CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2557688

Available online at: http://www.iajps.com ***Review Article***

LIVER CIRRHOSIS CAUSES AND MANAGEMENT

Ramy A. Abdalla [1], Hashem Abdulwhab Jaml Allil [2], Jumanah Khalid Attiyah [2], Mansour A. Arishi [3], Asma Saleh Ahmad Alsaeed [4], Waleed Eid Alraddadi [2], Khlood Abdulali Alharbi [5], Elaf Mohammed Taha Ibraheem Fakeih [6], Ziyad Waleed Iskander [2], Fahad Saad Almathkar [6], Asma Saad Al Ahmari [7], Tahani Saleh A. Alsaery [8], Ahmed Abdullah Hakami [9]

[1]Consultant internal medicine, Aljedaany Hospital-Jeddah, Ramyahmedsamy@yahoo.com, 0568881532., [2]Ibn Sina National College For Medical Studies, [3]Internal medicine registrar, King Khalid Hospital, Tabuk., [4]King Faisal university, [5]King Abdullah Medical Complex, [6]Umm Al-Qura University, [7]Armed Forces Hospital Southern Region., [8]King Fahad Armed Forces Hospital., [9]PHCC-Ministry of health.

Abstract:

Introduction: *Cirrhosis can be caused by many different mechanisms that involve hepatic injury and damage that could result in necroinflammation and fibrogenesis; histologically it is known by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, these can cause significant distortion of the liver vasculature architecture. This kind of distortion can result in higher resistance to portal blood flow which end up in portal hypertension and in hepatic synthetic dysfunction.Clinically, cirrhosis has been known as an end-stage disease that can lead to death, unless liver transplantation is conducted, and the only preventive methods have been screening for oesophageal varices and carcinoma.Recently, this has been studied, because 1-year mortality in cirrhosis differs very widely, from one percent to fifty percent depending on the clinical decompensations Histopathologists have suggested that the histological term cirrhosis must be substituted by advanced liver disease, to underline the dynamic processes and different prognosis of the disorder. Furthermore, fibrosis, even in the cirrhotic range, regresses with specific therapy, such as antiviral treatment for chronic hepatitis B or C.*

Aim of work: *In this review, we will discuss liver cirrhosis.**Methodology:*** *We did a systematic search for liver cirrhosis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.**Conclusions:*** *Cirrhosis is considered a worldwide trending cause of morbidity and mortality particularly in developed nations, it is thought to be one of the most common cause of death worldwide but about 4th in central Europe. Cirrhosis has been found to be not a single disease, but one that can be further divided into distinct clinical prognostic stages, with 1 year mortality ranging from one percent to fifty percent depending on the stage. In this review article we discussed the most recent understanding of cirrhosis as a dynamic process and outline current therapeutic options for prevention and management of complications of cirrhosis. The concept in management of patients with cirrhosis must be prevention and early intervention to stabilise disease progression and to avoid or delay clinical decompensation and the need for liver transplantation.*

Key words: *liver cirrhosis, presentation, causes, epidemiology, management.*

Corresponding author:

Ramy A. Abdalla,

Consultant internal medicine,

Aljedaany Hospital-Jeddah,

Ramyahmedsamy@yahoo.com, 0568881532.

QR code

Please cite this article in press Ramy A. Abdalla et al., ***Liver Cirrhosis Causes And Management.,*** *Indo Am. J. P. Sci, 2019; 06(02).*

INTRODUCTION:

Cirrhosis can be caused by many different mechanisms that involve hepatic injury and damage that could result in necroinflammation and fibrogenesis; histologically it is known by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, these can cause significant distortion of the liver vasculature architecture. [1] This kind of distortion can result in higher resistance to portal blood flow which end up in portal hypertension and in hepatic synthetic dysfunction.

Clinically, cirrhosis has been known as an end-stage disease that can lead to death, unless liver transplantation is conducted, and the only preventive methods have been screening for oesophageal varices and carcinoma.

Recently, this has been studied, because 1-year mortality in cirrhosis differs very widely, from one percent to fifty percent depending on the clinical decompensations [2] Histopathologists have suggested that the histological term cirrhosis must be substituted by advanced liver disease, to underline the dynamic processes and different prognosis of the disorder.4 Furthermore, fibrosis, even in the cirrhotic range, regresses with specific therapy, such as antiviral treatment for chronic hepatitis B or C. [3]

In this review, we will discuss the most recent evidence regarding liver cirrhosis.

METHODOLOGY:

We did a systematic search for liver cirrhosis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: liver cirrhosis, presentation, causes, epidemiology, management.

Epidemiology

Cirrhosis is a trending cause of morbidity and mortality in developed countries. It is considered the fourteenth most common cause of death in adults globally however the 4th in central Europe; it leads to in more than 1·03 million deaths per year globally. [4] Cirrhosis is the main cause of 5500 liver transplants yearly only in Europe.9 The main causes in more developed countries are hepatitis C virus, alcohol misuse, and, increasingly, non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in sub- Saharan Africa and most parts of Asia.

Pathophysiology

The switch from chronic liver disease to cirrhosis consists of inflammation, activation of hepatic stellate cells with fibrogenesis, angiogenesis, and parenchymal
extinction injuries caused by vascular occlusion. [5] This process can lead to evident hepatic microvascular modifications, known by sinusoidal remodelling (extracellular matrix deposition from proliferating activated stellate cells leading to capillarisation
of hepatic sinusoids), formation of intra hepatic shunts, and hepatic endothelial dysfunction. [6] The endothelial dysfunction is distinguished by insufficient release of vasodilators, of which the most relevant one is nitric oxide. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase, with associated increased release of vasoconstrictors (mainly adrenergic stimulation and thromboxane A2, but also activation of the renin-angiotensin system, antidiuretic hormone, and endothelins). [7]

Diagnosis

Almost all chronic liver disease is particularly asymptomatic until cirrhosis with clinical decompensation presents. Decompensations involves ascites, sepsis, variceal bleeding, encephalopathy, and non-obstructive jaundice. Imaging techniques including ultrasonography, CT, or MRI of an irregular and nodular liver together with impaired liver synthetic function is necessary for the diagnosis of cirrhosis. Other results include small and shrunken liver, splenomegaly, and evidence of portosystemic collaterals. Differential diagnosis involves congenital hepatic fibrosis, nodular regenerative hyperplasia, and non-cirrhotic portal hypertension. A liver biopsy is rarely required however studies provided a definitive diagnosis and confirmation of the causes in cases of ambiguity. The transjugular approach yields samples of equal quality to the percutaneous one.

In early cirrhosis though conventional imaging can lead to false-negative diagnosis so other strategies are needed. Non-invasive markers of fibrosis are becoming increasinly utilized; they are much more informative at the extremes of the liver fibrosis range.

Natural course

Cirrhosis must not be considered a terminal disease anymore and the idea of a dynamic process is becoming more acceptable. A prognostic clinical

classification with four distinct stages has been suggested with significant differentiation likelihoods of mortality: stage 1 has an an approximate mortality of one percent annually, and stages 2, 3, and 4 have about mortality rates of three, twenty, and fifty percent, respectively. Infections and renal failure have been categorized as stage 5, with more than sixty percent 1-year mortality. [8]
Acute decompensations can result in organ failure, the mortality is estimated to be around 30%; [9] noteworthy, mortality is more evident in previously compensated patients than in those with previous decompensation, which proposes higher tolerance of the latter through the effects of the inflamatory response.

More prognostication is critical, particularly for patients in the early asymptomatic stage. The classical qualitative histological classification doesn't have a stage beyond cirrhosis, thus they cannot be used to refine prognosis further. Semiquantitative histological subclassify cation based on nodular size and septal width is
associated with both HVPG and clinical outcomes. [10] classification based on quantitative fibrosis assessment with collagen proportionate area in liver
tissue is also linked with HVPG and clinical outcomes and is a highly promising. [11]

Population screening
The growing problem of liver disease and the problem of late presentation with decompensation emphasis the necessity for population screening to recognize patients with chronic liver disease, likewise to screening for cardiovascular risk factors.

Lifestyle changes and general measures
Lifestyle modifications can to be overlooked in the management of cirrhosis, As life expectancy is based to be short and the benefit is hard to measure. Though results come from cohort or case-control studies, lifestyle advice should still be given to all patients, as it can be easily implied with less risk of adverse-events or cost. Insulin resistance, obesity, and the metabolic syndrome are pathophysiologically associated with nonalcoholic fatty liver disease, however they have dangerous effects irrelevant of liver disease etiologies. Obesity is considered an independent predictor of cirrhosis in alcoholic liver disease, [12] and the presence of metabolic syndrome is linked with more severe fibrosis and cirrhosis in chronic liver disease. [13] In a study, obesity was independently linked with decompensation events, altogether with HVPG and serum albumin.30 Furthermore, insulin resistance and metabolic syndrome were independently linked with liver linked mortality. [14]

Insulin resistance can predict the occurrence of hepatocellular carcinoma in cirrhosis, and in big cohorts, both diabetes and metabolic syndrome34 elevated the risk of hepatocellular carcinoma. Overweight patients with compensated cirrhosis must therefore be advised to lose weight to lower their longterm risk of liver complications. In patients with decompensated cirrhosis, maintenance of adequate nutrition is important to avoid loss of muscle mass. These patients tend to have low tolerance to long-term fasting, with early onset of gluconeogenesis and subsequent muscle depletion. These adverse effects are likely also in cirrhosis of other causes thereby increasing the risk of variceal bleeding. Only stopping alcohol can improve survival in alcoholic cirrhosis. [15] In patients with chronic hepatitis C, alcohol intake elevates the risk of cirrhosis and decompensated liver disease 2 to 3 times, even with moderate intake. Furthermore, alcohol intake is considered an independent risk factor for hepatocellular carcinoma in chronic hepatitis C and nonalcoholic steatohepatitis. [16] a

Thus, patients with cirrhosis irrespective of the stage should be advised to stop drinking alcohol with counselling. There are many multidisciplinary alcohol care teams can lower the risk of acute hospital admission and enhance the quality of care. [17] In many centers, abstinence irrespective of liver disease etiology is required for the patient to be considered for liver transplantation.

Smoking is linked with more severe fibrosis in chronic hepatitis C, non-alcoholic steatohepatitis, and primary biliary cirrhosis and can elevate the risk of hepatocellular carcinoma in chronic hepatitis B. Cannabis use make it even worse in case of fibrosis in chronic hepatitis C. So, stopping smoking should be adviced to prevent progression of liver disease and to help eligibility for liver transplantation. Smoking elevates the post-transplant morbidity and mortality as well. [18]

Antioxidants have a potential preventive role in cirrhosis. Coffee can improve all-cause mortality but is also linked with a significant decrease in fibrosis in liver disease of various causes and with decreased risk of hepatocellular carcinoma.

Doctors should always consider drug interactions and

the possible need for dose reductions when prescribing for patients with cirrhosis.

Cause-specific treatments

Patients suffering from cirrhosis should be managed when possible for the underlying liver disease to stop disease progression; treatment consists of immunosuppression for auto immune hepatitis, venesection for haemochromatosis, and copper chelators or zinc for Wilson's disease. Patients who suffer from viral hepatitis should be further assessed for antiviral treatment. Management with tenofovir for five years led to regression of cirrhosis associated with hepatitis B virus. In patients with hepatitis-C-related cirrhosis without ascites, achievement of sustained virological response signifycantly decrease liver-related morbidity and mortality. There was also regression of cirrhosis in a subgroup of patients. This technique can also be implemented in patients with hepatitis C listed for liver transplantation because of hepatocellular carcinoma rather than complications of portal hypertension. The recently licensed direct-acting antiviral medications boceprevir and telaprevir found to increase the rates of sustained virological response in patients with genotype one.

Portal hypertension, varices, and variceal bleeding

Portal hypertension is considered the main cause of most of the complications of cirrhosis and mortality. HVPG is a good marker of portal hypertension and has great prognostic value. Portal hypertension is present when the HVPG is more than five mm Hg. But, clinically significant portal hypertension and the threshold for development of oesophageal varices is above ten mm Hg. Patients with HVPG of less than ten mm Hg had a ninety percent chance of not progressing to decompensation during median follow-up of four years, while for those with HVPG of more than ten mm Hg the incidence of hepatocellular carcinoma was six times higher than in patients with lower HVPG. [19]

Managements involve nonselective β blockers for varices, irrespective of size, or endoscopic band ligation for medium or large varices. An RCT of timolol for preprimary prevention of varices formation did not find any significant benefit.

The main prophylaxis of variceal bleeding should be given to all patients with varices, particularly those that are large or have red signs. Non-selective β blockers and endoscopic band ligation are equally effective in prevention of bleeding and reduction of mortality. Findings from a large meta-analysis of non-selective β blockers versus placebo showed that the number of patients needed to treat with non-selective β blockers to prevent 1 death is 16.

Non-selective β blockers was found to decrease cardiac output and cause splanchnic vasoconstriction thereby decreasing portal inflow, and decreasing azygous vein blood flow and variceal pressure, than the reduced portal inflow. They could also decrease the total effective vascular compliance. Carvedilol is a β blocker with vasodilating capabilities due to α1-blockade; it lowers the intrahepatic vascular resistance, which leads to a greater fall in HVPG than with conventional non-selective β blockers.

In an RCT, carvedilol was found to be more effective than endoscopic band ligation for primary prophylaxis of bleeding. A decrease in HVPG of at least twenty percent or to less than 12 mm Hg is associated with a marked decrease in variceal rebleeding compared with patients in whom these changes are not achieved, and defines patients receiving non-selective β blockers as responders. Measurement of acute haemodynamic response to propranolol could be a substitute for repeated HVPG measurements, because it can predict the risk of first bleeding,

Endoscopic band ligation involves the placing rubber elastic bands on medium or large varices; it is repeated until the lesions are eradicated. Studies recommend the use of nonselective β blockers as primary prophylaxis, as they are cheaper and more effective and obviate the need for the expertise that endoscopic band ligation needs.

Ascites

In cirrhosis, portal hypertension and splanchnic vasodilation, caused by increased production of nitric oxide is the primary mechanism of ascites. The effective blood volume is maintained as a result of a compensatory increase in cardiac output. But, as cirrhosis develops, this mechanism is not sufficient and homoeostatic activation of vasoconstrictor and antinatriuretic factors develops, with subsequent water and salt retention. Eventually, the retained fluid accumulates in the peritoneal cavity as a result of increased portal pressure.

Type 1 hepatorenal syndrome is characterized by a doubling of serum creatinine concentrations within two weeks, while type 2 has a more stable, less progressive course.

CONCLUSIONS:

Cirrhosis is considered a worldwide trending cause of morbidity and mortality particularly in developed nations, it is thought to be one of the most common cause of death worldwide but about 4th in central Europe. Cirrhosis has been found to be not a single disease, but one that can be further divided into distinct clinical prognostic stages, with 1 year mortality ranging from one percent to fifty percent depending on the stage. In this review article we discussed the most recent understanding of cirrhosis as a dynamic process and outline current therapeutic options for prevention and management of complications of cirrhosis. The concept in management of patients with cirrhosis must be prevention and early intervention to stabilise disease progression and to avoid or delay clinical decompensation and the need for liver transplantation.

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