Aside from the many metabolic and synthetic functions of the liver, it also plays a crucial part in the maintenance of other organ systems. This is why any alterations in its functions, such as in liver cirrhosis and portal hypertension can result in detrimental effects on the major organs and tissues remote from the liver such as the lungs, heart, and kidneys. Although liver diseases can affect different extrahepatic organ systems, there is somewhat a similar pattern when it comes to the development of the pathophysiology. One of the many extrahepatic syndromes that can manifest in patients having liver problems such as cirrhosis and portal hypertension is the hepatorenal syndrome.

Overview

The term hepatorenal syndrome has been around since 1932. It was used to describe the kidney failure that is associated with biliary tract surgery. Later on, studies have shown that this kidney failure is a result of the massive alterations in the splanchnic arterial vasculature present when there is liver cirrhosis or acute liver injury.

In fact, one may not be able to observe any histopathological abnormalities at all, except
in some cases where there is a **coexisting renal disorder**. With this in mind, restoration of function following the correction of the main problem is very much possible in patients with hepatorenal syndrome.

**Epidemiology of Hepatorenal Syndrome**

Hepatorenal dysfunction occurs in almost ¼ of all the patients hospitalized for liver cirrhosis. Among the cases, **prerenal azotemia** is the most common cause of kidney failure, with **acute tubular necrosis** as the second.

Hepatorenal syndrome commonly occurs with some of the other complications associated with liver cirrhosis. To name a few, it could exist with **ascites**, **spontaneous bacterial peritonitis**, and **other infections**.

The **high morbidity and mortality** associated with hepatorenal syndrome, along with its **reversible nature** has led the management of patients having this condition to be focused on **prevention and prompt management**.

**Pathophysiology of Hepatorenal Syndrome**

![Image: "Figure demonstrating the correlation between hemodynamics and clinical consequences in ascites and hepatorenal syndrome" by Samir. License: CC BY 3.0](image)

Because of the complexity of the events leading to hepatorenal syndrome, the knowledge base of the pathogenesis of the condition is still yet to be completed. However, there are 3 main components known that contribute to the development of the syndrome. These are the following:

- Splanchnic and systemic arterial vasodilation
- Renal vasoconstriction
- Cardiac dysfunction

**Splanchnic arterial vasodilation**

The overall decrease in the blood pressure that happens during the progression of portal hypertension in patients with **liver cirrhosis** can be attributed to the splanchnic and systemic arterial vasodilation. The vasodilation leads to the pooling of blood in the splanchnic beds and in the dependent areas of the body, resulting in the **decrease in**
the circulating blood volume. All these events are known to be mediated by certain substances such as:

- Nitric oxide
- Carbon monoxide
- Glucagon
- Prostacyclin
- Adrenomedullin
- Endogenous opiates

Early in the progression, the body tries to compensate for the decreased circulating blood volume by **increasing the heart rate and cardiac output**. More and more compensatory mechanisms are activated as the splanchnic arterial vasodilation continues on until all of these are exhausted.

### Renal artery vasoconstriction

The decrease in the circulating blood volume resulting from the previous mechanism also triggers the **kidney** to conserve water and salts. This leads to a compensatory renal vasoconstriction, and sodium and water retention. This is done through the activation of the **renin-angiotensin-aldosterone system or RAAS**.

![The renin-angiotensin-aldosterone system increases blood volume and pressure](Image)

Other mechanisms involved include the **activation of the sympathetic nervous system**, release of the **arginine vasopressin** and other intrarenal mechanisms. Intrarenal events that lead to renal vasoconstriction may include the alteration in the release or activation of vasoactive substances such as **endothelins**, **prostaglandins**, **kallikreins**, and **F2-isoprostanes**.

The maintained decrease in the **circulating blood** volume leads to a continual increase in **renal vascular resistance** resulting in a decrease in the **renal perfusion** and **glomerular filtration rate**.
Cardiac dysfunction

Many studies have suggested that the coexistence of impaired cardiac function and liver cirrhosis has greatly contributed to the development of hepatorenal syndrome in patients with liver cirrhosis. In patients who primarily have liver cirrhosis, cardiac function may be impaired due to the decrease in the cardiac perfusion resulting in poor cardiac output.

Clinical Features of Hepatorenal Syndrome

Hepatorenal syndrome is mainly an impairement in the function of the kidney and is not necessarily accompanied by structural defects. Therefore, imaging tests may not be helpful in coming up with a diagnosis. The diagnosis is done by exclusion of other causes of kidney dysfunction.

Certain criteria set by the International Ascites Club Consensus Workshop in the year 2007 are used in order to aid in the diagnosis of hepatorenal syndrome. These are the following:

- Cirrhosis with ascites
- Serum creatinine level ≥ 1.5 mg/dL
- Lack of improvement in the serum creatinine level to ≤ 1.5 mg/dL after at least 2 days of diuretic withdrawal and intravenous volume expansion with albumin
- Absence of shock
- No recent use of nephrotoxic agents
- Absence of intrinsic renal disease

It is important to note that for patients who have not had any history of kidney disease, an increase in the serum creatinine level by 50 % beyond the baseline to a level higher than 1.5 mg/dL should be used as a criterion.

Medication taken by the same patient should also be assessed prior to coming up with a diagnosis of hepatorenal syndrome because many medications such as diuretics, lactulose, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs can cause alterations in the intravascular volume and pressure status.

Classification of Hepatorenal Syndrome

Hepatorenal syndrome is classified into 2 types:

**Type 1** - rapidly progressive; serum creatinine may reach levels higher than 2.5 mg/dL in less than 2 weeks; mostly caused by instances where hemodynamic stability is severely declined in the presence of liver cirrhosis (e.g. severe bacterial infections, gastrointestinal bleeding, surgical procedures, acute liver injury).

**Type 2** - progresses slowly as compared to type 1 but is still very fatal (median survival of only 6 months); serum creatinine levels rarely go beyond 2.5 mg/dL; can be seen in patients with severe ascites; may be followed by type 1 hepatorenal syndrome once hemodynamic instability ensues or any of the aforementioned triggers occur.

Management and Prevention of Hepatorenal
Syndrome

As mentioned, the reversible nature of the disease coupled with the fatal outcomes if the hepatorenal syndrome is untreated has put a lot of emphasis on the preventive aspect of the management.

Prevention:

- Intravascular volume is maintained in patients with liver cirrhosis by addressing problems such as overdiuresis, diarrhea, gastrointestinal bleeding, and large-volume paracentesis.

- Other factors that can contribute to kidney failure such as the presence of nephrotoxins and infections such as spontaneous bacterial peritonitis and bacteremia should also be managed.

- Bleeding from esophageal and gastrointestinal varices is prevented by prophylactic pharmacologic and surgical modalities. Prophylactic antibiotics may be given to avert infections while intravenous colloids such as albumin are administered to restore intravascular volume.

Medical therapy

- Certain medications are administered to address the vascular changes associated with liver cirrhosis in an effort to restore intravascular volume and normal arterial pressure.

  - Terlipressin- A vasopressin 1 receptor agonist vasoconstrictor that is still currently evaluated by the FDA for use in patients with hepatorenal syndrome. It is associated with cardiovascular adverse effects when used without albumin. Hence, its use should be closely monitored. Studies have shown that patients with a less severe renal dysfunction respond better to this drug which supports its use early in the course of the disease.

  - Midodrine and octreotide- An α1-adrenergic agonist and a somatostatin analog respectively which work to antagonize endogenously produced vasodilators. It is used with albumin in some studies and was found to have
favorable results with regards to the serum creatinine level and arterial pressure. Since it is only orally administered and has a good safety profile, it is preferred over other medical regimens, although its efficacy is not yet established.

- **Norepinephrine**—An intravenously administered \( \alpha_1 \)-adrenergic agonist that is also used with albumin that has been suggested to be preferred over terlipressin by 2 studies. Like terlipressin, however, it also has significant cardiovascular effects.

### Radiologic and surgical therapy

- **Transjugular intrahepatic portosystemic shunt:** One way to decrease the pressure in the portal circulation is by inserting a shunt directing blood from the portal circulation towards the systemic circulation. This decreases the pressure in the portal circulation, thereby relieving the splanchnic bed from the reflex vasodilation. This improves venous return and ultimately the overall circulation. It has been proven to be highly effective for patients with **type 2 hepatorenal syndrome**. However, this modality is known to worsen the existing liver dysfunction due to alterations in the blood supply of the liver.

- **Liver Transplantation:** This modality is highly suggested for patients with liver disease who wish to reverse the renal manifestations. However, it has been proven that patients who undergo liver transplantation even before the hepatorenal syndrome has occurred have better outcomes as compared to those who already have hepatorenal disease at the time of undergoing the procedure.

- Studies have also demonstrated that the use and favorable response of medical regimens such as vasopressin analogs prior to the performance of the surgery has outcomes that are comparable to those who have undergone the surgery with no medications beforehand. This affirms the use of medications before finalizing the decision to perform surgery in cases of hepatorenal syndrome.

- A recent increasing trend in care of patients with hepatorenal syndrome is Simultaneous Liver Kidney Transplantation. Patients who are recommended SKLT include those with (1) eGFR of 30 mL/min or less for 4-8 wk; (2) proteinuria > 2 g/d; and (3) biopsy proven interstitial fibrosis or glomerulosclerosis.

### Others

- There are still other treatment modalities that are being studied and tested recently. One of which is the use of **extracorporeal albumin dialysis with molecular adsorbent recirculating system** (MARS). This procedure is able to remove the toxins that are water-soluble and albumin-bound in the systemic circulation, thereby decreasing the overall creatinine levels.

- Another approach that is being developed is the use of **vasoconstrictive medical therapies** such as dopamine and octreotide with albumin. However, studies have shown that there is still much to be improved in this area of management for patients with hepatorenal syndrome.
Prognosis

- Recovery of renal function is commonly seen with liver transplant. The prognosis is poor unless transplant is performed within a short period of time.
- MELD scores are 75 to 80% accurate in predicting survival in HRS patients. MELD score uses the INR, serum bilirubin, serum creatinine, and etiology of cirrhosis to stratify patients based on risk.

Review Question

The correct answer can be found below the references.

Which among the following data gathered from a patient who does not have a history of renal disease is important to consider in coming up with a diagnosis of hepatorenal syndrome?

A. A rise in the serum creatinine level from 0.6 mg/dL to 1.3 mg/dL
B. Urine output of 60 cc/hr
C. Mean arterial pressure of 80 mm Hg
D. Heart rate of 102 bpm

References


Correct answer: A

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