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# POTENTIAL PLEIOTROPIC EFFECTS OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS IN DIABETIC KIDNEY DISEASE

Diabetic kidney disease (DKD) is the leading cause of renal failure, necessitating renal replacement therapy globally. In a recently published narrative review of the evidence-based therapies of DKD, DPP-4 inhibitors have been addressed as one of the four effective therapeutic approaches. DPP-4 inhibitors or gliptins are currently approved as anti-hyperglycaemic agents for type 2 diabetes mellitus, with well-proven efficacy and safety. Besides glycaemic control, they offer other benefits, including promoting pancreatic β-cell mass and function, prolonging the satiety time and improving the lipid profile.

Dipeptidyl peptidase-4 (DPP-4) is a multifunctional serine ectopeptidase that cleaves and modifies a plethora of substrates, including regulatory peptides, cytokines and chemokines. Regarding its numerous substrates and extensive expression inside the body, multitasking DPP-4 has been assumed to participate in different pathophysiological mechanisms. DPP-4 inhibitors or gliptins are increasingly used for the treatment of type 2 diabetes mellitus. Several reports from experimental and clinical studies have clarified that DPP-4 inhibitors exert many beneficial pleiotropic effects beyond glycaemic control, which are mediated by anti-inflammatory, anti-oxidant, anti-fibrotic and anti-apoptotic actions.

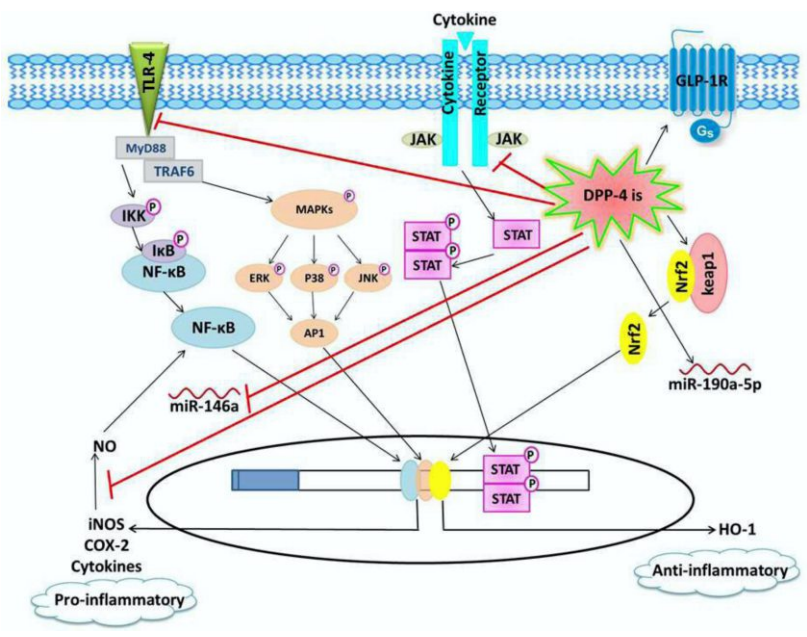
In accordance with this, one study suggested DPP-4 inhibitors as one of the albuminuria-lowering agents,which can be effectively used by crossover rotation to overcome resistance to renin–angiotensin –aldosterone system (RAAS) inhibitors. The renal distribution of DPP-4 involves the proximal tubular brush border, Henle's loop, distal and collecting ducts and glomerular epithelial and endothelial cells. The increased expression/activity of DPP-4 has been linked to the onset and progression of DKD. The upregulation of DPP-4 in diabetic glomeruli could have a role in DKD pathogenesis in several ways; DPP-4 can reduce the natriuretic and diuretic effects of GLP-1 in the kidney. DPP-4-induced inactivation of SDF-1α could exaggerate hypoxia-induced podocyte loss. The interaction between DPP-4 and extracellular matrix (ECM) proteins, such as integrin-β1, promotes endothelial-to-mesenchymal transition (EndMT) by inducing vascular endothelial growth factor receptor-1 (VEGFR-1) in endothelial cells. The membrane-bound DPP-4 can also promote EndMT via activating the cation-independent mannose 6-phosphate receptor to stimulate the TGF-β/Smad signalling pathway. Moreover, sDPP-4 released from endothelial cells as a result of AGE/RAGE interaction can activate mannose 6-phosphate receptors to further stimulate AGE/RAGE signalling in a reciprocal manner. Finally, DPP-4 can modulate the immune and inflammatory responses in the diabetic kidney through its effects on different inflammatory cells and mediators.

Hyperglycemia is the most proximal provocative factor implicated in the initiation and progression of DKD. It is well known that DPP-4 inhibitors can effectively neutralize this important aetiological factor and achieve euglycaemia in a GLP-1R-dependent manner. The pathogenesis of DKD also involves the activation of a plethora of potential biochemical pathways including but not limited to the activation of diacylglycerol

(DAG)/protein kinase Cβ (PKCβ) and AGE/RAGE axes and RAAS, oxidative stress, inflammation, albuminuria, EndMT and glomerular hyperfiltration.

In the setting of hyperglycemia, the increased PKCβ signalling abolishes the renal beneficial GLP-1R-mediated effects via ubiquitination and downregulation of GLP-1R in the glomerular tissues. The activation of DAG/PKCβ signalling can also contribute to DKD development through the induction of ECM accumulation, podocyte apoptosis and inflammation. In addition, PKCβ acts in a reciprocal way to increase oxidative stress, as it activates mitochondrial NOX to induce ROS generation; meanwhile, ROS and AGEs increase DAG levels to stimulate PKCβ.Several experimental studies have demonstrated that DPP-4 inhibitors can inhibit PKCβ phosphorylation/signalling in GLP-1R-dependent and GLP-1R-independent mechanisms, abolishing its injurious effects on the diabetic kidney.

Sitagliptin attenuated diabetic nephropathy in experimental studies through its anti-inflammatory effects mediated by the downregulation of the protein tyrosine phosphatase-1B/Janus kinase-2/signal transducer activator of transcription-3 axis. It protected against DKD in patients with type 2 diabetes via downregulating and decreasing the levels of kidney injury markers and pro-inflammatory cytokines. In addition, DPP-4 inhibitors exerted effects through activation of the nuclear factor erythroid-2-related factor-2 (Nrf-2)/ haem oxygenase-1 pathway and downregulation of the TLR-4/NF-κB pathway. Furthermore, sitagliptin also exerted anti-oxidant, anti-inflammatory and anti-apoptotic effects in experimental cyclosporine-induced nephrotoxicity via upregulation of Nrf-2 and suppression of TNF-α, NF-κB and Bax.




*Schematic presentation of the proposed anti-inflammatory effects of DPP-4 inhibitors*

*DPP-4is downregulate pro-inflammatory pathways, including TLR-4/NF-κB, JAK/STAT and iNOS/NO/NF-κB pathways, leading to decreased expression of inflammatory mediators, such as cytokines, COX-2 and iNOS.*
*On the other hand, DPP-4is induce the anti-inflammatory signalling cascades, including GLP-1R/cAMP/protein kinase A and Keap1/Nrf2/HO-1.*

Extensive research has revealed that the disturbed expression or activity of the multitasking DPP-4 may be involved in various pathological conditions, including inflammatory and immune-mediated and cardiovascular disorders. Accordingly, DPP-4 inhibitors have been demonstrated many pleiotropic actions, which would enable them to have a decisive role in various disease entities, including neurological, cardiovascular, renal, hepatic and pulmonary diseases. Several experimental studies have clarified the positive effects of DPP-4 inhibition on renal pathogenic processes, including oxidative stress, inflammation, natriuresis, apoptosis, albuminuria and fibrosis under diabetic and non-diabetic conditions. DPP-4 inhibitors exerted renoprotective effects primarily on the podocytes and the endothelial cells rather than on the mesangial cells. This finding has been confirmed by many large-scale clinical trials.

***Source:*** *S A Mangoura, et.al; touch reviews in Endocrinology. 2024; 20(2):19–29*

# MEFENAMIC ACID IN DENTAL PAIN CONTROL: CLINICAL EVIDENCE AND PRACTICAL CONSIDERATION

Odontogenic pain, resulting from inflammation of dental and periodontal tissues, is among the most frequent and distressing complaints encountered in dental practice. Effective and timely pain management is thus a cornerstone of successful dental care. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the first-line pharmacologic intervention for managing dental pain due to their dual analgesic and anti-inflammatory actions. Among them, mefenamic acid has emerged as a commonly prescribed option, particularly in regions where its cost-effectiveness and availability make it a favorable choice. Mefenamic acid has demonstrated analgesic properties, likely resulting from its inhibition of the cyclooxygenase (COX) enzymes, which decreases pain and the inflammatory response associated with prostaglandin synthesis. Clinical research has consistently validated its efficacy in treating post-extraction, pulpitis, and periodontal pain.

## Other Mechanisms: Ion Channels and Neurogenic Inflammation

Beyond COX inhibition, emerging evidence suggests mefenamic acid may also modulate pain through additional pathways:

Modulation of Voltage-Gated Sodium Channel Activity (Nav1.7, Nav1.8): Mefenamic acid has been shown to decrease the excitability of pain-transmitting sodium channels, which diminishes nerve activity in inflammatory states.

Inhibition of Nuclear Factor Kappa B (NF-κB) Signalling: Mefenamic acid inhibits the production of pro-inflammatory cytokines, such as IL-6 and TNF-α. Unrestricted use of mefenamic acid increases the amount of anti-inflammatory and analgesic cytokines. Thus, the cytokines responsible for inflammation are blocked together with the pathways responsible for their generation. The additional mechanisms further enhance the already broad-spectrum effectiveness of the drug in inflammatory pain, such as odontogenic pain. However, these mechanisms are still under active research, and clinical translation of this evidence remains ongoing.

### Comparative Efficacy with Other Analgesics

The effectiveness of mefenamic acid in controlling odontogenic pain has been demonstrated across multiple studies.

### Mefenamic Acid vs Ibuprofen / Diclofenac / Naproxen

Clinical evidence confirms that mefenamic acid has comparable efficacy to ibuprofen for dental pain with better tolerability of gastrointestinal. This difference may be clinically significant for gastrointestinal intolerance, a common reason for NSAID discontinuation. Mefenamic Acid vs Meta-analyses suggest that mefenamic acid, naproxen, and diclofenac have similar effectiveness in managing pain associated with dental procedures & in clinical trials, mefenamic acid demonstrated a reduced incidence of adverse effects relative to naproxen and diclofenac. The degree of drug response is unique to each patient, and factors such as age, comorbidities, and concomitant medications must be considered.

## Post-Extraction Pain

Mefenamic acid has demonstrated effectiveness in managing pain following tooth extraction-a procedure frequently associated with moderate to severe postoperative discomfort. Clinical trials have shown that

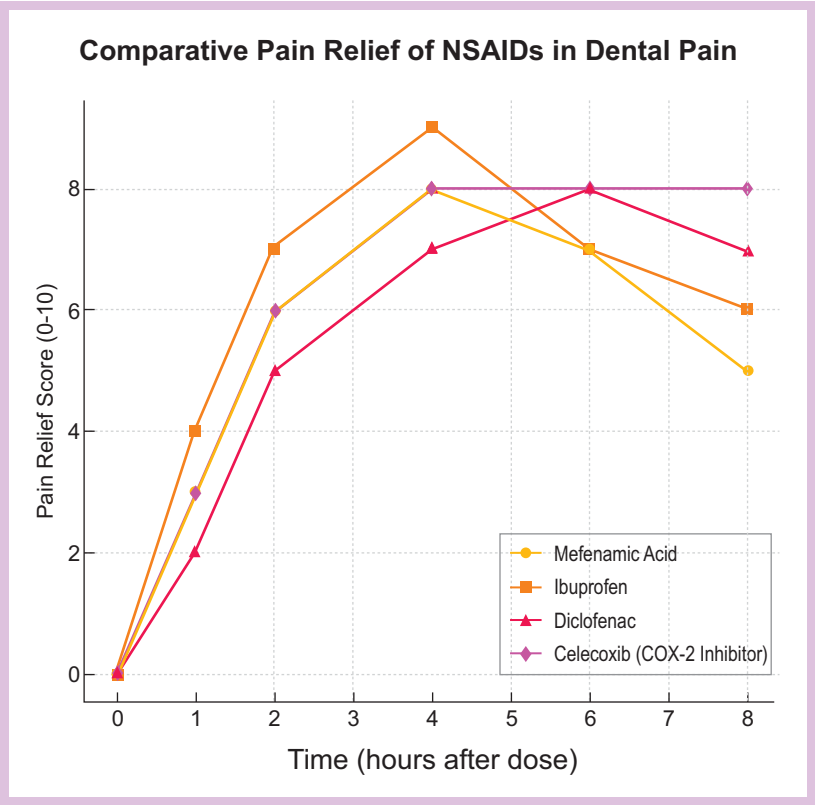
mefenamic acid provides comparable pain relief to ibuprofen and diclofenac within the first 24-48 hours post-extraction. Its use in post-operative settings has also been linked with reduced swelling and improved patient satisfaction.

## Pulpitis

Acute irreversible pulpitis is a major cause of dental pain, characterized by spontaneous and lingering pain due to inflamed pulp tissue. Mefenamic acid's anti-inflammatory and central analgesic properties make it suitable for alleviating this pain, especially when definitive endodontic treatment is delayed. Some studies suggest that mefenamic acid may offer superior relief compared to acetaminophen, particularly in the early phase of inflammation.

## Periodontal Pain

Periodontal disease and post-periodontal surgery pain represent another significant source of odontogenic discomfort. Mefenamic acid has been utilized to control pain and inflammation in such cases. Due to its balanced efficacy and moderate duration of action, it is often preferred in mild to moderate periodontal pain scenarios.




## Mefenamic Acid vs. Selective COX-2 Inhibitors

Mefenamic acid is not an exception to the general rule regarding its effect on the GI mucosa; certain risks to the functioning of the gastrointestinal tract accompany its use. On the other hand, mefenamic acid is more advantageous in providing rapid pain control than selective COX-2 inhibitors, such as celecoxib, which have a better gastrointestinal side effect profile. Mefenamic acid may provide more rapid analgesia and be beneficial in post-operative inflammation and more severe cases of acute dental pain, where a more rapid analgesic response is desired. There are concerns of cardiovascular side effects with COX-2 inhibitors, which must be considered in comparison to the gastrointestinal side effects of non-selective / preferential NSAIDs.

***Source:*** *Zakir H, et.al; Ricos Biology Journal, April, 2025, Vol.*



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