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Review Article

SGLT2 Inhibitors: A Modern Approach to Cardio-Renal-Metabolic Protection

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Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as an important therapeutic class offering significant cardio-renal-metabolic protection beyond glycaemic control in type 2 diabetes mellitus. Initially developed as glucose-lowering agents, these drugs are now recognized for their beneficial effects on heart failure, chronic kidney disease, and metabolic dysfunction-associated steatotic liver disease (MASLD). By inhibiting renal glucose and sodium reabsorption in the proximal tubule, SGLT2 inhibitors promote glucosuria, natriuresis, osmotic diuresis, and restoration of tubuloglomerular feedback, leading to improved cardiovascular and renal outcomes. Clinical studies have demonstrated reductions in albuminuria, slowing of chronic kidney disease progression, and decreased hospitalization for heart failure in both diabetic and non-diabetic patients. Emerging evidence also supports their role in improving hepatic steatosis, liver enzyme abnormalities, and metabolic parameters in patients with MASLD and metabolic dysfunction-associated steatohepatitis (MASH). Their application in compensated cirrhosis and refractory ascites is increasingly being explored, although caution is necessary in advanced liver disease because of risks related to volume depletion, renal dysfunction, electrolyte disturbances, and infections. Overall, SGLT2 inhibitors represent a modern multidimensional therapeutic approach with expanding applications across cardiovascular, renal, and hepatic medicine.

Keywords: Sodium-Glucose Transporter 2 Inhibitors, Heart Failure, Chronic Kidney Disease, Fatty Liver.

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Introduction

Sodium-Glucose Cotransporter-2 inhibitors (SGLT2 inhibitors or "gliflozins") have changed the way many chronic diseases are treated. These drugs were first introduced as glucose-lowering agents for patients with type 2 diabetes mellitus (T2DM), but over the last decade they have shown important benefits that extend far beyond glycaemic control. They are now considered key therapies for cardiovascular disease, chronic kidney disease, and metabolic liver disease.[1,2] By 2026, the clinical focus has shifted from simple glucose reduction toward organ protection, especially involving the heart, kidneys, and liver.[1–3]

Pathophysiological Basis: SGLT2 inhibitors act mainly in the proximal convoluted tubule of the kidney by blocking the sodium-glucose cotransporter-2 protein, which normally reabsorbs nearly 90% of filtered glucose.[4] Blocking this transporter leads to glucosuria and mild natriuresis.[4,5] The glucose remaining within the renal tubules creates osmotic diuresis, increasing urinary water excretion.5 SGLT2 transporters are also functionally linked with the sodium-hydrogen exchanger-3 (NHE3), an important mediator of proximal tubular sodium reabsorption.[6] Inhibition of SGLT2 reduces NHE3 activity and further promotes sodium excretion.[6] These physiological effects produce several important systemic benefits:

Hemodynamic Effects: Mild natriuresis and osmotic diuresis reduce plasma volume and systemic vascular resistance, resulting in blood pressure reduction without major sympathetic activation.[7]

Renal Protection: SGLT2 inhibitors restore tubuloglomerular feedback by increasing sodium delivery to the macula densa, leading to afferent arteriolar vasoconstriction and reduction of intraglomerular pressure. This nephroprotective effect is enhanced when combined with ACE inhibitors or angiotensin receptor blockers (ARBs), which dilate the efferent arteriole and further lower intraglomerular hypertension.[8]

Metabolic Benefits: Caloric loss through glucosuria

promotes weight reduction and decreases visceral adiposity. In addition, increased ketone body utilization may improve insulin sensitivity and metabolic efficiency. These mechanisms are particularly relevant in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).9

SGLT2 Inhibitors and Liver Disease

MASLD and MASH: Growing evidence supports the use of SGLT2 inhibitors in patients with MASLD and metabolic dysfunction-associated steatohepatitis (MASH).[10] Recent meta-analyses have demonstrated significant reductions in hepatic steatosis measured by MRI-PDFF, together with improvements in liver enzymes such as ALT, AST, and GGT. Emerging evidence also suggests potential anti-fibrotic effects, although large biopsy-based trials are still needed.[11] Non-invasive markers such as FibroScan and the FIB-4 index have shown favourable trends in patients treated with SGLT2 inhibitors. Current recommendations from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) consider SGLT2 inhibitors useful adjunctive agents in patients with T2DM and MASLD because of their cardiovascular and renal protective properties.[11,12]

Use in Cirrhosis: The role of SGLT2 inhibitors becomes more challenging in advanced chronic liver disease.

Compensated Cirrhosis (Child-Pugh A): In compensated cirrhosis, the cardiovascular and renal benefits may outweigh potential risks. Observational studies suggest a possible reduction in hepatic decompensation events.[13]

Decompensated Cirrhosis (Child-Pugh B and C): In decompensated liver disease, careful patient selection is essential because natriuresis and diuresis may worsen circulatory instability.[14]

Potential Risks

Acute Kidney Injury and Hepatorenal Syndrome: The diuretic effect of SGLT2 inhibitors may precipitate renal dysfunction in patients with reduced effective circulatory volume or impaired renal perfusion.[14] SGLT2 inhibitors lower the renal threshold for glucose excretion from approximately 180 mg/dL to nearly 70–90 mg/dL, allowing osmotic diuresis even when blood glucose levels are near normal.[15]

Electrolyte Disturbances: Hyponatremia is common in advanced cirrhosis and is associated with hepatic encephalopathy, hepatorenal syndrome, and poor survival.[16] Serum sodium levels below 130 mEq/L significantly increase the risk of hepatorenal syndrome and mortality. Each small decline in serum sodium within the range of 125–140 mmol/L has been associated with worsening prognosis.[17]

However, unlike loop diuretics, SGLT2 inhibitors mainly promote free water excretion through osmotic diuresis and may sometimes improve dilutional hyponatremia rather than worsen it. Significant hypokalemia or severe hyponatremia is relatively uncommon because distal tubular diluting mechanisms remain largely preserved.[18] The MELD-Na score used for liver transplant prioritization is based on measured serum sodium regardless of whether hyponatremia is medication-related or disease-related.[19]

Infection Risk: Genitourinary fungal and bacterial infections remain an important concern, particularly in immunocompromised cirrhotic patients.[20]

Emerging Role in Refractory Ascites

An interesting emerging application is the use of SGLT2 inhibitors in refractory ascites. Preliminary reports suggest that osmotic diuresis through glucosuria may improve fluid control through mechanisms different from conventional loop diuretics, potentially reducing the need for repeated paracentesis.[21] More prospective clinical trials are required before routine recommendation can be made.

Cardiovascular Benefits

Heart Failure: SGLT2 inhibitors are now considered foundational therapy for both heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), regardless of diabetic status.[22] In heart failure and chronic kidney disease, increased sodium delivery to the macula densa triggers adenosine-mediated afferent arteriolar vasoconstriction, thereby reducing intraglomerular pressure.[8]

Unlike loop diuretics, which predominantly reduce intravascular volume, SGLT2 inhibitors preferentially reduce interstitial fluid volume. This may explain why patients experience improvement in edema and congestion with less reflex sympathetic activation or hypotension.[23] The natriuretic effect is strongest during the first 48–72 hours, while osmotic diuresis persists as long as glucosuria continues.[24]

Chronic Kidney Disease: SGLT2 inhibitors significantly reduce albuminuria and slow CKD progression.[25] A modest initial fall in estimated glomerular filtration rate (eGFR), usually around 3–5 mL/min/1.73 m², is commonly observed after therapy initiation. This reversible change reflects reduced intraglomerular pressure and is generally considered a marker of long-term nephron protection.[25]

Acute Care Applications: Recent studies have expanded the role of SGLT2 inhibitors into acute cardiovascular settings, including acute heart failure and post-myocardial infarction care.[26] Ongoing trials continue to evaluate their broader role in acute medicine.

Future Perspectives

By 2026, SGLT2 inhibitors are increasingly viewed as "smart diuretics" because they optimize volume status while preserving renal microvascular function. Their use in early metabolic liver disease is becoming more established; however, management in advanced cirrhosis should remain individualized and multidisciplinary.[15] Future prospective trials focusing on liver-related mortality, fibrosis regression, and histological outcomes will further define their role in hepatology.[10,11]

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Authors' Contribution

MH: Conception.

MH: Design of the work.

MH: Data acquisition, analysis, or interpretation.

MH: Draft the work.

MH: Review critically for important intellectual content.

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