Quarter 2, 2026 | VOLUME 14 | NUMBER 4

Medical Bulletin

BLUE CROSS LIFE SCIENCES Division of Blue Cross Laboratories Pvt Ltd.

EFFECT OF DAPAGLIFLOZIN ON GLYCEMIC CONTROL AND LIPID PROFILE IN PATIENTS WITH TYPE 2 DIABETES AND DYSLIPIDEMIA

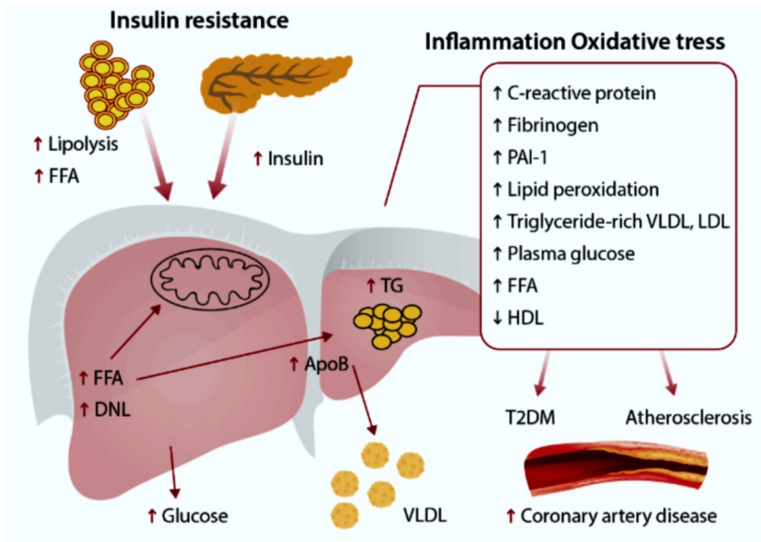
Type 2 Diabetes Mellitus (T2DM) has emerged as a major global public health challenge. The global prevalence increased from 537 million adults in 2021 to 589 million in 2024 and is projected to reach 853 million by 2050. India represents a major contributor to this burden, with adult T2DM prevalence rising from 33 million in 2000 to 72 million in 2021 and expected to reach 125 million by 2045. Early disease onset, reduced β-cell reserve, increased visceral adiposity, genetic predisposition, and sedentary lifestyle patterns contribute to the accelerated disease trajectory in Indian populations.

Dyslipidemia is a frequent and clinically significant comorbidity in T2DM, characterized by elevated triglycerides (TG), increased small dense low-density lipoprotein (sd-LDL), and reduced high-density lipoprotein (HDL). These abnormalities substantially increase cardiovascular (CV) risk and contribute to the progression of heart failure (HF). The combined effects of hyperglycemia and dyslipidemia promote insulin resistance (IR), oxidative stress, endothelial dysfunction, chronic inflammation, and lipotoxicity, thereby accelerating atherosclerosis and HF development.

Insulin Resistance and Diabetic Dyslipidemia

Insulin resistance plays a central role in the pathogenesis of diabetic dyslipidemia. Reduced insulin sensitivity enhances hepatic production of very-low-density lipoprotein (VLDL) through increased apolipoprotein B-100 synthesis. Simultaneously, insulin resistance activates hormone-sensitive lipase (HSL) in adipose tissue, increasing free fatty acid (FFA) release into circulation. Excess FFAs are taken up by the liver and peripheral tissues, leading to ectopic lipid accumulation, lipotoxicity, and further impairment of insulin signalling.

Insulin resistance also reduces lipoprotein lipase (LPL) activity in skeletal muscle and adipose tissue, impairing clearance of TG-rich lipoproteins. The resulting hypertriglyceridemia promotes conversion of large buoyant LDL (lb-LDL) into sd-LDL, which is highly atherogenic. Collectively, these mechanisms explain the typical lipid pattern observed in T2DM-elevated TG, VLDL, LDL-C, and reduced HDL-C-associated with increased CV risk.



Link between insulin resistance and metabolic dyslipidemia

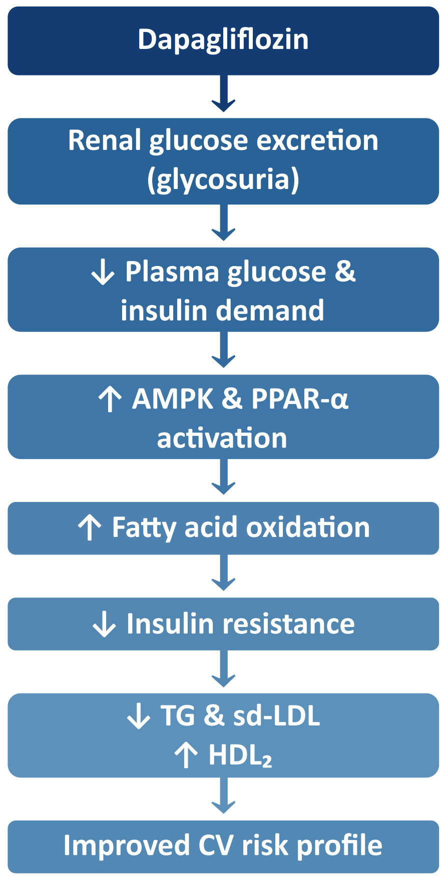
Role of SGLT2 Inhibitors in Metabolic Modulation

Sodium-Glucose Transporter 2 inhibitors (SGLT2i) lower plasma glucose by inhibiting renal glucose reabsorption, leading to glycosuria. Beyond glycemic control, SGLT2 inhibitors exert favorable pleiotropic effects, including weight reduction, blood pressure lowering, improved insulin sensitivity, and beneficial lipid modulation.

Large cardiovascular outcome trials such as DAPA-HF and EMPEROR-Reduced have demonstrated significant reductions in HF hospitalization and CV mortality with SGLT2 inhibitors, independent of diabetic status. Although lipid parameters were not primary endpoints in these trials, emerging evidence suggests that SGLT2 inhibitors exert indirect but clinically meaningful effects on lipid metabolism.

Dapagliflozin: Mechanistic Insights on Lipid and Insulin Metabolism

Dapagliflozin's metabolic benefits are thought to be mediated through enhanced fatty acid oxidation and improved insulin sensitivity, involving activation of AMP-activated protein kinase (AMPK) & peroxisome proliferator-activated receptor-α (PPAR-α). These pathways promote mitochondrial efficiency, increase fat utilization, and favorably influence lipoprotein metabolism. Pre-clinical studies have demonstrated preservation of pancreatic islet architecture with SGLT2 inhibitors, an effect not consistently observed with sulfonylureas or GLP-1 receptor agonists. In addition, activation of sirtuin-1 (SIRT1) under nutrient-depleted conditions enhances skeletal muscle mitochondrial oxidative capacity, improving insulin sensitivity and reducing lipotoxicity.



Metabolic Effects of Dapagliflozin

Impact on Lipid Profile and Cardiovascular Risk

In patients with T2DM, dapagliflozin therapy has been associated with reductions in triglycerides and sd-LDL, along with an increase in large buoyant LDL particles. This compositional shift explains the modest rise in total LDL-C observed with therapy and is considered less atherogenic. Dapagliflozin also increases HDL2, the cardioprotective HDL subfraction, without significantly affecting HDL3. A positive correlation between improvements in HOMA-IR and reductions in triglyceride levels over 24 weeks suggests a close link between enhanced insulin sensitivity and lipid metabolism.

Conclusion

Dapagliflozin provides clinically relevant benefits beyond glycemic control by improving insulin sensitivity and favorably modulating lipid profiles in patients with T2DM and dyslipidemia. Its ability to reduce atherogenic sd-LDL, increase cardioprotective HDL2, and improve metabolic efficiency supports its role as an important adjunct in comprehensive cardiometabolic risk management, particularly in patients with coexisting T2DM and heart failure.

Source: *Bhaganagarapu L S et.al; Endocrine, Metabolic & Immune Disorders -Drug Targets, 2026, 26, e18715303398749.*

PLEIOTROPIC ACTIONS OF TELMISARTAN IN NEURO-PROTECTION: MOLECULAR PERSPECTIVES

Telmisartan, a potent angiotensin II type-1 receptor blocker as well as partial PPAR-gamma agonist, has emerged as a versatile therapeutic agent with diverse pharmacological actions beyond its primary indication for essential hypertension. Its unique mode of action entails the targeted and enduring inhibition of the angiotensin II type-1 (AT1) receptor's reactivity to angiotensin II, while preserving the functionality of other receptor systems implicated in cardiovascular control. This selectivity not only forms the basis of its powerful antihypertensive action but also lays the groundwork for its diverse pharmacological characteristics.

In addition to its role as an angiotensin receptor blocker (ARB), telmisartan exhibits partial agonist activity toward the peroxisome proliferator-activated receptor gamma (PPAR-γ). This unique dual activity confers a myriad of additional benefits, including antioxidative, anti-inflammatory, and antiproliferative effects exhibiting pleiotropic effects of telmisartan, offering advantages on metabolic syndrome, neuroprotection, and nephroprotection emphasizing its potential as valuable therapeutic agent across various diseases. Telmisartan, beyond its antihypertensive action as an angiotensin II type-1 receptor (AT1R) blocker, exhibits significant neuroprotective effects through anti-inflammatory, antioxidant, and anti-apoptotic mechanisms.

Neuroinflammation and Telmisartan

Angiotensin receptor II induces inflammation and oxidative stress via reactive oxygen species (ROS) production through the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Toll-like receptors (TLRs) and PPARγ receptors in the central nervous system (CNS) play vital roles in neuroinflammation. Excessive RAS activation, especially through AT1 receptors, contributes to brain inflammation. IL-1β, generated by microglia, has diverse roles and is implicated in neurodegenerative disorders.

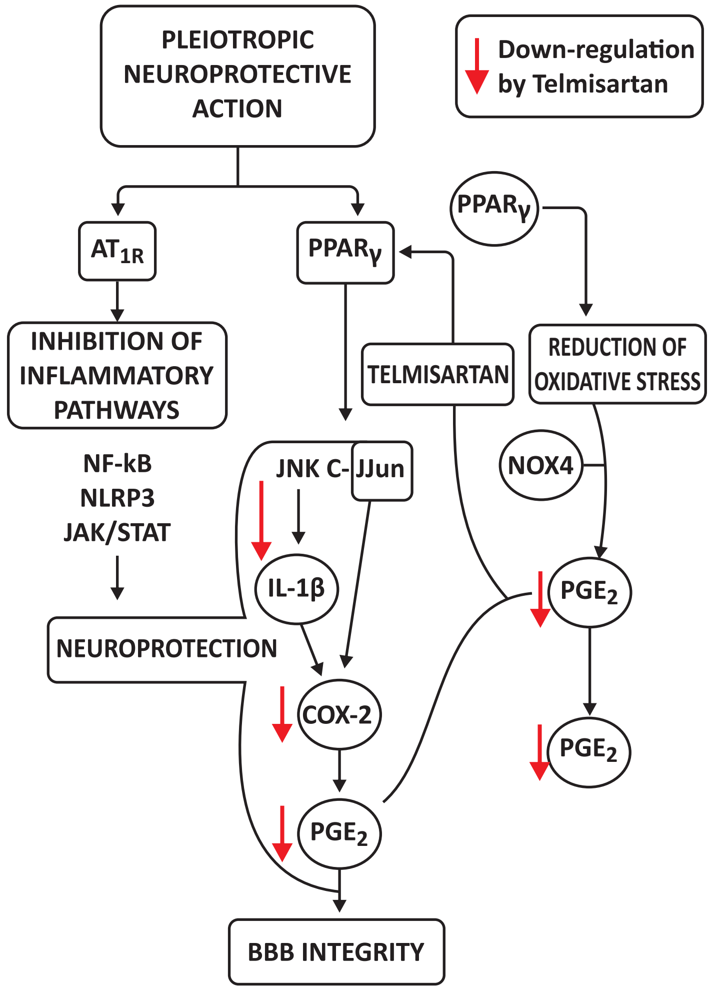
Telmisartan demonstrates a multifaceted approach to neuroprotection by modulating specific pathways associated with inflammation and oxidative stress. PPARγ activation leads to a dose-dependent increase in sterile alpha and armadillo-motif-containing protein (SARM) expression, a negative regulator of pro-inflammatory cytokines. Telmisartan reduces lipopolysaccharide (LPS) induced inflammation in neuronal cells via SARM activation through TLR4 signalling independently of AT1R. Telmisartan reduces Interleukin (IL)-1β-induced cyclo-oxygenase (COX)-2 expression, prostaglandin (PG) E2 release, and ROS production. Telmisartan mitigates IL-1β-induced upregulation of IL-1R1 receptor and NOX-4 mRNA expression. Telmisartan attenuates hydrogen peroxide-induced COX-2 gene expression & reduces c-Jun N-terminal kinase (JNK/c-Jun) activation.

Additionally, partial PPARδ agonistic property was considered crucial for reducing cytokine levels and improving cognitive decline. Telmisartan also restores neural activity in stressed brain regions, impacting serotonin transporter expression via PPARδ activation. Its anti-inflammatory and antioxidant properties, partially through PPARδ agonism.

Telmisartan also disrupts Nucleotide-binding oligomerization domain like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activation, reducing IL-1β induced inflammation. Its sustained AT1R inhibition diminishes cerebral edema post transient brain injury, while also maintaining blood–brain barrier integrity. Telmisartan shows promise as a therapeutic agent for brain injury and cerebral edema management. It prevents nerve cells from injury by decreasing the apoptotic pathway, inhibiting caspase-3 activity, and reducing inflammatory cytokines. In conditions like chronic constriction injury (CCI), renin angiotensin aldosteron system (RAAS) overactivation is associated with increased inflammatory mediators, oxidative stress, and pain-related markers. Telmisartan, by modulating RAAS components and down regulating signalling pathways like Janus Kinase 2(JAK2)/Signal Transducer and Activator of Transcription 3 (STAT3) and P38-MAPK (mitogen-activated protein kinase), exerts beneficial effects in neuropathic pain modulation. Telmisartan's neuroprotective effects are independent of PPARγ activation, as confirmed in preclinical studies.

Key Neuroprotective Mechanisms

- Reduction of Neuroinflammation
  - Inhibits AT1R-mediated activation of nuclear factor-κB (NF-κB) NADPH oxidase, and ROS production
  - Suppresses microglial release of IL-1β, COX-2, PGE_2, and NOX-4
- Modulation of PPAR Pathways
  - Partial PPAR-γ and PPAR-δ agonism → decreases pro-inflammatory cytokines, improves neuronal survival
  - Enhances negative regulators of inflammation (e.g., SARM) via TLR4 signalling inhibition
- Oxidative Stress Attenuation
  - Reduces hydrogen peroxide-induced neuronal injury
  - Inhibits JNK / c-Jun and downstream stress-activated pathways
- Neuronal Survival & Anti-Apoptosis
  - Decreases caspase-3 activation
  - Limits neuronal degeneration in ischemia, trauma, and neuropathic pain models
- Blood-Brain Barrier & Cerebral Edema Protection
  - High lipophilicity enables CNS penetration
  - Inhibits NLRP3 inflammasome, preserving BBB integrity post-TBI.



Integrated pleiotropic neuroprotective actions of telmisartan.

Conclusion

Telmisartan offers a multimodal neuroprotective profile, via both PPAR-dependent & PPAR-independent pathways acting on inflammation, oxidative stress, apoptosis, and RAAS dysregulation, positioning it as a promising therapeutic agent for its pleiotropic neuroprotective effects beyond blood pressure control. Clinical neurotherapeutic implications with potential benefit in neurodegenerative diseases, adjunct role in depression, cognitive decline, neuropathic pain, and traumatic brain injury should be explored clinically.

Source: *Ahire et al. Future Journal of Pharmaceutical Sciences, 2024, 10:84; Ernawati I et.al; MNJ (Malang Neurology Journal) Vol. 6, No. 1, January 2020.*

Dr. Prabhu Kasture (MD, DPH)
Director Medical Services & Pharmacovigilance
Phone No.: 022-66638043
Email: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt Ltd., Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013.
Website: http://www.bluecrosslabs.com