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Review Article

Repurposing SGLT2 Inhibitors for Cirrhotic Ascites: From Mechanistic Research to Clinical Exploration

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Abstract

Cirrhotic ascites develops when portal hypertension and arterial under-filling chronically activate neuro-hormonal pathways that drive renal sodium-water retention. Augmented proximal tubular sodium reabsorption, predominantly mediated by the apical sodium/hydrogen exchanger 3 (NHE3), plays a fundamental role in this process. Given the spatial coupling of NHE3 and the sodium-glucose cotransporter 2 (SGLT2), selective SGLT2 inhibition reduces NHE3 activity via functional suppression within the apical microdomain. The increased sodium chloride delivery to the macula densa augments tubuloglomerular feedback and modulates the renin–angiotensin–aldosterone system. Early clinical investigations, ranging from case reports and retrospective analyses to pilot randomized trials, indicated potential benefits in controlling ascites and reducing decompensation events. However, their limited sample size, heterogeneous endpoints, and predominantly observational design constrain the generalizability of the findings. This review concentrates on the molecular mechanisms and emerging clinical evidence supporting the therapeutic potential of SGLT2 inhibitors in the management of cirrhotic ascites.

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Introduction

In cirrhosis, portal hypertension and splanchnic arterial vasodilation chronically activate neurohumoral systems, including the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system, and arginine vasopressin. Neurohormonal activation drives augmented tubular sodium reabsorption, and the proximal tubule acts as a dominant effector.[1] Augmented proximal tubular sodium reabsorption not only promotes ascites formation but also reduces the luminal sodium gradient available to distal nephron channels, thereby diminishing the effectiveness of diuretics, a phenomenon commonly referred to as diuretic resistance.[2] Clinically, the development of ascites marks a notable transition from compensated to decompensated cirrhosis. Each year, approximately 5–10% of patients with compensated cirrhosis progress to ascites.[3] Once ascites develops, the five-year mortality increases to about 44%.[4] Outcomes are even worse in patients with refractory ascites, in whom early referral for liver transplantation should be considered.[5]

Mechanistically, the sodium/hydrogen exchanger 3 (NHE3) is the principal mediator of proximal tubular sodium reabsorption.[6] The spatial colocalization of NHE3 and the sodium–glucose cotransporter 2 (SGLT2) in the same apical microdomain provides a mechanistic rationale whereby pharmacologic inhibition of SGLT2 may concurrently reduce NHE3 activity, thereby attenuating excessive proximal sodium reabsorption. These insights support the development of proximal tubule–targeted therapeutic strategies.

This review integrates the current understanding of cirrhosis pathophysiology with proximal tubular mechanisms, highlights their contributions to ascites formation and diuretic resistance, and discusses the mechanistic basis and emerging clinical evidence supporting the use of SGLT2 inhibitors.

Disrupted sodium–water homeostasis: the core driver of ascites and the limitation of conventional diuretics

Under normal physiological conditions, the proximal tubule reabsorbs approximately 60% of filtered sodium, primarily via the NHE3, while the SGLT2 accounts for about 5% through 1:1 sodium–glucose coupling.[7] In cirrhosis models or in states of reduced effective arterial volume, both transporters in the proximal tubule are upregulated, thereby reducing sodium delivery to the distal nephron.[8] In the compensated stage, increased cardiac output partially counteracts splanchnic vasodilation, and neurohumoral activation remains mild. Once decompensation occurs, cardiac output declines, and sustained activation of the RAAS together with arginine vasopressin can markedly enhance proximal sodium–chloride reabsorption.[9,10] In carbon tetrachloride (CCl_4)-induced ascitic rats, proximal NHE3 expression levels and brush-border lo-

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calization increase by 40–60%, exhibiting an inverse correlation with urinary sodium excretion.[11] Clinically, patients with ascites demonstrate greater fractional proximal sodium reabsorption despite preserved eGFR, resulting in a diminished natriuretic response to furosemide compared with controls. After sodium chloride (NaCl) infusion, proximal reabsorption remains unchanged in decompensated cirrhosis, whereas it decreases by approximately 15% in healthy subjects.[12] Thus, upregulation of proximal tubular Na^+ transport underlies cirrhotic Na^+ retention and contributes to the limited efficacy of standard diuretics; however, direct evidence of NHE3 alterations in cirrhotic patients remains limited.

First-line diuretic therapy for ascites typically includes spironolactone, either alone or in combination with a loop diuretic.[3] Loop diuretics inhibit Na^+–K^+–$2Cl^-$ cotransporter 2 (NKCC2) in the thick ascending limb, thereby increasing distal NaCl delivery and promoting natriuresis. However, simultaneous inhibition of NKCC2 at the macula densa (MD) reduces NaCl sensing, stimulates juxtaglomerular renin release, and further amplifies the already activated RAAS.[13] The ensuing angiotensin II/aldosterone signaling upregulates sodium–chloride cotransporter (NCC) and epithelial sodium channel (ENaC), increases Na^+ reabsorption, and induces the "braking phenomenon" during prolonged therapy, whereby the natriuretic response diminishes despite dose escalation.[14,15]

Molecular basis of SGLT2-mediated natriuresis

Heart failure and decompensated cirrhosis share a key pathophysiological feature, namely effective arterial hypovolemia. A reduction in cardiac output or systemic vascular resistance lowers arterial blood volume, leading to chronic activation of the sympathetic nervous system and the RAAS, which in turn enhances renal sodium reabsorption. The resulting fluid retention manifests as pulmonary or peripheral edema in heart failure, whereas it predominantly leads to ascites in cirrhosis.[16] SGLT2 inhibitors improve cardiorenal outcomes in heart failure and are incorporated into the four foundational therapies for heart failure with reduced ejection fraction, comprising an ARNI (or ACE inhibitor/ARB), a β-blocker, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor. They have also been explored for fluid management in cirrhotic ascites.[17]

SGLT2 is highly expressed on the brush border of the proximal tubule and, as a Na^+-dependent glucose transporter, mediates reabsorption of filtered glucose. It comprises 14 transmembrane helices arranged into a "rocking bundle" and a "stationary scaffold," functioning in concert with its chaperone protein MAP17.[18] Because Na^+ reabsorption via SGLT2 is strictly stoichiometrically coupled to glucose transport, even RAAS-induced upregulation of SGLT2 increases total renal Na^+ reabsorption by only 3–5%.[19] Therefore, selective SGLT2 blockade alone would be expected to exert only a limited natriuretic effect.

NHE3, located on the luminal membrane of the proximal tubule, mediates Na^+/H^+ exchange. NHE3 and the SGLT2–MAP17 complex are organized and stabilized by the PDZ domain–containing protein PDZK1, forming a functional scaffold that coordinates sodium and glucose transport.[20,21] Functional studies demonstrate that SGLT2 inhibition reduces proximal tubular sodium reabsorption in part by suppressing NHE3 activity, thereby amplifying natriuresis beyond what would be expected from direct blockade of SGLT2 alone.[22] In non-diabetic rats with post-MI heart failure, *in vivo* microperfusion showed that the SGLT2 inhibitor empagliflozin directly inhibited proximal NHE3 activity while preserving GFR and restoring euvolemia (Fig. 1).[23]

However, the precise molecular events governing this SGLT2–NHE3 interplay remain under investigation. While inhibitory phosphorylation of NHE3 was initially proposed as a primary pathway,[22] recent data indicate a more complex picture. For instance, a study in healthy volunteers showed that a single dose of empagliflozin increased fractional sodium excretion without altering NHE3 phosphorylation or abundance in urinary exfoliated tubular cells.[24] This suggests that the functional shift in proximal Na^+ handling does not rely solely on phosphorylation. Furthermore, downstream transporter adaptation significantly shapes the phenotype during prolonged use. In normotensive rats, empagliflozin inhibited proximal NHE3 yet upregulated expression and phosphorylation of distal NCC; in hypertensive rats, NHE3 inhibition occurred without NCC upregulation.[25] These findings support a network view in which distal compensation can partially offset proximal NHE3 inhibition under some backgrounds. Pair-feeding/drinking experiments showed that SGLT2 inhibition maintained a small but sustained increase in urinary sodium and water, producing a mild negative fluid balance that revealed an intrinsic natriuretic tone.[26] In conclusion, current data do not support a universal increase in NHE3 phosphorylation; rather, this mechanism appears to be context-dependent and warrants further exploration, specifically within the cirrhotic environment.

Taken together, these findings indicate that inhibition of proximal tubular NHE3 is the dominant driver of SGLT2 inhibitor–induced natriuresis, and that the resulting increase in distal sodium delivery far exceeds the small amount of sodium that is directly cotransported with glucose by SGLT2 itself. In humans, a lithium clearance study demonstrated that SGLT2 inhibition diverts more than 7% of the glomerular filtrate Na^+ load to the distal nephron, markedly exceeding the transporter's theoretical 3–5% contribution.[19,27] In line with these observations, clinical studies in heart failure have shown that natriuretic and glycosuric responses are not tightly positively correlated and may even be inversely related.[28,29]

Modulation of the SGLT2i-neurohumoral axis

By inhibiting proximal tubular sodium–glucose reabsorption, SGLT2 inhibitors increase NaCl delivery to the thick ascending limb, enhancing the ionic load sensed by the MD.[30] The classical model attributes the activation of tubuloglomerular feedback (TGF) to an elevation in luminal NaCl concentration.[31,32]

Experimental evidence indicates that chloride, rather than sodium, is the principal trigger of the TGF response. TGF is abolished when the loop of Henle is perfused with an isoosmotic, chloride-free solution,[33] whereas replacement of luminal sodium with N-methyl-D-glutamine in the presence of chloride preserves TGF activation.[34]

SGLT2 inhibition also suppresses NHE3 activity, raising luminal bicarbonate concentrations in tubular fluid,[35] which may lead to a disproportionate elevation in urinary Na^+ relative to Cl^-. When the increase in distal tubular Cl^- is modest, the MD continues to sense a "low Cl^-" state, keeping TGF suppressed. Future studies should clarify how urinary chloride dynamics influence RAAS activity following SGLT2 inhibition.

Theoretically, increased chloride delivery to the MD can enhance TGF and suppress RAAS activity; however, clinical findings are more complex. Osmotic diuresis and modest natriuresis transiently reduce plasma volume, eliciting a short-lived increase in plasma renin activity, whereas aldosterone levels exhibit minimal or no change. Both parameters generally return to baseline with continued therapy.[36,37] In

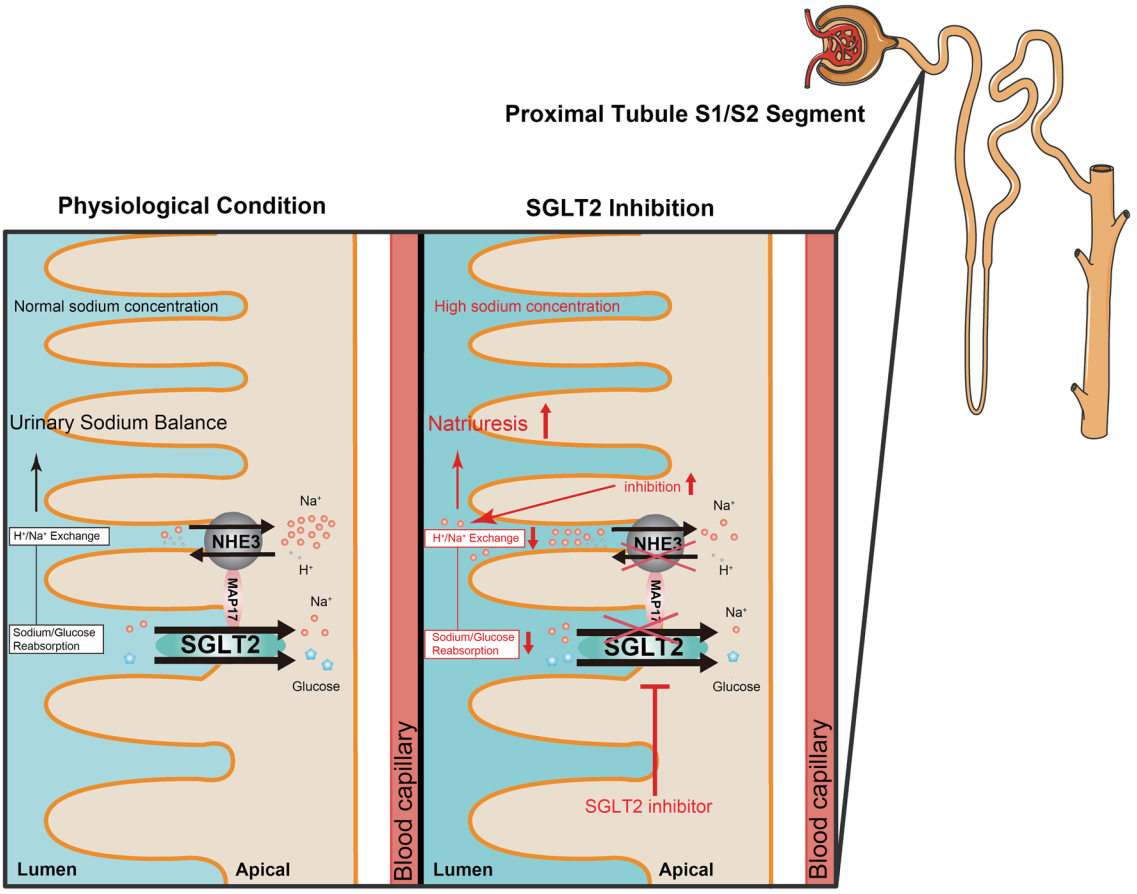

Fig. 1. Molecular mechanisms for the SGLT2 inhibitor–mediated reduction in proximal tubular sodium reabsorption. SGLT2, sodium glucose cotransporter 2; NHE3, sodium hydrogen exchanger 3; MAP17, membrane associated protein of 17 kDa; S1/S2, S1 and S2 segments of the proximal tubule; Na+, sodium ion; H+, hydrogen ion.

randomized trials of SGLT2 inhibitors in heart failure, a decline in eGFR of 3–5 mL/min/1.73 m^2 is mainly observed during the first weeks, while values generally return to baseline by 12 weeks and subsequently decline at a slower rate than in control subjects.[38] Importantly, these heart failure–based trials have not demonstrated an increased incidence of orthostatic hypotension despite a modest 4–5 mm Hg reduction in systolic blood pressure.[39–41]

It is also necessary to take into account the complex effects of SGLT2 inhibition on neurohumoral regulation. For instance, in salt-loaded Dahl salt-sensitive rats, the SGLT2 inhibitor dapagliflozin blunted salt-induced hypertension and enhanced natriuresis without significantly altering circulating or intrarenal RAAS components.[42] In this low-renin model, the drug primarily improved tubular sodium handling in a RAAS-independent manner. Similarly, in hypertensive BPH/2J mice, dapagliflozin lowered blood pressure in association with sympathoinhibition by reducing renal tyrosine hydroxylase and norepinephrine levels, suggesting a RAAS-independent neurohumoral modulation.[43] Collectively, these studies illustrate that SGLT2 inhibitors do not universally modulate neurohumoral status via RAAS alone; rather, their effects are modulated by background renin status, salt intake, and sympathetic tone. Future studies in cirrhosis should therefore track these neurohumoral markers dynamically to determine which pathway predominates in the setting of advanced liver disease.

Effects of SGLT2 inhibitors on compensatory sodium reabsorption and sodium redistribution

Inhibition of proximal tubular sodium reabsorption by SGLT2 inhibitors is accompanied by compensatory adaptations in downstream nephron segments. In rodent models, the thiazide-sensitive NCC is consistently upregulated,[25] whereas responses of the NKCC2 and the ENaC vary depending on the experimental model. In a proteomic study of 1,134 participants, SGLT2 inhibitor therapy was associated with upregulation of carbonic anhydrase isoforms and urotensin II. The former may enhance sodium–bicarbonate reabsorption in proximal and collecting tubules, while the latter can stimulate NKCC2 in the loop of Henle, providing a mechanistic explanation for the attenuation of natriuresis after several days of treatment.[44] Evidence regarding ENaC is inconsistent. In diabetic rats, empagliflozin reduces α- and γ-ENaC expression,[45] whereas in normotensive rats treated for 14 days, ENaC remains unchanged while NCC is upregulated, highlighting model-dependent effects.[25]

In addition to their natriuretic effects, SGLT2 inhibitors may influence overall body sodium distribution, including a reduction in non-osmotic tissue sodium. A randomized controlled trial (RCT) utilizing ^{23}Na magnetic resonance imaging (MRI) demonstrated that six weeks of dapagliflozin (10 mg once daily) reduced skin sodium concentration by approximately 20 mmol/L in adult patients with type 2 diabetes, whereas placebo had no effect. Consistently, in a cohort of

74 patients with heart failure, three months of empagliflozin similarly decreased sodium content in skin and skeletal muscle. Post hoc analysis of EMPA-KIDNEY confirmed that SGLT2 inhibitors could modify body sodium storage in skin and muscle tissues without influencing overall body weight or fat mass, supporting mobilization of non-osmotic sodium from the skin–fascia compartment.[46]

This sodium storage site is located in the skin and subcutaneous fascia, which are rich in negatively charged sulfated glycosaminoglycans.[47] High aldosterone states activate the keratinocyte- and sweat duct–mineralocorticoid receptor/ENaC pathway, further promoting sodium binding to glycosaminoglycans.[48] Decompensated cirrhosis, characterized by persistent RAAS activation and elevated aldosterone levels, is therefore expected to resemble that observed in heart failure, thereby contributing to ascites formation. Loop diuretics primarily remove intravascular and tubular sodium and water and have limited capacity to mobilize tissue sodium, which may render them less effective than SGLT2 inhibitors for sodium redistribution.[49,50] To date, ^{23}Na MRI data in patients with cirrhosis and refractory ascites are lacking. Imaging-based studies evaluating the effects of SGLT2 inhibitors and loop diuretics in this population represent a notable direction for future research.

Clinical evidence and safety profile of SGLT2 inhibitors for cirrhotic ascites

Since 2020, clinical evidence with SGLT2 inhibitors in cirrhotic ascites has evolved from single-patient reports and small case series to feasibility studies and pilot RCTs. The earliest publications consisted of single-patient case reports and very small series, including three patients with refractory ascites, one patient with intractable pleuroascites, and one patient dependent on ascites-concentrating reinfusion.[17,51,52] More recently, Qin *et al*. documented complete resolution of pleuroascites and sustained natriuresis in another refractory case treated with empagliflozin.[53] Another case report described two patients with diabetes mellitus and cirrhosis-related ascites who experienced sustained reductions in ascites volume after three years of SGLT2 inhibitor therapy, without serious adverse events.[54] All patients exhibited remarkable improvement in fluid overload and hyponatremia following treatment with dapagliflozin or empagliflozin.[17,51] In addition, a retrospective cohort analysis suggested that exposure to SGLT2 inhibitors was associated with fewer end-stage liver disease events, hospital readmissions, and paracenteses.[55]

Since 2024, several pilot trials have demonstrated that empagliflozin reduced both ascites volume and the need for therapeutic paracentesis without the emergence of new safety concerns.[56–59] The first nationwide real-world analysis, involving approximately 10,000 adults, found that the use of SGLT2 inhibitors was associated with 32% fewer severe hepatic outcomes, 53% fewer episodes of hepatorenal syndrome, 46% fewer paracenteses, and a 33% reduction in hospitalization rates (Table 1).[17,51–63] Although these findings are promising, the majority of existing studies provide only level III–IV evidence and are constrained by small sample sizes or retrospective design. This highlights the urgent need for large, multicenter RCTs stratified by Child–Pugh class and incorporating longitudinal RAAS profiling and urinary electrolyte assessments to establish definitive efficacy and mechanistic insights (Supplementary Table 1).

Across four large-scale RCTs of empagliflozin in patients with diabetes, heart failure, and chronic kidney disease published in *The New England Journal of Medicine*,[40,64–66] the incidence rates of urinary tract infection, hypoglycemia, and hepatotoxicity were comparable to placebo, whereas the incidence of genital mycotic infections increased modestly (Table 2).[40,64–66] The low risk of hypoglycemia with SGLT2 inhibitors suggests that they primarily act by lowering the renal glucose threshold rather than exerting a direct glucose-lowering effect,[67] and non-diabetic participants excrete substantially less urinary glucose than patients with diabetes.[68] Mechanistically, the increased downstream glucose load to the S2/S3 segments of the proximal tubule elicits a compensatory increase in SGLT1-mediated transport.[69] This renal transport reserve provides a detailed explanation for the consistently low rates of hypoglycemia across diabetic individuals and patients with heart failure or CKD.

Neither randomized trials nor real-world studies have demonstrated an increased incidence of urinary tract infections, possibly because enhanced urine flow mitigates the glucosuria-associated infectious risk.[70] In contrast, SGLT2 inhibitors are consistently associated with a higher incidence of genital mycotic infections. In individuals without prior genital disease, the annual risk is approximately 10.8% in women and 2.7% in men,[71] rates that are similar to those observed in randomized trials. The most frequent manifestations are candidal vulvovaginitis in women and balanitis or posthitis in men, which generally resolve rapidly with standard antifungal therapy or temporary discontinuation of SGLT2 inhibitors. Given that cirrhosis predominantly affects men, the overall risk–benefit profile remains promising for the use of SGLT2 inhibitors in this population; nevertheless, genital infection should be prespecified as an important safety endpoint in future randomized trials. Importantly, existing large RCTs of SGLT2 inhibitors included few patients with decompensated cirrhosis, so complications that are particularly relevant in this population, such as the risk of spontaneous bacterial peritonitis, potential alterations in gut microbiota due to glucosuria, and the risk of hepatic encephalopathy, have been insufficiently characterized. These risks should be prioritized as key safety endpoints in future trials.

In relation to ammonia metabolism, preclinical studies have indicated that SGLT2 inhibition could enhance renal ammonium excretion through NHE3 inhibition and Rhcg upregulation.[22] In contrast, the DAPASALT study reported a transient decline in fractional urea excretion, which subsequently normalized promptly,[72] indicating that the overall impact of SGLT2 inhibition on ammonia handling remains unresolved.

Hyponatremia represents a frequent complication of decompensated cirrhosis, raising concern that natriuresis induced by SGLT2 inhibition could exacerbate this disturbance. Nevertheless, data from large-scale randomized trials in heart failure, supported by post hoc evidence, demonstrated that SGLT2 inhibitors do not increase the incidence of hyponatremia and may improve serum sodium concentrations,[73] with similar findings also reported in cirrhotic cohorts.[59] Accordingly, future randomized trials should prospectively designate serum sodium as a prespecified safety endpoint and stratify analyses according to baseline sodium concentration and Child–Pugh classification to refine the assessment of risks and benefits associated with SGLT2 inhibition in the management of cirrhotic ascites.

In hypertensive populations, SGLT2 inhibitors lower blood pressure by approximately 3–5 mmHg.[74] In decompensated cirrhosis, baseline blood pressure is often low; therefore, the risk of symptomatic or orthostatic hypotension should be carefully evaluated, ideally with ambulatory or wearable blood pressure monitoring as a safety endpoint in future trials.[75,76]

Finally, the hemodynamic effects of SGLT2 inhibitors on the hepatic circulation warrant careful consideration. Although

Table 1. Summary of clinical studies investigating SGLT2 inhibitors in cirrhotic ascites

	Study type	Sample size	Population characteristics	Intervention & follow-up	Main findings	OCEBM level	Level of evidence	Main limitations	Child-Pugh
1	Case series (2020)[17]	3	Refractory ascites and T2DM	SGLT2i; 46 w	Ascites and edema resolved	4	IV	Small sample size; no control	C
2	Case report (2021)[51]	1	PBC + Refractory hydrothorax and ascites	Empagliflozin 10 mg/d; 4 w	Resolution of ascites and pleural effusion	4	IV	Single case; short follow-up	C
3	PSM cohort (2021)[55]	846	Veterans,SGLT2i vs DPP4i	SGLT2i use vs non-use; 36 m	Mortality reduced by 67%	3	IIIa	Retrospective; potential confounding factors	NR
4	Case report (2022)[52]	1	Refractory ascites	Empagliflozin 10 mg/d;28 d	No need for paracentesis, reduced ascites	4	IV	Single case	C
5	Open label, phase I/II (2024)[57]	10	Decompensated cirrhosis	Empagliflozin 10 mg/d; 4 w	Good pharmacokinetics and safety; alleviates ascites	2b	IIb	Small sample size; no control	B/C
6	Pilot case series (2024)[58]	14	Refractory ascites	Empagliflozin 10 mg/d;3 m	24-hour urinary sodium increased; no need for paracentesis	4	IV	Small sample size; single center	C
7	Retrospective study (2024)[61]	300	T2DM and ascites	Dapagliflozin 10 mg/d(A/B) or 5 mg(C);6 m	Improved glycemia control; reduced diuretic requirement	3	IIIa	Non-randomized; ascites grading unavailable	A/B/C
8	RCT (2024)[59]	42	Refractory ascites	Empagliflozin 10 mg/d; 3 m	Reduced need for paracentesis	2	II	Small sample size; open-label	C
9	Case report (2025)[62]	4	Refractory ascites	Dapagliflozin 10 mg/d; 6 m	Ascites completely resolved	4	IV	Small sample size; no control	C
10	RCT (2025)[56]	40	Recurrent ascites	Dapagliflozin 10 mg/d vs placebo;6 m	Improved ascites control; increased incidence of AKI	2	II	Small sample size; low event rate	B/C
11	PSM cohort (2025)[60]	10 660	Cirrhotic ascites required diuretic	SGLT2i+diuretic vs diuretic;3 y	HRS reduced by 53%; paracentesis reduced by 46%	3	IIIa	Based on ICD and EMR, lack of baseline data	B/C
12	Single-arm study (2025)[63]	14	Diuretic-resistant ascites	Empagliflozin 10mg/d; 12w	well-tolerated; improved diuresis	3	III	Small sample size; no control	C
13	Case report (2025)[53]	1	ALD + Refractory hydrothorax and ascites	Empagliflozin 10 mg/d; 6 m	Resolution of ascites and pleural effusion, Diuretics discontinued, urinary sodium increased	4	IV	Single case	C
14	Case report (2025)[54]	2	Refractory ascites	Luseogliflozin 5 mg/d; 3y	Resolution of ascites	4	IV	Single case	B

T2DM, type 2 diabetes mellitus; PBC, primary biliary cholangitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor; ALD, alcoholic liver disease; DPP4i, dipeptidyl peptidase 4 inhibitor; NR, not reported; OCEBM, Oxford Centre for Evidence-Based Medicine. Evidence grading: "OCEBM Level" follows the 2011 OCEBM hierarchy (Level I = highest, Level IV = lowest) and is mapped to the corresponding "Level of Evidence" column.

Table 2. Four large trials of empagliflozin

	EMPA-REG OUTCOME[66]		EMPEROR-Reduced[40]		EMPEROR-Preserved[64]		EMPA-KIDNEY[65]	
	Empagliflozin (N = 4,687, 10 mg & 25 mg)	Placebo (N = 2,333)	Empagliflozin (N = 1,863)	Placebo (N = 1,863)	Empagliflozin (N = 2,996)	Placebo (N = 2,989)	Empagliflozin (N = 3,304)	Placebo (N = 3,305)
Serious hypoglycemia	63 (1.3)	36 (1.5)	27 (1.4)	28 (1.5)	73 (2.4)	78 (2.6)	77 (2.3)	77 (2.3)
Serious urinary tract infection	82 (1.7)	41 (1.8)	19 (1.0)	15 (0.8)	57 (1.9)	45 (1.5)	52 (1.6)	54 (1.6)
Genital infection	301 (6.4)	42 (1.8)	31 (1.7)	12 (0.6)	67 (2.2)	22 (0.7)	NR	NR
Serious genital infection	301 (6.4)	42 (1.8)	6 (0.3)	5 (0.3)	8 (0.3)	8 (0.3)	1 (<0.1)	1 (<0.1)
Serious hyperkalemia	NR	NR	NR	NR	NR	NR	92 (2.8)	109 (3.3)
Serious acute kidney injury	45 (1.0)	37 (1.6)	NR	NR	NR	NR	107 (3.2)	135 (4.1)
Liver injury	NR	NR	NR	NR	115 (3.8)	155(5.2)	13 (0.4)	12 (0.4)
Hypotension	239 (5.1)	115 (4.9)	176 (9.4)	163 (8.7)	311 (10.4)	257(8.6)	NR	NR

NR, not reported.

SGLT2 inhibitors have been shown to reduce portal pressure in animal models of cirrhosis, as well as reduce splanchnic congestion, potentially via antifibrotic mechanisms,[77] direct clinical data in patients with decompensated cirrhosis are lacking. There is a theoretical concern that excessive hypovolemia could reduce hepatic perfusion in patients with already compromised effective arterial blood volume. Future trials must balance the benefits of ascites resolution against the potential risk of worsening hepatic ischemia or hepatorenal syndrome, particularly in patients with unstable hemodynamics.

Future research perspectives

Future research should aim to close mechanistic gaps while establishing a translational framework that connects molecular pathways to patient-centered outcomes. Priorities include quantifying the degree of SGLT2–NHE3 coupling and the context-dependent contribution of NHE3 phosphorylation, delineating how SGLT2 inhibition modulates the RAAS and sympathetic tone, and defining the net impact on proximal and nephron-wide sodium reabsorption. The application of ^{23}Na MRI to assess sodium and water retention in cirrhosis, as well as dynamic changes in therapeutic response, represents a promising approach.

From the perspective of drug development, structural and genetic data support that SGLT2 functions in the proximal tubule as a complex with its accessory protein MAP17. MAP17 is required for full SGLT2 activity, and loss-of-function variants in MAP17 can cause familial renal glucosuria despite an intact SLC5A2 coding sequence, underscoring the functional importance of this microdomain. Recent cryo-electron microscopy structures of the human SGLT2–MAP17 complex bound to clinical inhibitors[21] provide a framework to design microdomain-targeted or allosteric modulators that might preserve NHE3-mediated natriuresis while inducing less glucosuria. Although such "natriuretic-biased, low-glucosuria" agents remain purely hypothetical at present.

In parallel, a translational pathway is needed to connect mechanistic insights with clinical outcomes. The analytical validity and clinical utility of candidate mechanistic biomarkers should be established, including urinary chloride and urinary exosomal phosphorylated NHE3 for treatment monitoring. An initial clinical step may involve exploratory studies in patients with refractory ascites and impaired urinary sodium excretion, with fractional excretion of sodium and neurohumoral markers as primary endpoints.[78] If SGLT2 inhibition exhibits sustained natriuretic efficacy in this context, it would warrant progression to multicenter RCTs with clinically relevant endpoints, including hospital readmission, paracentesis frequency, and all-cause mortality. Finally, given that the natriuretic mechanism of SGLT2 inhibition is likely to be broadly shared across agents in this class, and that the domestically developed SGLT2 inhibitor henagliflozin has already entered clinical studies in heart failure,[79] future research should also consider evaluating henagliflozin for the treatment of ascites in patients with cirrhosis.

Conclusions

SGLT2 inhibitors attenuate proximal tubular sodium reabsorption through a proximal microdomain comprising SGLT2, MAP17, and NHE3. Downstream effects include modulation of the RAAS and sympathetic nervous system, potentially redistributing tissue sodium. These mechanisms directly address the low distal sodium delivery that underlies diuretic resistance in cirrhotic ascites. Early clinical observations in-

dicate promising effects on natriuresis and reductions in ascites burden, with a safety profile consistent with experience from other trials involving SGLT2 inhibitors. Although the current evidence remains preliminary and limited, a coherent translational pathway from "mechanistic rationality" to "clinical feasibility" has been initially established, providing a solid basis for subsequent high-quality clinical validation.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study conception, outline of the manuscript (YuanG), drafting of the manuscript (YuanG, YunG), figure preparation, literature search (YunG), critically revised the manuscript, final quality control (ZH, DJ). All authors have approved the final version and publication of the manuscript.

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