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Review Article

Definition, Etiology, Pathophysiology and Management of Liver Cirrhosis

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Abstract

Cirrhosis can be defined histologically as a diffuse process in which the normal anatomical lobules are replaced by architecturally abnormal nodules separated by fibrous tissue. Stage 3 cirrhosis encloses the advancement of swelling in the abdomen and advanced liver scarring. The etiology of cirrhosis differs based on geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease being the consummate ubiquitous causes in western countries, whereas chronic hepatitis B is the initial cause of liver cirrhosis. The transition from chronic liver disease to cirrhosis encloses inflammation, initiation of hepatic stellate cells with following fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion. Only abstinence from alcohol ameliorates survival in alcoholic cirrhosis. Treatment of the underlying disease can frequently impasse or even reverse the progression of early-stage cirrhosis. The mainstay of primary prophylaxis is the use of nonselective β-adrenergic blocking agents such as propranolol or nadolol. Somatostatin and octreotide cause a reduction in portal pressure and port-collateral blood flow through inducing splanchnic vasoconstriction without causing the systemic effects consociated with vasopressin. Prophylactic antibiotic therapy should be prescribed for all patients with cirrhosis and acute variceal bleeding.

Keywords: Definition, Etiology, Liver Cirrhosis, Pathophysiology, Management

Introduction

Cirrhosis results from different mechanisms of liver injury that lead to necro-inflammation and fibrogenesis; histologically it is characterized by diffuse nodular regeneration enveloped by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture.[1,2] Cirrhosis is an advanced stage of liver fibrosis accompanied by vascular remodeling. It is the end sequence of any chronic liver disease for which liver transplantation is the only curative option.

Stage of Liver Cirrhosis

Cirrhosis in itself is already a late stage of liver affliction. There are four stages of liver cirrhosis: Stage I: Cirrhosis encloses certain scarring of the liver, but few symptoms. This stage is thought-out as compensated cirrhosis, where there are no complications, Stage II: cirrhosis involves worsening portal hypertension and the advancement of varices; Stage III: cirrhosis encloses the development of swelling in the abdomen and advanced liver scarring. This stage marks as decompensated cirrhosis, with serious complications and possible liver failure; Stage IV: Cirrhosis can be life threatening and people have developed end-stage liver disease, which is fetal without a transplant. The natural history of cirrhosis is ordinarily characterized by an asymptomatic stage of compensated cirrhosis pursued by a symptomatic stage of decompensated cirrhosis. In clinical practice, decompensated cirrhosis is delineated by complications owing to portal hypertension and impaired liver function, enclosing ascites, varicella haemorrhage, hepatic encephalopathy and jaundice.[3]

Etiology of Liver Cirrhosis

The most common causes of cirrhosis are chronic liver diseases affiliated to alcohol consumption (alcoholic liver disease (ALD)), hepatitis C virus infection and obesity and/or other components of the **metabolic liver disease** (hemochromatosis; Wilson's disease; alpha 1-antitrypsin deficiency; nonalcoholic steatohepatitis ("fatty liver"); cystic fibrosis). Escalating evidence from animal studies indicates that the translocation of bacteria and bacterial products (e.g. endotoxin) from the intestinal lumen into the systemic circulation, sequencing in endotoxemia, is a contributing factor in the pathogenesis of several chronic liver diseases by inducing inflammatory changes in the liver.[4,5] The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease (NAFLD) being the consummate ubiquitous causes in western countries,[6-8] whereas chronic hepatitis B is the primary cause of liver cirrhosis.[9-11] Liver cirrhosis has multiple disparate causes, involve inherited diseases such as hemochromatosis and wilson's disease.[12-16] and **immunologic disease** such as primary biliary cirrhosis, primary sclerosing cholangitis [17-20], and autoimmune hepatitis, **Vascular disease** such as budd-chiari; cardiac failure,[21] **Medications (**isoniazid, methyldopa, amiodarone, methotrexate, tamoxifen, retinol (vitamin A), propylthiouracil, didanosine).

Pathophysiology of Liver Cirrhosis

The transition from chronic liver disease to cirrhosis includes inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion.[23,24] This process leads to remarkable hepatic microvascular changes, characterized by sinusoidal remodeling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarisation of hepatic sinusoids), formation of intra hepatic shunts (owing to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction.[25] The endothelial dysfunction is characterized by inadequate release of vasodilators, of which the most indispensable is nitric oxide. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a sequence of inadequate protein-kinase-B-dependent phosphorylation, lack of cofactors, escalated scavenging sequencing from oxidative stress, and high concentrations of endogenous inhibitors of nitric oxide), with coincident escalated production of vasoconstrictors (chiefly adrenergic stimulation and thromboxane A2, but also initiation of the renin-angiotensin system, antidiuretic hormone, and endothelins).[26] Liver cirrhosis may be classified into two phases, the compensated one and the decompensated one. During the compensated phase, there are no symptoms and portal pressure is still beneath the limit for the onset of ascites and varices. In the second decompensated one, portal pressure escalates much more above the limit for the advancement of clinically evident complications of portal hypertension and patients are at pitfall to develop life-threatening complications (ascites, varices, sepsis, especially spontaneous bacterial peritonitis, encephalopathy, non-obstructive jaundice, hepatocellular carcinoma).[27,28] Contributing factors are represented by an unbalance among vasodilating (especially nitric oxide) and vasoconstriction (especially

endothelins) molecules, which eventually leads to escalated intrahepatic resistance and portal hypertension. Hemodynamic complications of liver cirrhosis are frequently demonstrated when the hepatic venous pressure gradient (HVPG) is higher than 10 mmHg.[27,29] Portal hypertension arises from the coincident escalate in portal flow resistance owing to deposition of fibrous scar within the liver compartment and the so-called vascular dysfunction. Cirrhotic patients with portal hypertension and the portal-systemic collaterals at distinctive levels are characterized by the presence of peripheral arterial vasodilation, particularly in the splanchnic compartment, characterized by escalated venous pre-load and cardiac output, together with de-escalated peripheral arterial resistances. In liver cirrhosis, both portal hypertension and splanchnic vasodilation, owing to escalated release and production of nitric oxide, contribute to the onset and the maintenance of ascites.[27,30] Proximal sodium retention and the non-osmotic release of ADH, owing to hypovolemia, trigger free water retention and the consequent hyponatremia.

Management of Liver Cirrhosis

Lifestyle Changes and General Measures: Lifestyle changes tend to be overlooked in the management of cirrhosis, because life expectancy is judged to be short and the benefit is sophisticated to measure. Lifestyle modifications improves citolytic indices and ameliorate hepatic steatosis, monitored either with ultrasound,[27,31,32] or other techniques. Insulin resistance, obesity, and the metabolic syndrome are pathophysiologically linked with nonalcoholic fatty liver disease, but they have deleterious effects regardless of liver disease aetiology. Obesity is an independent predictor of cirrhosis in alcoholic liver disease,[23,33] and the presence of metabolic syndrome is consociated with further severe fibrosis and cirrhosis in chronic liver disease.[34] Overweight patients with compensated cirrhosis (clinical stages I and II) should therefore be advised to lose weight to lower their long-term peril of liver complications. In patients with decompensated cirrhosis, maintenance of adequate nutrition is significant to avoid loss of muscle mass.[23,35] Such patients have low tolerance to long-term fasting, with early onset of gluconeogenesis and subsequent muscle depletion, which can also contribute to advancement of hepatic encephalopathy. Alcohol intake is deleterious in patients with alcoholic cirrhosis but also in those with liver disease of other causes. In alcoholic cirrhosis, alcohol ingestion increases hepatic venous pressure gradient and porto collateral blood flow[23,36] these outcomes are likely also in cirrhosis of other causes thereby escalating the peril of variceal bleeding.

Only abstinence from alcohol ameliorates survival in alcoholic cirrhosis.[23,37] In patients with chronic hepatitis C, alcohol intake escalates the pitfall of cirrhosis and decompensated liver disease two to three times, even with moderate intake.[23,38] Moreover, alcohol intake is an independent risk factor for hepatocellular carcinoma in chronic hepatitis C,[23,39] and nonalcoholic steatohepatitis.[23,40] Therefore, all patients with cirrhosis regardless of clinical stage should be advised to abstain from alcohol with relevant counseling if appropriate.[41]

Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible, because the antigenic response becomes weaker as cirrhosis progresses.[23,42] Cigarette smoking is consociated with further severe fibrosis in chronic hepatitis C, non-alcoholic steatohepatitis, and primary biliary cirrhosis and possibly escalates the pitfall of hepatocellular carcinoma in chronic hepatitis B.[23,43] Cannabis use worsens fibrosis in chronic hepatitis C.[23,44] Smoking cessation therefore should be advocated to obviate progression of liver disease and to facilitate eligibility for liver transplantation. Smoking also escalates post-transplant morbidity and mortality.[23] Treatment of the underlying disease can often halt or even reverse the progression of early-stage cirrhosis. Patients with alcoholic cirrhosis must abstain, since continued alcohol consumption drives hepatitis which favors hepatic fibrogenesis and decompensation. Liver function frequently worsens in the first 2-3 weeks of withdrawal since alcohol has an immunosuppressive consequence. Treatment of HBV or HCV infections with antiviral agents has been consociated with liver histological improvements. The administration of adefovir and entecavir in HBV infections has determined a histological improvement over a period of 240 weeks.[27,45] The nucleoside/nucleotide analogs cause viral suppression of over 99%, the regression of fibrosis. The disadvantages involve the unlimited duration of treatment, the low rate of loss of HBsAg and the seroconversion to anti-HBs. Treatment with tenofovir for 5 years sequenced in liver fibrosis regression in cirrhotic patients.[27,46] Patients with compensated replicating HCV-cirrhosis benefit from interferon-based antiviral treatment. Viral eradication and a consequently lowered pitfall of hepatic decompensation and hepatocellular carcinoma can be achieved in up to 40 and 70% of patients with genotypes 1 and 2 or 3, respectively. In a recent meta-analysis 75 out of 153 biopsy-proven cirrhotics

revealed reversal of cirrhosis on biopsy after successful treatment, but sequences need conformation in view of biopsy sampling variability. How far maintenance interferon for 3-4 years can obviate hepatic decompensation or hepatocellular carcinoma in subjects with stage 3 or 4 fibrosis who did not respond to interferon-ribavirin therapy is recently evaluated in large prospective trials (HALT-C, EPIC-3 and COPILOT). Long-term treatment with oral nucleoside and nucleotide inhibitors of HBV polymerase may not only retard or reverse cirrhosis but were also displayed to obviate complications of end stage liver disease. In a 3-year study of lamivudine for HBV, follow up liver biopsies suggested reversal of cirrhosis in 8/11 patients (73%) and in 436/651 patients with HBV-cirrhosis treated with lamivudine for a mean of 32 months a >50% reduction of hard clinical endpoints, as defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death affiliated to liver disease was attained. In replicating HBV-cirrhosis (>105 copies/mL) lamivudine treatment often resulted in clinical improvement, even after decompensation. The high rate of lamivudine resistance which reaches 56% and 70% after 3 and 4 years of treatment, respectively, is now of lesser concern, since equally well tolerable optional like adefovir, entecavir or telbivudine, or their combinations are available which reveal lower rates of viral resistance and a distinctive mutational profile. In one large study, adefovir treatment was successfully used in patients with lamivudine resistance pre-transplant, leading to suppression of HBV viral replication to undetectable levels in 76% of patients with either stabilization or improvement in CTP score and a 90% survival.[22] Treatment of primary biliary cholangitis aimed at slowing the disease and prolonging life involve ursodeoxycholic acid. Immunosuppressant medications have been widely used, but their effectiveness should be confirmed. Biliary obstructions and secondary liver cirrhosis perhaps benefit from biliary decompression.[27,47]

Portal Hypertension, Varices, and Variceal Bleeding

Portal hypertension, rather than hepatocyte failure perse, is the underlying cause of consummate of the complications of cirrhosis and subsequent mortality. Hepatic venous pressure gradient is a good surrogate marker of portal hypertension and has robust prognostic power.[23,48] Formation of oesophageal varices is the first clinically relevant outcome of portal hypertension and represents clinical stage 2 of cirrhosis. Recent recommendations are that all patients with cirrhosis should be screened for varices.[23,49] The peril of advancement and growth of varices is 7% per year,[23,50] and that of first variceal bleeding is 12% per year.[23,51] Pre-primary, primary, and secondary prophylaxis strategies to obviate variceal bleeding are available. Treatment options

Treatment options involve nonselective β blockers for varices, regardless of size, or endoscopic band ligation for medium or large varices. The management of varices encloses three strategies: primary prophylaxis; treatment of acute variceal hemorrhage; secondary prophylaxis.[51]

Primary Prophylaxis

Primary prophylaxis of variceal bleeding should be offered to all patients with varices, especially those that are large or have red signs. The mainstay of primary prophylaxis is the use of nonselective β-adrenergic blocking agents such as propranolol or nadolol. These agents reduce portal pressure by reducing portal venous inflow via two mechanisms which is de-escalate in cardiac output through β1-adrenergic blockade; and de-escalate in splanchnic blood flow through β2-adrenergic blockade as well as de-escalating azygous vein blood flow and variceal pressure, which is more remarkable than the reduced portal in flow.[52] They can also reduce total effective vascular compliance.[53] Carvedilol is a β blocker with vasodilating properties resulting from α1-blockade; it de-escalates intrahepatic vascular resistance, which leads to a greater fall in hepatic venous pressure gradient than with conventional non-selective β blockers.[54] Endoscopic band ligation consists of placing rubber elastic bands on medium or large varices; it is repeated until the lesions are eradicated. Use of nonselective β blockers advocated as primary prophylaxis, because they are cheap and effective and obviate the need for the expertise that endoscopic band ligation requires. Moreover, non-selective β blockers also obviate bleeding from portal hypertensive gastropathy and have disparate beneficial effects. Endoscopic band ligation has a small iatrogenic risk of death, owing to bleeding from post-banding ulcers.[23,55] It is an endoscopic therapy that consists of placing rubber bands around varices until the varices are obliterated and thought-out for the ensuing patients. Endoscopic therapy is recommended to the patients with contraindications to therapy with nonselective β-adrenergic blockers, patients with high-risk medium to large varices.

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Acute Variceal Bleeding

Vasoactive Medications

Patients with acute variceal bleeding need a combination of intravenous vasoactive medications to reduce portal pressure (terlipressin, somatostatin, or octreotide for 2–5 days) and endoscopic therapy, preferably endoscopic band ligation, within 12 h of bleeding.[56] They should also receive a 5-day course of antibiotics, because infection is pathophysiologically linked with variceal bleeding[57] and antibiotics reduce early re-bleeding and mortality.[58] Somatostatin and octreotide cause a reduction in portal pressure and port-collateral blood flow through: inducing splanchnic vasoconstriction without causing the systemic effects consociated with vasopressin. The recently recommended dosing of octreotide for variceal bleeding consists of an initial IV bolus of 50 mcg followed by a continuous IV infusion of 50 mcg/h.

Vasopressin Medications

The vasoconstrictive effects of vasopressin are not restricted to the splanchnic vascular bed. Potent systemic vasoconstriction induces peripheral resistance, which reduces cardiac output, heart rate, and coronary blood flow; myocardial ischemia or infarction, arrhythmias, mesenteric ischemia, ischemia of the limbs, and cerebrovascular accidents. A recommended dosing strategy for vasopressin is a continuous IV infusion of 0.2 to 0.4 units/min, which can be increased to a maximal dose of 0.8 units/min, and vasopressin should only be used at the highest effective dose continuously for a maximum of 24 hours. It should always be administered with IV nitroglycerin at a starting dose of 40 mcg/min (which can be escalated to a maximum of 400mcg/min). Short-term prophylactic antibiotic therapy not only reduces spontaneous bacterial peritonitis and other infections but also reduces the incidence of rebleeding and escalates short-term survival. Prophylactic antibiotic therapy should be prescribed for all patients with cirrhosis and acute variceal bleeding. A short course of oral norfloxacin 400 mg twice daily or IV ciprofloxacin when the oral route is not available.

Secondary Prophylaxis

Patients who have already experienced a variceal bleed need a combination of endoscopic band ligation and nonselective β blockers, because this strategy significantly reduces the peril of rebleeding, although it does not affect the risk of mortality compared with either treatment alone.[59]

Conclusion

Cirrhosis sequences from distinctive mechanisms of liver injury that lead to necro-inflammation and fibrogenesis. Stage 1 cirrhosis encloses some scarring of the liver, but few symptoms. This stage is thought-out as compensated cirrhosis, where there are no complications. The natural history of cirrhosis is ordinarily characterized by an asymptomatic stage of compensated cirrhosis followed by a symptomatic stage of decompensated cirrhosis. Liver cirrhosis has multiple other causes, encloses inherited diseases such as hemochromatosis and wilson's disease, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. In liver cirrhosis, both portal hypertension and splanchnic vasodilation, owing to escalated release and production of nitric oxide, contribute to the onset and the maintenance of ascites. Overweight patients with compensated cirrhosis (clinical stages I and II) should therefore be advised to lose weight to lower their long-term risk of liver complications. Nonselective β-adrenergic blocking agents reduce portal pressure by reducing portal venous inflow via two mechanisms which is de-escalate in cardiac output through β1-adrenergic blockade; and de-escalate in splanchnic blood flow through β2-adrenergic blockade as well as de-escalating azygous vein blood flow and variceal pressure, which is more remarkable than the reduced portal in flow. The recently recommended dosing of octreotide for variceal bleeding consists of an initial IV bolus of 50 mcg followed by a continuous IV infusion of 50 mcg/h.

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Data Sources

Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, and Cochrane database. Search terms included: definition, etiology, pathophysiology and management of liver cirrhosis.

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Competing Interests

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