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Role of dipeptidyl peptidase 4 inhibitors Diabeties Naphropathy

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A B S T R A C T :

Diabetic nephropathy (DN) is one of the most common causes of end-stage renal disease (ESRD), both in terms within T2DM patients and all the patients. Dipeptidyl peptidase-4 inhibitorsDPP-4 inhibitors, which are most commonly used for glycemic control in T2DM, also drew attention for their renoprotective effects. The mechanisms and clinical and comparative effectiveness of DPP-4 inhibitors in DN are summarized in this review, with an emphasis on their advantages and disadvantages.

1. INTRODUCATION

As the prevalence of T2DM has been increasing, DN has recently become more prevalent, highlighting the necessity of therapeutic methods with comprehensive control on blood sugar and kidney protection. Whereas conventional therapies address regulation of blood glucose, newer treatments such as DPP-4 inhibitors may exert beneficial effects independent of glycemia. DPP-4 also affects non-incretin substrates, some of which are in inflammatory, oxidative, and fibrotic pathways thus participating in DN pathophysiology. It is not only the specific property of anti-diabetic treatment that created such interest in DPP-4 inhibitors, but also their ability to be renoprotective. The data from patients and animal work demonstrate that DPP-4 inhibitors can be additionally helpful in coping with kidney damage-induced in such way as decreasing the intensity of the inflammation, inducing the reduction of reactive oxygen species, regulating the endothelial function, keeping podocyte integrity, and altering renal fibrosis. Not only the renin-angiotensin-aldosterone system usually involved in these processes may be affected by DPP-4 inhibitors, but they also seem to balance changes in natriuresis, the latter two supporting the kidney function. Diabetic nephropathy is the result of a combination of multiple factors, occurring in the kidney, of which the more important pathologically could be glomerular hyperfiltration, oxidative stress caused by high levels of blood sugar and formation of advanced glycation end-products (AGEs), and the inflammatory and fibrotic pathways activated specifically. The DPP-4 activity may be blocked with a strategy equal to the threat, as it is formed by the mentioned pathogenic pathways. Thus, for example, GLP-4, in the kidney, was shown to have anti-inflammatory and anti-oxidant-thyroid effects, and DPP-4 inhibition prolongation of its activity may result in renal benefits. Further studies suggest that DPP-4 inhibitors are not only substrates but also direct regulators of others such as stromal cell-derived factor-1α (SDF-1α) which are involved in the repair and regeneration of tissues, indicating another level of direct action of DPP-4 inhibitors on the substrates. Many DPP-4 inhibitors, for example sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin, have been thoroughly tested in both preclinical and clinical studies to establish their renal protective properties. Interestingly, linagliptin is the most remarkable one of them due to its peculiar pharmacokinetics; it is eliminated mainly through the bile and does not need a dose change in patients having kidney dysfunction. Clinical trials like CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus) have disclosed the renal security and effectiveness of DPP-4 inhibitors, although results were inconclusive for hard renal endpoints such as ESRD progression.

2. Renal Protection by DPP-4 Inhibition

DPP-4 inhibitors Incretin hormones are released into the fasting circulation in response to meals, and these hormones induce GLP-1 and GLP-1–dependent insulin secretion Thus, one main characteristic of DPP-4 inhibitors is their ability to decrease glucose secretion and suppress glucagon release. In addition to their hypoglycemic properties, DPP-4 inhibitors also perform various actions that help in kidney protection:A DPP-4 is a serine protease acting on numerous cells such as renal proximal tubular epithelial cells, podocytes, and endothelial cells. It gets rid of various substrates thus progressing vascular homeostasis, and also immune regulation like GLP-1, stromal cell-derived factor-1α (SDF-1α), and brain natriuretic peptide (BNP) (Kanasaki, 2018). DPP-4 activity can be the cause in the kidney of the inflammation, fibrosis, and endothelial dysfunction—crucial factors contributing to the chronic kidney disease (CKD) progression. The DPP-4 inhibitors have a pivotal role in the renoprotective effect by minimizing inflammation and oxidative stress. In the machines' test, the DPP-4 inhibition weakened the infiltration of renal macrophages and the expression of pro-inflammatory cytokines such as TNF-α and IL-6 (Kato & Natarajan, 2014). Moreover, by conserving the activity of GLP-1 and SDF-1α, the new copy of DPP-4 inhibitors promotes anti-inflammatory pathways, and thus it enhances the endothelial repair mechanism. It has been found through clinical studies that DPP-4 inhibitors are not only safe for the renal part of the body but also can protect the kidney. One such clinical trial is CARMELINA, which was looking at linagliptin in patients with type 2 diabetes and kidney disease at a high risk of complications. The results from this trial showed that the probability of losing kidney function was the same. Even if adverse events still cropped up, overall, there was a net effect on renal disease. This outcome is none other than one neutral to adverse renal disease (Menne et al., 2019). The same goes for the MARLINA-T2D study, which revealed a mild, but statistically non-significant

downward trend in albumin excretion rate, thus the potential implication of the treatment of diabetic kidney disease (Groop et al., 2019).

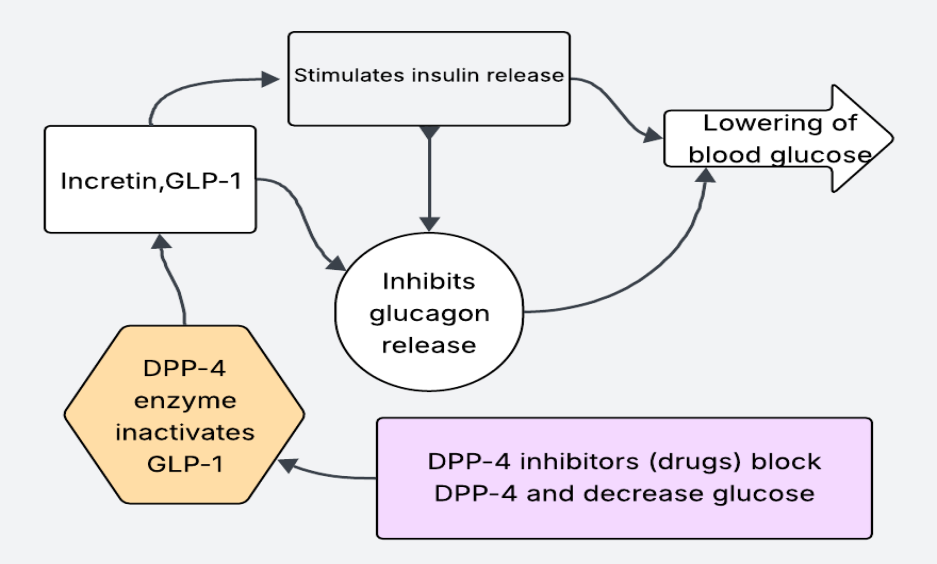

Fig.1

- **Anti-inflammatory and Antioxidant Effects**: These drugs have the ability to limit inflammation and oxidative stress in the kidneys, thereby reducing the severity of DN.
- **Antifibrotic Actions**: The agents restraining the fibrotic cascade can save the structure of the kidney targeted and therefore it function will remain efficient.
- **Alteration of Autophagy:** The presented studies gave an insight that glomerular autophagy can be reactivated by DPP-4 inhibitors such as linagliptin, thus podocyte health would be maintained and albuminuria reduced.
- **Diuretic Function:** DPP-4 inhibitors induce the excretion of salt and water from the kidneys and, as a consequence, might mitigate intraglomerular hypertension, one of the factors causing the progression of diabetic nephropathy.

Drug	Sitagliptin	Saxagliptin	Linagliptin	Alogliptin
Dosage Form	25,50,100mg tablets	2.5,5mg tablets	5mg tablets	6.25,25mg tablets
Usual Dosage	100mg once daily	2.5, 5mg once daily	5mg once daily	25 mg once daily
Bioavaliability	87%	67%	30%	100%
Protein Binding	38%	negligible	70-90%	20%
Time to peak	1-4h	2-4h	1.5h	1.2h
Metabolism	Hepatic	Hepatic	Not extensively metabolized	Not extensively metabolized
Half-life	12.4h	2.5-3.1h	12h	21h
ADR	Nasopharyngitis URI,peripheral edema	UTI,HA,URI	Arthalgia nasopharyngitis, URI	Nasopharyngitis URI,HA

Table 1.DPP-4inhibitor classifications:

3. Clinical Evidence Supporting Renal Benefits

DPP-4 inhibitor usage in several clinical trials and subsequent meta-analyses were the main focus for the evaluation of the renal outcomes of patients. The key findings were:

- Albuminuria Reduction: A significant decrease in the incidence of both micro and macroalbuminuria has been revealed by DPP-4 inhibitors.
- eGFR Stability: DPP-4 inhibitors have also been known to be the causative agents of the increased eGFR although the decline of estimated

glomerular filtration rate (eGFR) in some studies was mentioned to be minor.

- Safety Profile: Generally speaking, DPP-4 inhibitors are well-tolerated in the overwhelming majority of cases with the adverse events rates being low, so they can be used in the case of patients with the renal problem of any severity.

Comparative Efficacy with Other Antidiabetic Agents

In comparison with the other antidiabetic classes, mainly sodium-glucose cotransporter 2 (SGLT2) inhibitors, DPP-4 inhibitors are the type of drugs that demonstrate only modest renal benefits:

- **SGLT2 Inhibitors:** These drugs have proven most efficacious in the albuminuria progression and ESRD risk reduction.
- **GLP-1 Receptor Agonists:** Despite the fact that GLP-1 receptor agonists equally contribute to renal benefits, their efficacy is offset by the fact that most of them are injectable; this, in return, leads to a significant number of side effects and increased drug dependence, hence limiting their practical utility when compared to DPP-4 inhibitors administration administrable through the mouth route.

4.Limitations and Considerations

Although the data is suggestive, there are several limitations:

- Small Length of Study: There are many trials with quite short follow-up periods which makes it difficult to evaluate long-term renal outcomes.
- Different Features of DPP-4 Inhibitors: Variances in pharmacokinetics and pharmacodynamics between different DPP-4 inhibitors require different considerations for each.
- Absence of Direct Comparisons: There is a small number of studies that compare DPP-4 inhibitors directly with other antidiabetic agents in relation to renal outcomes.

Conclusion

DPP-4 inhibitors are a significant complement to the treatment of DN, providing feature benefits that are not limited to the glycemic control of the blood glucose level. Their anti-inflammatory, antifibrotic, and natriuretic actions are beneficial to the kidneys and, besides, the extent to which others somehow surpass their anti-diabetic properties is less. Because of their good safety record, especially in individuals who have problems with their kidneys, DPP-4 inhibitors are a suitable alternative for the treatment of T2DM together with concomitant DN. Further studies should be designed to concentrate on long-term developments and to compare different treatments to determine more specifically the real situation of the preservation of the kidneys through DPP-4 inhibitors.

REFRENCES:

1. Kim YG, et al. Effects of Dipeptidyl Peptidase-4 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Metab J. 2019;43(1):59-78. PMC+5PubMed+5PMC+5
2. Kanasaki K. The role of renal dipeptidyl peptidase-4 in kidney disease: renal effects of dipeptidyl peptidase-4 inhibitors with a focus on linagliptin. Clin Sci (Lond). 2018;132(4):489-507. Portland Press
3. Kanasaki K, et al. SGLT2 Inhibitor Empagliflozin and DPP4 Inhibitor Linagliptin Reactivate Glomerular Autophagy in db/db Mice, a Model of Type 2 Diabetes. Int J Mol Sci. 2020;21(8):2987. MDPI
4. Kato M, et al. Diabetes, hypertension, and chronic kidney disease progression: role of DPP4. Am J Physiol Renal Physiol. 2016;311(5):F917-F925. Physiology Journals
5. Cao Y, et al. Comparative efficacy of novel antidiabetic drugs on cardiovascular and renal outcomes in patients with diabetic kidney disease: A systematic review and network meta-analysis. Diabetes Obes Metab. 2022;24(1):23-35. Wiley Online Library
6. Yabe D, et al. Antiproteinuric effect of DPP-IV inhibitors in diabetic and non-diabetic kidney diseases. J Diabetes Investig. 2020;11(6):1351-1359. PubMed
7. Sharma S, et al. Renal Outcomes Associated with the Use of Non-Insulin Antidiabetic Pharmacotherapy: A Review of Current Evidence and Recommendations. Diabetes Ther. 2020;11(12):2793-2813. PMC
8. **McGill JB, Sloan L, Newman J, et al.** (2013). Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. *Diabetes Care*, **36**(2), 237–244. https://doi.org/10.2337/dc12-0712
9. **Menne J, et al.** (2019). Linagliptin and cardiovascular and kidney outcomes in people with type 2 diabetes and kidney disease: CARMELINA randomized trial. *The Lancet*, **394**(10208), 1520–1529. https://doi.org/10.1016/S0140-6736(19)31370-4
10. **Kato M, Natarajan R.** (2014). Diabetic nephropathy—emerging epigenetic mechanisms. *Nature Reviews Nephrology*, **10**(9), 517–530. https://doi.org/10.1038/nrneph.2014.116
11. Groop, P. H., Cooper, M. E., Perkovic, V., Emser, A., Woerle, H. J., von Eynatten, M., & Nauck, M. A. (2019). Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and kidney disease: the MARLINA-T2D trial. *Diabetes, Obesity and Metabolism, 21*(7), 1610–1619. https://doi.org/10.1111/dom.13733
12. Kanasaki, K. (2018). The role of renal dipeptidyl peptidase-4 in kidney disease: renal effects of DPP-4 inhibitors with a focus on linagliptin. *Clinical Science, 132*(4), 489–507. https://doi.org/10.1042/CS20171281
13. Kato, M., & Natarajan, R. (2014). Diabetic nephropathy—emerging epigenetic mechanisms. *Nature Reviews Nephrology, 10*(9), 517–530.

https://doi.org/10.1038/nrneph.2014.116

14. Menne, J., Dumann, E., Gause-Nilsson, I., & Lin, J. (2019). Linagliptin and cardiovascular and kidney outcomes in people with type 2 diabetes and kidney disease: CARMELINA randomized trial. *The Lancet*, *394*(10208), 1520–1529. https://doi.org/10.1016/S0140-6736(19)31370-4

15. Sharma, S., Tiwari, S., & Weiss, R. H. (2020). Renal outcomes associated with the use of non-insulin antidiabetic pharmacotherapy: A review of current evidence. *Diabetes Therapy*, *11*, 2793–2813. https://doi.org/10.1007/s13300-020-00901-5