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Letter to the Editor

SGLT2 Inhibitors: A New Dawn for Recurrent/Refractory Cirrhotic Ascites

Yuan Gao[1], Lai Wei[2], Dorothy Da Zhang[3], Yu Chen[1] and Bing Hou[3*]

[1]Department of Hepatology, Youan Hospital, Capital Medical University, Beijing, China; [2]Hepatopancreabiliary Center, Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China; [3]Xenorm MedInfo Center, Beijing, China

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To the editor,

There remains a huge unmet need for treatment of cirrhotic ascites. In this letter, we propose that the sodium-glucose cotransporter-2 (SGLT2) inhibitor may be a promising complement for current therapy.

Ascites is the commonest complication of decompensated liver cirrhosis, and it significantly deteriorates quality of life and shortens survival. Loop diuretics and mineralocorticoid receptor antagonists are the mainstay of pharmacological treatments,[1] but decades of use have brought little survival benefit. Moreover, recurrent or refractory ascites often leads to unplanned re-hospitalization for patients with decompensated cirrhosis and consequently causes a substantial economic burden.

Renin-angiotensin-aldosterone-system (RAAS) overactivation and a subsequent reduction in urinary sodium excretion are the pivotal mechanisms of ascites formation.[1] Thus, the pharmacological treatment aims to achieve a negative sodium balance by promoting natriuresis. By inhibiting the sodium-potassium-chloride cotransporter 2 and then increasing sodium chloride concentration in the luminal fluid of distal convoluted tubule, loop diuretics exert their prominent natriuretic effect during the acute phase of ascites treatment. However, prolonged use of loop diuretics can induce renal adaption, which increases reabsorption of sodium in the distal segments of the nephron and results in a gradual decline in net sodium excretion. With reduced sodium excretion, the diuretic effect of loop diuretics would be greatly attenuated, which is termed "braking phenomenon".[2] Moreover, inhibition of the sodium-potassium-chloride cotransporter 2 in macula densa cells by loop diuretics, such as furosemide, will in turn stimulate renin production to further activate RAAS (Fig. 1).

As a neurohormonal modulator, spironolactone is often used to block mineralocorticoid receptors and counteract RAAS overactivation. In clinical practice, it is nevertheless challenging to titrate the optimal dose of spironolactone because of its very slow pharmacokinetic characteristics.[3] More seriously, the dose-dependent hyperkalemia and gynecomastia may lead to drug dose reduction or discontinuation. Notably, in ascitic condition, sodium reabsorption is increased mainly at the proximal convoluted tubule, which results in a significant decrease in sodium concentration in distal nephron segments.[4] Consequently, diuretics acting on distal nephron segments, such as loop diuretics or mineralocorticoid receptor antagonists, frequently fail during the treatment of advanced ascites, even in patients with normal renal function. Given the above, novel treatments for recurrent/refractory cirrhotic ascites are needed.

SGLT2 inhibitors have shown promise as a treatment of ascites. They belong to a class of oral medications used to treat type 2 diabetes that act through inhibiting the reabsorption of glucose and sodium in the proximal convoluted tubule (Fig. 1).[5] The mechanism suggests that they might be synergistic with loop diuretics and mitigate the braking phenomenon.[6] In fact, their ability to promote urinary excretion of solutes leads to regulatory approval for the treatment of advanced heart failure in nondiabetic patients in the US and Europe.[7] As both advanced heart failure and decompensated liver cirrhosis are characterized by overactive RAAS and fluid-sodium retention, it is plausible that SGLT2 inhibitors may also be suitable for treating recurrent/refractory cirrhotic ascites.[8]

It is encouraging that regression of ascites and lower extremity edema have been reported after treatment of patients with cirrhosis and comorbid diabetes with SGLT2 inhibitors without obvious adverse events.[8,9] The correction of hyponatremia observed in these case reports suggests that SGLT2 inhibitors may facilitate normalization of RAAS (Table 1). If so, such drugs would complement current pharmacological treatments for ascitic patients. Given that the benefits of SGLT2 inhibitors in patients with advanced heart failure are independent of glycemia, they merit further investigation in patients with cirrhotic ascites regardless of the presence or absence of comorbid diabetes.

Safety is always the first priority when a new class of agents is introduced into the treatment of cirrhotic ascites. Current data show that the risks of liver dysfunction or hypoglycemia associated with SGLT2 inhibitors in patients without diabetes are not greater than those associated with placebo.[7] Moreover, hepatic impairment has no appreciable impact on the pharmacokinetics of SGLT2 inhibitors.[10] Initial dip of estimated glomerular filtration rate and mild blood pressure drop observed with SGLT2 inhibitors have raised concerns of hepato-renal syndrome, but such changes are not found to alter the state of RAAS.[6]

Abbreviations: RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.

***Correspondence to:** Bing Hou, Xenorm MedInfo Center, No. 30 Xueyuan Road, Beijing 100083, China. ORCID: https://oricd.org/0000-0002-4613-1095. Tel/Fax: +86-10-88443312, E-mail: hou_bing@hotmail.com

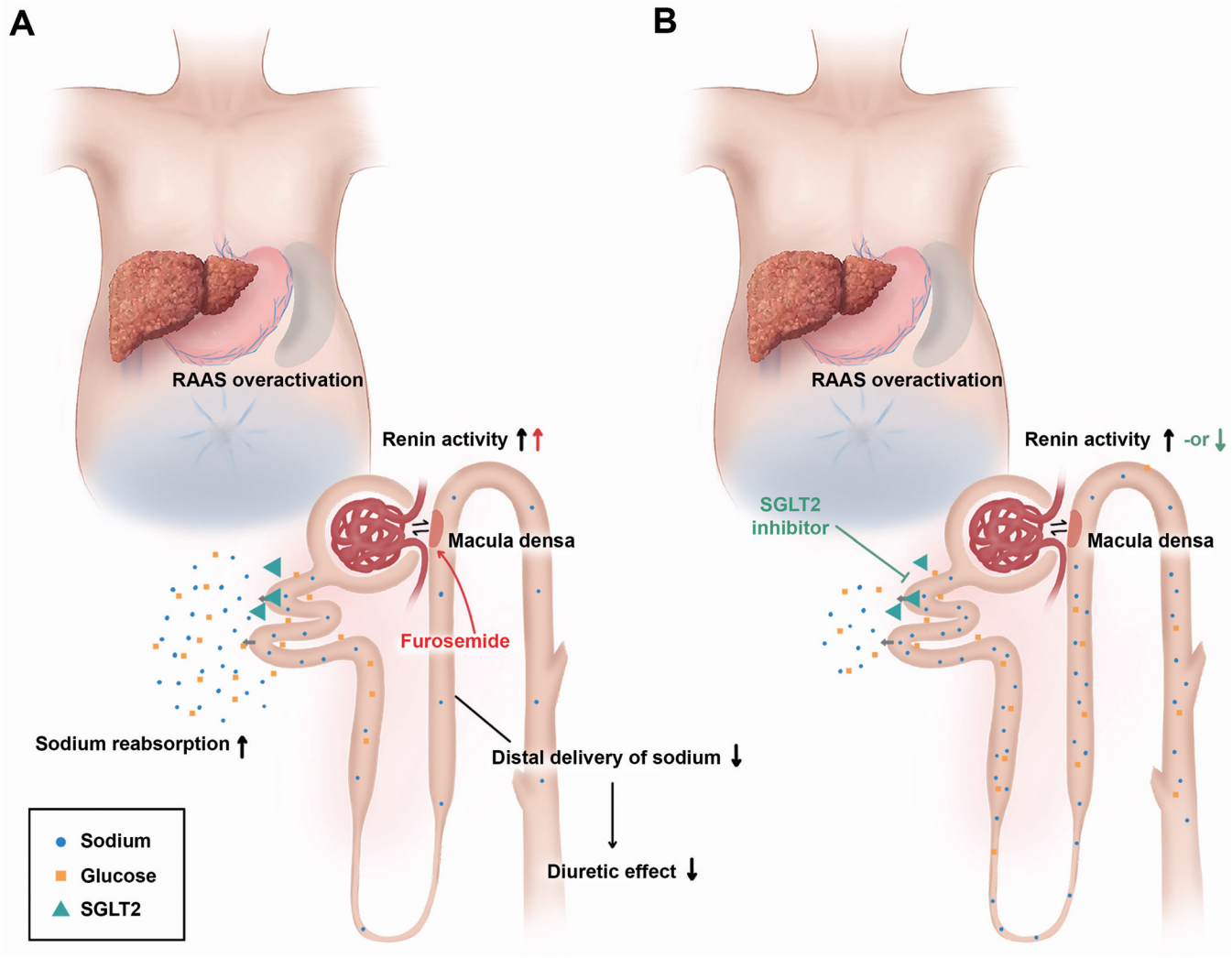

Fig. 1. Pathophysiology of cirrhotic ascites and the mechanism of action of SGLT2 inhibitors. (A) In cirrhotic ascites, overactivation of RAAS results in marked increase of sodium reabsorption at the proximal tubule and reduction of solute delivery to the distal nephron. Loop diuretics such as furosemide inhibit the Na-K-2Cl cotransporter in macula densa cells, which leads to further increase of renin secretion. (B) SGLT2 inhibitors inhibit the reabsorption of glucose and sodium in the proximal tubule but not sodium sensing at the macula densa. As a result, SGLT2 inhibitors promote urinary excretion of solutes without stimulating further secretion of renin. RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.

Although SGLT2 inhibitors seem unlikely to trigger hepatorenal syndrome in absence of an aggravation of RAAS status, an exploratory study is need to investigate their effects on sodium excretion and neurohormonal changes among patients with cirrhotic ascites. As SGLT2 inhibitors prompt urinary glucose excretion, there may be concerns of an increased risk of urogenital infection in cirrhotic patients, who are generally immunocompromised. Given that the amount of glucose excreted following administration of SGLT2 inhibitors is dependent on the plasma glucose level, this uncommon complication might be less pronounced in cirrhotic patients, especially those with normal plasma glucose level. Nevertheless, the issue should be taken into account in future clinical trials.

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Conflict of interest

LW has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2013. Other authors have no conflict of interest related to this publication.

Author contributions

YG and BH conceived the manuscript, YG and DZ drafted the manuscript, and YG, LW, YC, and BH revised the manuscript.

Table 1. Characteristics and clinical outcomes of cirrhotic patients with fluid retention and receiving SGLT2 inhibitors

Patient	Age (y)	Sex	Signs and symptoms	SGLT2 inhibitors used	Serum Na/K (mmol/L)		Body weight (Kg)		Fasting glucose (mg/dL)		Outcomes
					Baseline	After treatment	Baseline	After treatment	Baseline	After treatment	
No. 1 [Ref. 8]	63	F	Ascites and peripheral edema; Discontinuation of diuretics for encephalopathy	Empagliflozin	139/4.2	140/4.2	63	58.1	86	90	Free of ascites, edema and encephalopathy
No. 2 [Ref. 8]	64	F	Ascites and poorly controlled diabetes; Discontinuation of diuretics for severe hyponatremia	Canagliflozin	120/4.1	141/4.7	57.6	51	140	121	Hyponatremia corrected; Free of ascites and edema (off diuretics)
No. 3 [Ref. 8]	53	M	Severe peripheral edema without ascites and diuretics-related acute kidney injury	Canagliflozin	135/4.9	145/4.4	81	69.9	187	151	Free of ascites and edema
No. 4 [Ref. 9]	54	F	Hepatic hydrothorax, peripheral edema, refractory ascites and deteriorating hyperglycemia	Empagliflozin	133/4.39	140/3.71	NS	NS	286	116	Hepatic hydrothorax improved dramatically; Free of ascites and edema (off diuretics); Hemodynamic index and renal function improved

NS, not specified.

All authors approved the final version of the manuscript.

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