pathogenesis of diabetic nephropathy (Figure 5).<sup>2,91-94</sup>



**Figure 5** Incretins: Beyond type 2 diabetes.

### Pathophysiology

The increase in sodium excretion is accompanied by an increase in the renal waste of calcium, chloride, phosphate and bicarbonate, whereas the renal potassium handling is not usually affected.<sup>82,95-99</sup>

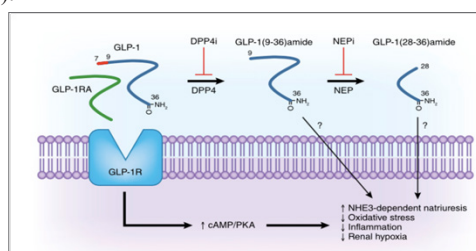
The natriuretic effect of GLP-1 may result from the inhibition of sodium hydrogen exchanger isoform 3 (NHE3) that is located at the proximal tubular cells. Native GLP-1 inhibitors block the function of this exchanger, possibly through the activation of protein kinase A (PKA). Additionally, GLP-1 antagonist receptors decrease the circulating concentrations of angiotensin II, an effect that also plays a role in the observed increase in renal sodium wasting.

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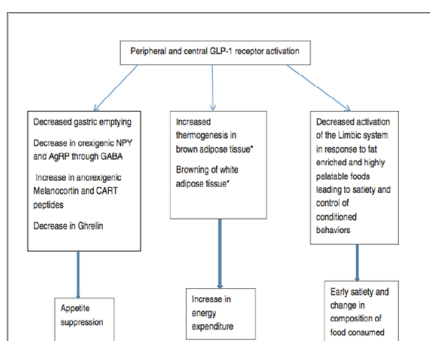
This reduction in angiotensin II levels follows the administration of GLP-1 possibly results from the increase in blood pressure values, the increased delivery of sodium to the macula densa and the reduced activity of tissue reninangiotensin-aldosterone system.<sup>97,101-104</sup>

The inhibition of DPP4 or the use of GLP-1 receptor agonist results in the increased activation in the kidney, leading cAMP (cyclic AMP receptor) the activation of protein kinase (A) (Figure 6). This mechanism becomes maladaptive in diabetes, however as hyperglycemia rise the expression and activity of sodium-glucose cotransporter (SGLT2) in the proximal tubule of the kidney. As a result, glucose reabsorption may be increased by 20% in individuals with poorly controlled diabetes. SGLT2 is a low affinity, high capacity glucose transport protein that reabsorbs 90% of filtered glucose.<sup>6,4568,92,106,107</sup>

The peripheral and central GLP-1 receptor activation that is presented below has so far been proven with animal evidence only (Figure 7).



**Figure 6** Effects of Diabetes Medications Targeting the Incretin System on the Kidney.



**Figure 7** Incretins: Beyond type 2 diabetes.

## Targets in Diabetic Kidney Disease

Glycemic targets in the presence of diabetic kidney disease should be individualized depending on the patient. Based on several pivotal trials in T2DM, the NKF KDOQI guidelines recommend intensive glycemic control (HbA1c 53

mmol/mol)[7%] to prevent or delay the progression of albuminuria and other macro and microvascular complications. Recent ADA (American Diabetes Association) guidelines also indicate that HbA1c below 53 mmol/mol (7%) has been shown to reduce the risk of microvascular complications on young adults. Landmark studies in patients with T2DM including Veteran Affairs Diabetes trial (VADT), the Action in Diabetes and

Vascular Disease: Preterax and Diamicon MR controlled Evaluation (ADVANCE) trial, and the Action to Control

Cardiovascular Risk in Diabetes (ACCORD) trial have provided consistent evidence that intensive glycemic control is the path to follow.<sup>108–112</sup>

ADA and NKF KDOQI guidelines suggest less stringent glucose control >53mmol/mol [7%] in patients with limited life expectancy,

advanced microvascular or macrovascular complications, and long duration of T2DM who are unable to attain the general treatment goal despite diabetes self management education, glucose monitoring and use of multiple diabetes drugs.<sup>104,113,114</sup>

## Objective

The glucose lowering effects are well proved by GLP-1 receptor agonist, but recently it has been hypothesized that GLP-1 receptor agonist receptors may exert also beneficial renal effects. So the aim of this article review is to expand the label to include patients that have Diabetic Nephropathy.

## Materials and methods

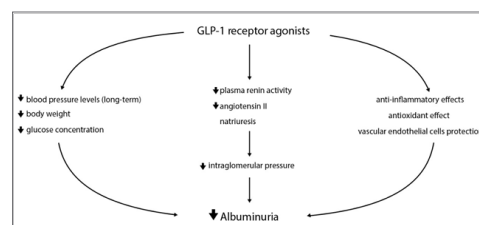
The following research was done using the next terms: MeSH “Diabetes Mellitus type 2”, “Diabetic Nephropathy”, “Enterohormones”, “Incretins”, “GLP-1”, “Renoprotection”. The results were reviewed for each of the authors

independently, continuing with references obtained from remarkable articles.

## Results

The academic research was obtained from PubMed database, with exclusion criteria from articles published no more than 5 years ago (2013-2018), found useful to work 119, previously mentioned.<sup>114–117</sup>

Patients with T2DM are at risk for diabetic kidney disease, especially when hyperglycemia, hypertension, or both conditions are poorly controlled. Early detection and continuous monitoring are critical for slowing the progression of this complication. Periodic measurements of both urinary albumin excretion and GFR in high risk patients are advisable. Choosing the optimal glucose lowering therapy (Analogues of GLP-1) in patients with diabetic kidney disease ultimately defines the success of the treatment regime (Figure 8).<sup>104,112</sup>



**Figure 8** Effects of incretin-based therapies on renal function.

## Conclusion

Accumulated evidence suggests that both glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors may affect renal function in both glucose lowering dependent and independent mechanisms of action. The clinical relevance of these observations is currently unknown, since only a few randomized clinical studies with renal endpoints have been conducted so far.

Clinical studies addressing renal endpoints in patients with diabetic and no diabetic kidney diseases are warranted to provide information whether the promising preclinical findings can be translated into clinical benefit for patients with renal diseases. In addition, there is evidence that incretin based therapy may facilitate natriuresis and anti-inflammatory lowering mechanisms.<sup>117–120</sup>



## Acknowledgements

None.

## Conflict of interest

The author declares that they have no competing interests.

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