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Medical Bulletin

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SGLT2 INHIBITORS CORRECTS ANEMIA IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE

Anemia occurs in 20% to 30% of patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) and is due to a spectrum of causes and underlying pathophysiologic pathways. Currently, clinical practice guidelines lack specific recommendations for adjuvant therapy to prevent the occurrence of anemia.

To mitigate anemia risk, patients with T2D and CKD should achieve their glycemic goals and maintain kidney functions by using appropriate glucose-lowering drugs, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors with proven kidney and cardiovascular benefits in patients with T2D, heart failure (HF), and/or CKD.

Recent evidence suggests that this class of drug may provide additional benefits in enhancing hematopoietic processes in patients with T2D and CKD. A post-hoc analysis of the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial showed that treatment with Dapagliflozin was associated with an increase in hematocrit, correction of anemia, and a reduced risk of incident anemia in patients with CKD with or without T2D. In fact, these effects were found to be consistent. Previous randomized controlled trials also have showed similar positive effects of SGLT2 inhibitors on blood parameters in patients with T2D with or without CKD as well as in patients with HF with or without T2D.

Another recent (year 2024) study in patients (n=13,799) with T2D and CKD stage 1 to 3 found that initiation of SGLT2 inhibitors was associated with a 19% decrease in incident anemia risk compared with initiation of glucagon like peptide-1 receptor agonists, thus giving an additional support to the above findings.

Potential mechanisms mediating enhanced erythropoietin production during SGLT2 inhibition

Four hypotheses have been proposed to explain how SGLT2 inhibitors might increase erythropoietin production

I. Renal cortical reoxygenation with rejuvenation of erythropoietin-producing cells (hypoxic interstitial fibroblast-like cells)

- Increased glucose reabsorption places a metabolic burden on the proximal renal tubules, causing tubulointerstitial hypoxia. This leads to specialized interstitial fibroblast-like cells in the renal cortex to transform into dysfunctional myofibroblasts, which would be incapable of erythropoietin production, but promote renal fibrosis. Inhibition of glucose reabsorption by SGLT2 inhibitors would alleviate the metabolic demands on the proximal tubules and reduce oxygen consumption, improving oxygenation in the renal cortex and allowing dysfunctional fibroblasts to revert to a phenotype which would be capable of erythropoietin synthesis. (Fig. 1)

II. Counter-regulatory distal sodium reabsorption leading to increased tubular workload and renal deep cortical and medullary hypoxia

- The action of SGLT2 inhibitors to block sodium reabsorption in the proximal renal tubule leads to increased delivery of sodium to more distal portions of the nephron, where it is absorbed by counter-regulatory mechanisms to limit the magnitude of natriuresis. These mechanisms include the reabsorption of sodium in the S3 segment and Loop of Henle, which increases oxygen consumption and causes hypoxia in the deep cortex and outer medulla stimulating interstitial fibroblast-like 1 cells. Changes in oxygen tension to the interstitial fibroblast-like cells thus enhances the synthesis of hypoxia-inducible factor-2α (HIF-2α), the main driver of erythropoietin synthesis. (Fig.1). Experimental studies have noted that SGLT2 inhibition reduces oxygen tension in the deep cortex and outer medulla, supporting the above claims.

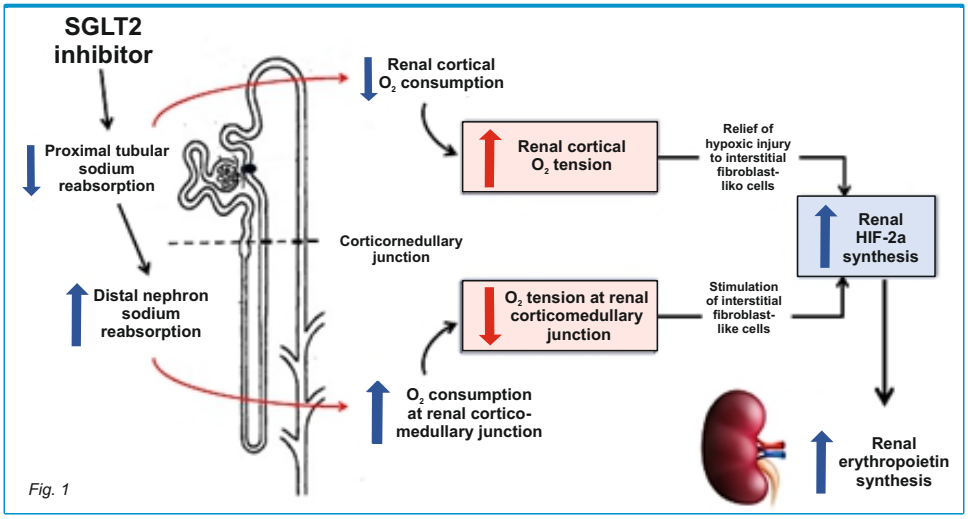


Fig. 1

III. Increased iron mobilization as an inducer of HIF-2α-mediated erythropoietin synthesis

- Anemia is characterized by increased levels of two major iron regulatory proteins-hepcidin and ferritin. Increase in the synthesis of hepcidin by the liver blocks the absorption of iron from the duodenum and the release of iron from the reticuloendothelial system. Increase in ferritin in heme-producing cells result in the sequestration of ferrous iron preventing its release into the cytosol. SGLT2 inhibition acts to derepress hepcidin and ferritin (and increase heme oxygenase-1), thus promoting increased iron availability in the cytosol. The combined effect of these cellular events would improve iron mobilization into erythroid precursors (thereby facilitating hemoglobin production) (Fig. 2)

IV. Direct HIF- 2α activation and enhanced erythropoietin gene transcription due to increased sirtuin-1 (SIRT1) signaling.

- SGLT2 inhibitors promote a state of starvation characterized by glycosuria, gluconeogenesis, ketogenesis and by up-regulation of nutrient deprivation signaling at a cellular level. The nutrient deprivation signals that are most relevant to the action of SGLT2 inhibitors are sirtuin-1 (SIRT1), sirtuin-3 and peroxisome proliferator-activated receptor-γ co-activator- 1α (PGC-1α). The induction of glycosuria stimulates the production of SIRT1 in the liver. Up-regulation of SIRT1 acts to stimulate the activity of both HIF-2α and erythropoietin. In parallel with these events, SIRT1 activation may promote the hepatic formation of a PGC-1α-HNF4 complex, which can bind to the promoter region of the erythropoietin gene, thus enhancing the transcription of erythropoietin in the liver. (Fig. 2)

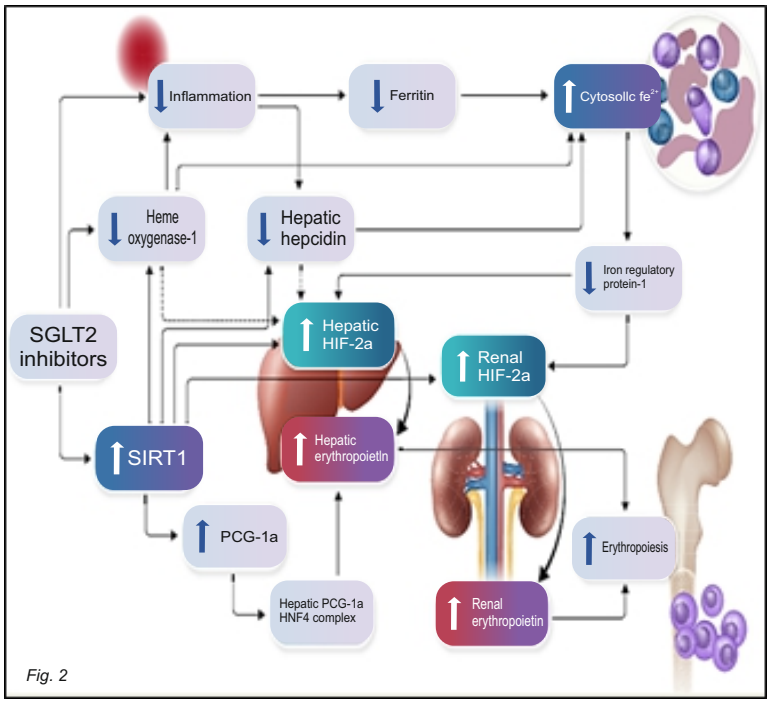


Fig. 2

Hence, taken together, these potential mechanisms and clinical evidences suggests the benefit of SGLT2 inhibitors with regard to anemia events in patients with T2D and CKD.

Source: Hu JC, et al. JAMA Network Open. 2024; 7(3):e240946, Packer M. European Heart Journal. 2023; 44(48): 5027-5035, Koshino A, et al. NEJM Evid 2023; 2 (6)

PROTECTIVE ROLE OF DIPEPTIDYL PEPTIDASE- 4 INHIBITORS ON ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that involves the accumulation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles. These contribute to the loss of neurons and synapses triggering progressive cognitive impairment.

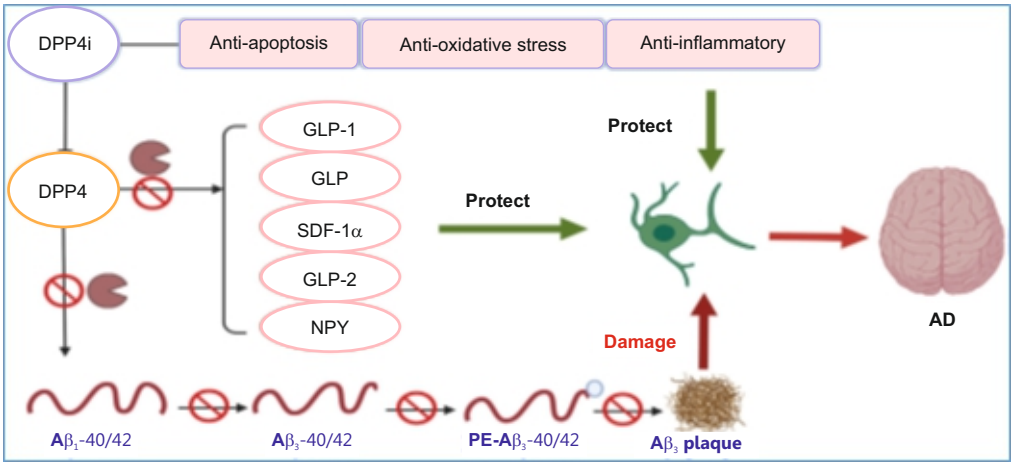
Evidence has suggested an association between type 2 diabetes (T2DM), cognitive decline and AD. Insulin resistance in brain and amyloidogenesis are principal pathological features of diabetes-related cognitive decline and development of Alzheimer's disease. This hypothesis is supported by evidences as below;

1. Hyperglycemia can substantially increase levels of Aβ protein.
2. Increased formation and accumulation of methylglyoxal [a potent precursor of advanced glycation end products (AGEs)] in diabetes has been linked to an increased risk of AD. AGEs can contribute in the formation of amyloid plaques and neurofibrillary tangles and methylglyoxal can impair the integrity of blood brain barrier (BBB). Both playing a role in the progression of AD.
3. AD is called 'type 3' diabetes due to the involvement of insulin resistance in its pathology. Dysfunction in brain insulin signalling is likely a pivotal factor initiating pathological changes in AD.

Besides, diabetes and AD share many risk factors, which includes hyperlipidemia, metabolic syndromes, oxidative stress and inflammation, mitochondrial dysfunction, genetic and lifestyle factors. Diabetes can also cause intracerebral micro- and macrovascular lesions to disrupt brain blood flow, contributing to an increased AD risk.

Therefore, maintaining glucose under control in T2DM patients may serve as an effective way for preventing AD development. Dipeptidyl peptidase (DPP) 4 inhibitors (DDP4is), a class of glucose lowering medications have shown neuroprotective potential in recent studies.

Evidence from both clinical and pre-clinical studies has suggested that inhibition of DPP4 may be protective against AD and mechanisms supporting it are summarized below:



❋ **Direct impact of DPP4i on reduction of Aβ deposition**

DPP4 can cleave Aβ1-42 and Aβ1-40, the crucial components of amyloid deposits in AD patients, into Aβ3-42 and Aβ3-40. Subsequently, glutamyl cyclase transforms them into non-degradable pyroglutamate- amyloid beta3- 40/42 (pE-Aβ3-40/42). DPP4i can improve AD by inhibiting Aβ plaque deposition independent of GLP-1 signalling pathways.

A clinical study on elderly T2DM patients with mild cognitive impairment revealed a significant increase in the plasma Aβ1-

42/Aβ1-40 ratio in the DPP4i treatment group compared to the control group (sulfonylurea). The findings suggested an improvement in Aβ burden associated with DPP4i. In addition, a study found that inhibition of DPP4 significantly reduced the activity of β-secretase, the most important enzyme to hydrolyze amyloid precursor protein (APP) to produce abnormal Aβ peptides.

❋ **DPP4i increases the bioavailability of neuroprotective DPP4 substrates**

Glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), are DPP4 substrates. Both can penetrate the BBB and bind to their receptors in brain tissues to exert an effect. Studies have found significantly reduced expression of GLP-1 and GLP-1 receptor (GLP-1R) in the AD brain. GLP-1 exerts neuroprotective benefits by decreasing the levels of amyloid precursor protein and glycogen synthase kinase- 3β (GSK-3β), reducing Aβ deposition and tau phosphorylation, which are hallmarks of AD, as well as restoring insulin signalling pathway. It can also protect against neuronal degeneration by improving mitochondrial function and cellular proliferation, alleviating neuroinflammation and apoptosis. GIP can inhibit the apoptosis of cerebellar granule cells, and the activation of GIP receptor can promote the proliferation of neuronal progenitor cells. Stromal-derived factor-1α (SDF-1α), another DPP4 substrate is associated with neuroprotection and neurogenesis and the expression level of SDF-1α is significantly reduced in AD patients. Neuropeptide-Y (NPY), also a DPP4 substrate, widely expressed in the central nerve system attenuates neuroinflammation, promotes neuro-proliferation and the production of sufficient trophic support for the growth of new neurons. Overexpression of NPY via DPP4i may be protective against AD. Therefore, use of DPP4i can significantly increase the bioavailability of these substrates.

❋ **Anti-inflammation, anti-oxidation, and anti-apoptosis properties of DPP4i**

DPP4i may offer additional neurocognitive benefits through anti-inflammation, anti-oxidation and anti-apoptosis. Pre-clinical studies have showed these respective benefits. Pro-inflammatory cytokines in the hippocampus, such as TNF-α, IL-6, and NF κB, were significantly reduced after the administration of DPP4i.

DPP4i has been also shown to alleviate oxidative stress. After the treatment of DPP4i, the levels of glutamate and nitric oxide had decreased significantly in the hippocampus, while the concentration of glutathione increased significantly. Moreover, DPP4i was found to reduce neuronal cell apoptosis and promote neurogenesis. Vildagliptin use was found to prevent neuronal apoptosis in hippocampus, reduce the expression of apoptosis-related proteins and increased neurotrophic factors in experimental models of T2DM.

There are several clinical studies which have supported the neuroprotective effects of DPP4i in AD. In studies of older patients with T2DM and cognitive impairment, treatment with a DDP4 inhibitor was associated with a slower deterioration of cognitive function mainly attentional and executive functions. In comparison to sulphonylurea, DPP-4 inhibitor use was associated with a 34% reduced risk of dementia ($p < 0.001$) and 36% reduced risk of AD ($p < 0.001$) in the same type of population. These findings were also corroborated by a recent 2021 meta-analysis.

Therefore, the above provides useful insights about DPP-4 inhibitors as a potential therapeutic treatment to be explored in preventing the development and progression of Alzheimer's disease.

Source: Jiang X, et al. Front. Pharmacol. 2024; 15:1361651, Kim YG, et al. J. Clin. Med. 2018; 8 (1): 28, Tang H, et al. J. Am. Geriatr. Soc. 2023; 71, 2096–2106.

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