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# Dietary salt in liver cirrhosis: with a pinch of salt!

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**Abstract**

Patients with liver cirrhosis are advised to limit their sodium consumption to control excessive fluid accumulation. Salt is the most common form in which sodium is consumed daily. Consequently, various recommendations urge patients to limit salt intake. However, there is a lack of consistency regarding the salt restriction across the guidelines. Moreover, there is conflicting evidence regarding the efficacy of salt restriction in the treatment of ascites. Numerous studies have shown that there is no difference in ascites control between patients with restriction of salt intake and those without restriction. Moreover, patients with cirrhosis may have several negative effects from consuming too little salt, although there are no recommendations on the lower limit of salt intake. Sodium is necessary to maintain the extracellular fluid volume; hence, excessive salt restriction can result in volume contraction, which could negatively impact the kidney function of a cirrhotic patient. Salt restriction in cirrhotic patients can also compromise nutrient intake, which can have a negative impact on the overall outcome. There is insufficient evidence to recommend restricted salt intake for all patients with cirrhosis, including those with severe hyponatremia. The existing guidelines on salt restriction do not consider the salt sensitivity of patients; their nutritional state, volume status and sodium storage sites; and the risk of hypochloraemia. This opinion article aims to critically analyse the existing literature with regard to the salt recommendations for patients with liver cirrhosis and identify potential knowledge gaps that call for further research.

## INTRODUCTION

Sodium is essential for fluid balance and cellular homeostasis.[1] Under normal conditions, effective sodium balance, and hence extracellular fluid volume, is maintained by a complex interplay between various systems that regulate renal sodium excretion.[2] For example, a progressive increase in sodium intake activates natriuretic systems while suppressing the sodium retaining systems to maintain effective sodium balance. However, in patients with liver cirrhosis, portal hypertension-related splanchnic vasodilatation reduces effective arterial blood volume, which in turn activates the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) and, in later stages, the arginine vasopressin, all of which result in renal sodium and fluid retention and, eventually, ascites.[3] Therefore, limiting sodium intake is suggested for the treatment of ascites in such patients.[4] Salt is the most common source of sodium consumed by humans; hence, the guidelines have focused on dietary salt restriction to achieve sodium limitation.

The data on the effectiveness of salt restriction for the management of ascites are not conclusive,[5–7] and there are still many inconsistencies in the guidelines for salt recommendations for patients with liver cirrhosis.[8–11] Although the guidelines have suggested the upper limit, a lower limit for salt consumption was not included. Severe salt restriction could potentially result in hyponatremia and cause volume contraction, which might adversely affect the kidney function of a cirrhotic patient. Salt restriction in cirrhosis compromises nutrient intake and has a negative impact on the overall outcomes.[12,13] There is a paucity of evidence regarding dietary salt recommendation for patients with compensated cirrhosis and decompensated cirrhosis with severe hyponatremia.[14,15] The ability of salt to expand extracellular volume, known as salt sensitivity, varies among individuals; thus, a 'one size fits all' approach to dietary salt recommendations may not be appropriate.[16] Furthermore, a new finding indicating

that sodium is also stored in a third compartment (interstitium and endothelial surface layer) in a non-osmotic equilibrium can have significant impact on our understanding of sodium intake and homeostasis in cirrhotic patients.[17] This opinion article covers all the aforementioned issues and emphasises the knowledge gaps and the need for additional research in the area.

## SALT AND CIRRHOSIS: IMPORTANT ISSUES

### How much salt should cirrhotic patients consume, and are the current recommendations supported by data?

The recommended limits of salt consumption for cirrhotic patients with ascites varies from 4.6 g to 6.9 g per day, although most guidelines recommend around 5 g of salt, which corresponds to a teaspoon of cooking salt [Table 1]. As per current recommendations, salt restriction should be considered for all cirrhotic patients with ascites, including those with refractory ascites. When it comes to the grade of ascites at which salt restriction should start, the International Ascites Club suggests grade 1, and the European Association for the Study of the Liver (EASL) suggests grade 2; however, the American Association for the Study of Liver Diseases (AASLD) does not provide any specific grade of ascites to this purpose.[8,9,11] The goal of salt restriction is to avoid sodium overload. Hence, the net sodium intake must be equal or lower than the sodium excretion; this can be achieved either by lowering the dietary salt intake or by increasing natriuresis using diuretics. For patients with grade 2 or higher ascites, salt restriction alone would be insufficient and diuretic therapy would need to be implemented. The first-line diuretics are often aldosterone antagonists, such as spironolactone, which can be administered alone or in conjunction with a loop diuretic such as furosemide. Restriction of fluid intake is required only in patients with dilutional hyponatraemia.

Several studies, including randomised controlled trials (RCTs), have examined the role of salt restriction in patients with cirrhosis and ascites.[5,6,7,12,13,18] The amount of salt

restriction ranged from a salt-free diet to 7 g of salt per day. The majority of these studies are old with varying methodology and sub-optimal quality, making it challenging to draw clear conclusions. Some of these studies found a faster elimination and better control of ascites with strict salt restriction.[5,6] Some studies found no difference in ascites control between patients with and without salt restriction.[12,18] Furthermore, two recent RCTs found that a salt-unrestricted diet (5–6.5 g/day) was superior than a salt-restricted diet (5 g/day) in resolving ascites in a larger proportion of patients (45% *vs* 16%) and in reducing the need for large volume paracentesis.[7,13] Authors proposed that worsening hyponatremia caused by salt restriction can weaken the effects of diuretics and reduces renal blood flow, both of which worsen ascites.[7] This idea is further supported by research showing that the use of hypertonic saline solutions in conjunction with diuretics enhance fluid mobilisation in patients with cirrhosis and refractory ascites.[19] The proposed mechanisms for these advantageous effects of salt loading include an increase in intravascular volume, an osmotic shift of fluid from the tissues, an increase in renal blood flow and a decrease in sympathetic tone. For the management of ascites in cirrhosis, each of these pathways is important. Therefore, although managing ascites is the fundamental premise of salt restriction in cirrhosis patients, there is conflicting evidence with regard to this claim.

**What adverse effects might cirrhosis patients experience with a salt-restricted diet?**

The significant adverse events with salt restriction reported by various studies include hyponatraemia, reduced caloric intake, higher risk of renal impairment, hepatic encephalopathy and mortality.[5,6,7,12,13] In a randomised trial, Reynolds *et al.* concluded that unrestricted salt intake decreased the likelihood of hyponatraemia and azotaemia.[5] The risk of hyponatremia is significantly increased by concurrent use of diuretic medication. Severe salt restriction makes the food unpalatable and alters dietary patterns, which might promote protein-calorie malnutrition and increase mortality risk.[4,20,21] Notably, malnutrition and sarcopenia are already prevalent in

patients with advanced cirrhosis.[22,23] In a study on cirrhotic patients with ascites requiring repeated paracentesis, salt restriction without nutritional support resulted in 3· 9-fold higher risk of mortality within one year, compared to that of unrestricted sodium intake with nutritional support.[13] In the small intestine, sodium absorption facilitates the absorption of chloride, amino acids, glucose and water.[24] Thus, severe salt restriction may affect the absorption of these substances, contributing to malnutrition.

Another issue concerns compliance with salt-restricted diet. The average salt consumption by the general population is significantly above the levels recommended by the World Health Organization. A recent systemic review reported that most European countries consume between 4.2 g to 18.5 g of salt per day per capita.[25] Salt intake in India and China is about 10 g per day.[26,27] A cross-sectional survey indicated that only about a third of cirrhotic patients were compliant with salt restriction, with an additional 45% incorrectly stating that they were.[28] Another potentially significant but unappreciated issue with low salt consumption, particularly with concurrent diuretic medication, is the development of hypochloraemia, i.e., a low level of serum chloride. Serum chloride, the most important anion in the blood, has received less attention in cirrhosis patients, even though hypochloraemia has been recognised as an important prognostic marker in patients with advanced cirrhosis. According to the findings of two recent studies, hypochloraemia may be an even better predictor of mortality in patients with decompensated cirrhosis than serum sodium.[29,30] The chloride reabsorption in renal tubule constitutes a crucial process for the auto-regulation of the acid-base balance as well as the electrochemical equilibrium. Moreover, hypochloraemia causes activation of the RAAS and the upregulation of NaCl channel in the distal convoluted tubules, which can aggravate sodium retention and contribute to diuretic resistance.[31]

Thus, existing evidence tends to suggest that severe salt-restricted diets (<5 g /day) may not significantly improve ascites control and could even lead to complications.

Considering the excessive salt consumption by the general population, a moderate salt restriction, with daily salt intake of no more than 5–6.5 g may be advisable for such patients. This translates to a 'no added salt diet' with avoidance of high sodium containing meals. Table 2 provides a list of foods with high sodium content so that doctors can counsel patients on their consumption. Also, one must be mindful while recommending salt restriction in advanced cirrhosis patients with hyponatremia because such patients generally have relative hypovolemia where salt restriction could cause volume contraction and renal dysfunction.

**Is unrestricted salt intake justified for patients with compensated cirrhosis?**

For patients with preascitic compensated cirrhosis, guidelines do not recommend a dietary salt restriction. Nonetheless, a study has found that even compensated cirrhosis patients retain sodium when faced with a high salt intake.[14] However, compensatory activation of atrial natriuretic peptide and inhibition of the RAAS result in a new steady state of sodium balance in such patients, which tends to prevent ascites. Nevertheless, Jalan *et al.* found that the degree of portal hypertension had a significant impact on the sodium handling capacity in patients with compensated cirrhosis.[15] In fact, it is now believed that clinically significant portal hypertension (CSPH) is the main driver of decompensation in cirrhotic patients.[32] Compensated cirrhotic patients with baseline hepatic venous portal gradient >20 mmHg had a 47% risk of decompensation in a mean duration of just 1.6 years, compared to <10% over 4 years when it is <10 mmHg.[33,34] Therefore, it is reasonable to assume that the compensatory natriuretic mechanism might get overwhelmed with the rising portal pressure, and as a result, sodium retention on a high dietary salt intake may result in decompensation in the form of ascites in compensated cirrhosis patients. Hence, until further data emerge, salt restriction may be considered in compensated cirrhotic patients with CSPH. This extrapolation, however, needs to be tested in a controlled trial.

**What are the implications of high salt intake for cirrhotic patients and the general population?**

Studies from different countries found the dietary salt intake in the general population at around 10 g per day.[25–27] Directly or indirectly, a high salt consumption adversely affects multiple organs in the body and may have some serious implications in patients with liver cirrhosis. Consuming excessive amounts of salt has been associated with oxidative stress, insulin resistance, vascular endothelial damage, sympathetic nerve sensitization, alteration of gut-microbiome and an increased risk of cancer [Figure 1]. There is a strong positive association between dietary salt intake and cardiovascular diseases.[35] Therefore, the World Health Organization has recommended a daily salt intake of less than 5 g per day, which is approximately 2 g of sodium, for the general population.[36] According to this viewpoint, the dietary salt recommendation for advanced cirrhosis patients is similar to that of the normal healthy population. In a population-based study, subjects with intermediate salt intake (6–10 g/d) and high salt intake (>10 g/d) were found to have a higher risk of hepatocellular carcinoma with multivariable hazard ratio (HR) of 1.49 and 1.9, respectively, compared to those with low salt intake (<6 g/d).[37] A recent cohort study from Iran reported that a high dietary intake of salt (9.5–15 g/d) increases the rate of mortality in patients with cirrhosis [HR 2.26]. Moreover, moderate salt restriction (daily salt of 3–5 g), as compared to salt elimination, decreases the risk of death [HR 0.72].[38]

**What could be the implications of salt sensitivity and third space sodium storage in patients with liver cirrhosis?**

The ability of salt to expand extracellular volume, known as salt sensitivity, varies among individuals. It is estimated that around 26% of normotensive and 51% of hypertensive persons are salt sensitive.[39,40] The rest of the individuals are salt resistant – their hemodynamic parameters are likely to be unaffected due to change in dietary salt consumption. Although the relevance of salt sensitivity in cirrhotic patients has never been assessed in the context of dietary salt intake, extrapolation of data from the

general population suggests that between half and three-quarters of patients would be salt resistant. It would be safe to assume that a major restriction in the dietary salt consumption at the cost of nutritional compromise would be undesirable in a large number of patients. Therefore, instead of having a 'one size fits all' salt recommendation for cirrhotic patients, the salt sensitivity of individual patients should also be considered.

Recently, a third compartment (skin interstitium and endothelial surface layer) of sodium storage sites, in which sodium can accumulate in a non-osmotic equilibrium and hence without concurrent water retention, have been identified.[41,42] This can have implications for sodium homeostasis, osmoregulation and the hemodynamic response to salt intake, all of which are quite relevant to patients with cirrhosis. In the third space, sodium can be osmotically inactivated following binding to negatively charged glycosaminoglycans.[42] Due to the changes in the dynamics of the interstitium, alterations in glycosaminoglycans and endothelial damage in cirrhotic patients, the amount of dietary salt intake can affect sodium homeostasis. Moreover, high interstitial sodium concentrations stimulate lymphangiogenesis *via* vascular endothelial growth factor-C, which helps in the mobilisation of excess fluid from the skin *via* lymphatics.[43] Therefore, it would be interesting to see whether a salt-restricted diet worsens a pre-existing lymphatic dysfunction in patients with advanced cirrhosis.[44]

**What are the practical issues with ensuring a pre-defined sodium consumption?**

Measuring sodium intake in individuals is challenging as sodium is so widespread in food items. Even with extensive food labelling, it is often difficult to quantify the sodium content of food. Commonly used approaches include 24-hour urine sodium measurement, 24-hour dietary recall and food-questionnaires.[45] Dietary sodium *intake* can be calculated by dividing the urine sodium excretion by 0.9, based on the assumption that 10% of sodium intake is lost through sweat and faeces, and thus urinary excretion accounts for 90% of intake. Thus, a 24-hour urine collection is

considered the most reliable method. However, a systematic review found that measured urinary sodium varied as widely as 76%–122% of ingested sodium amount, making it a 'not so reliable' test.[46] Thus, most of these methods would only give us a rough estimate of sodium consumption. Because moderate salt restriction might make the foods unappealing and affect overall nutrition, some strategies need to be adopted in order to ensure adequate nutrients intake. One of the strategies is to partially substitute sodium with potassium or other minerals, such as calcium or magnesium.[47] However, there are concerns about possible negative effects of such a replacement, such as hyperkalaemia with potassium-based salt, especially in cirrhotic patients with renal impairment or those taking potassium sparing diuretics. Additionally, flavours and sensory experiences can be imparted using herbs, spices and yeast extract. When used as salt alternatives, they have demonstrated good customer acceptance.[48]

## CONCLUSION

The inconsistencies in the recommendations for salt intake and conflicting evidence regarding the effectiveness of salt restriction for controlling ascites in cirrhotic patients necessitate further research.Presently, the term 'salt restriction' for cirrhotic patients appears to be a misnomer, given that the salt recommendation for normal populations is also the same. However, it is necessary to carefully evaluate the efficacy of varied levels of salt intake at various stages of cirrhosis, including those who also have concurrent hyponatraemia. Studies on salt restriction must consider the patients' salt sensitivity, nutritional status, volume status, sodium storage sites and hypochloraemia risk. The innovative ideas in this area would be to evaluate the efficacy and safety of low-sodium salt substitutes (such as potassium-based salt) and find ways to make low-sodium foods more palatable (by utilising herbs, spices and yeast extract, *etc.*) to ensure appropriate nutrition.

Until further data emerges, it seems appropriate for cirrhotic patients with ascites to consume 5–6 g of salt per day, which would mean avoiding foods with added salt. To increase adherence, prevent malnutrition and avoid harmful effects of excess salt consumption, it is crucial to educate patients about the recommended salt limit. A formal consultation with a nutritionist may be sought. It is necessary to set a lower limit for salt consumption since too much salt restriction has just as many negative effects as too much consumption. Finally, a personalised salt management, depending on the sodium balance, nutritional status and volume status of the patient may be required for some of these patients.

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