Liver Disease and Heart Failure

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15.1 Introduction

Liver disease prevalence and mortality has increased worldwide since 2000 [1] with an estimated 1.5 billion people living with liver disease [1]. There are an estimated 26 million people worldwide living with heart failure [2]. Awareness of the increased prevalence and knowledge of cardiohepatic interactions is important for primary care providers when providing care to patients. More specifically, cardiomyopathy can lead to or worsen liver disease and vice versa; liver disease can cause or worsen heart failure.

Hepatologists and cardiologists are not the only providers that need awareness of these coinciding conditions. Primary care providers are often the first provider a patient encounters when dealing with health complaints. Time until diagnosis can be lengthy, and quality of life can be poor for patients diagnosed with coinciding liver disease and heart disease [2]. Therefore, it is important for primary care providers to be well educated on the cardiohepatic interactions to identify symptomology promptly for overall improved patient care.

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15.2 Liver Disease Related to Heart Failure

Liver disease occurs with heart failure related to the circulatory connection. The liver receives 25% of cardiac output. The liver receives blood flow from the hepatic portal vein and the hepatic artery [3]. Receiving perfusion from these two sources ultimately protects the liver as the other perfusion source can compensate if necessary. The hepatic vein carries the blood through the inferior vena cava which leads to the right side of the heart [4]. When the heart cannot tolerate an increased venous return, it can cause a hepatojugular reflux. This occurs with an increase in jugular venous pressure and can be a noninvasive physical exam finding that can aid in diagnosis.

15.2.1 Liver Diseases and Conditions That Exacerbate Heart Failure

Specific liver diseases and conditions are seen when there is acute or chronic decrease in perfusion. Liver hypoperfusion and hepatic congestion are two major triggers for this [4]. These liver diseases and conditions then lead to or exacerbate heart failure. Liver diseases and conditions that will be discussed in further detail in their role with heart failure are cirrhotic cardiomyopathy, nonalcoholic fatty liver disease, and post-liver transplantation complications.

15.2.1.1 Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy (CCM) has been discussed in the literature since the 1960s but was originally thought to arise from alcoholism [5]. CCM is seen in patients with the absence of other heart diseases [5]. CCM is a condition related to heart failure and electrolyte abnormalities that leads to a decrease in cardiac output with an overall impaired cardiac function [6]. In advanced stages, CCM may lead to a hyperdynamic state and increased cardiac output. CCM is seen in 50 percent of patients with cirrhosis [7]. It generally has a delayed diagnosis related to its initial presenting symptoms [5]. Most patients with cirrhosis have left ventricular diastolic dysfunction with usual systolic function, but not all go on to have CCM [6].

There are three things that occur with CCM: systolic dysfunction, decreased diastolic function, and electrophysiological disturbances [4]. Cardiac dysfunction originates from splanchnic arterial vasodilation that occurs in patients with cirrhosis [6]. Systolic dysfunction relates to the impaired responsiveness to stress which leads to decreased contractility [5]. Diastolic dysfunction occurs in early stages of CCM and causes increase in filling pressures and decrease in ventricular relaxation [5]. Finally, patients with CCM experience electrophysiological disturbances. Patients with cirrhosis have prolonged QT intervals, but patients with CCM have more electrophysiological changes [5]. CCM patients have additional instances of electromechanical desynchrony and chronotropic incompetence [6]. Chronotropic incompetence is the inability of the sinus node to increase HR after exercise, leading to fatigue and exercise intolerance. QT prolongation makes these patients more

susceptible to ventricular arrhythmias. These circulatory abnormalities also relate to liver toxicity causing arterial dilation and hyperdynamic circulation [8].

Patients with CCM are often asymptomatic or experience very vague symptoms—fatigue and exercise intolerance [6]. Patients with CCM have peripheral dilation which masks many heart failure symptoms [6]. The diagnosis is typically made based on cardiac labs and diagnostics more so than patient presentation.

Prognosis of CCM is not encouraging for patients. Some treatments are contraindicated in cirrhosis but would be useful in the presence of heart failure, such as beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) [4]. Beta blockers are potentially contraindicated in the case of refractory ascites or infection. Liver transplantation is a possibility for these patients if their cardiomyopathy is well managed before transplantation [4]. There are risks to liver transplantation on the heart as well which will be described in later sections. It is important for health care providers to be able to differentiate CCM from cardiac cirrhosis. In CCM, the liver affects the heart and in cardiac cirrhosis the heart affect the liver.

15.2.1.2 Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) increases the risk of heart disease and heart failure in many ways [9]. NAFLD is a metabolic disorder that correlates with increased adipose tissue on the liver [9]. While NAFLD is most connected to coronary artery disease and buildup of coronary plaque, there are heart failure characteristics also seen—left ventricular diastolic dysfunction, morphological and valvular heart abnormalities, and cardiac rhythm disturbances [9].

As the obesity rates continue to rise in the United States, so does the prevalence of NAFLD. It is the most prevalent liver disease worldwide [5]. It is seen in an estimated 30% of healthy patients and 50–90% of patients with increased metabolic risks such as type 2 diabetes and dyslipidemia [5]. Both NAFLD and cardiovascular disease are seen in patients with metabolic syndrome; however, not all patients with NAFLD and cardiovascular disease will progress to heart failure.

There are many factors that trigger NAFLD to increase cardiac risk. Endothelial dysfunction causes greater atherosclerosis development that can affect heart function [9]. NAFLD leads to altered lipogenesis [9]. Thirdly, NAFLD increases systemic inflammatory markers [9]. NAFLD also can lead to insulin resistance [9]. Lastly, NAFLD causes greater oxidative stress in the body which increases cardiometabolic risk [5, 9]. These six pathophysiological mechanisms cause NAFLD to increase cardiovascular disease.

Patients need to meet four criteria to be diagnosed with NAFLD. They first need to have hepatic steatosis seen on imaging or from biopsy [9]. Secondly patients with NAFLD need to demonstrate they do not overconsume alcohol [9]. Thirdly, patients cannot meet criteria for other diagnoses for hepatic steatosis [9]. Lastly patients with NAFLD cannot have other causes of chronic liver disease [9]. Once all four of these criteria are met, patients can receive the official NAFLD diagnosis. Clinical manifestations vary depending on the level of fibrosis and the amount of cardiometabolic diagnoses—diabetes, hypertension, dyslipidemia, and obesity severity [5].

NAFLD can lead to hepatocellular carcinoma (HCC) and cirrhosis [10]. NAFLD is the third leading cause of HCC [10]. Patients with the combination of NAFLD and HCC are at increased risk for death related to other cardiometabolic factors attributing to NAFLD [10].

15.2.1.3 Heart Failure Following Liver Transplant

Roughly 12% of patients will have early onset heart failure after liver transplant [11]. Twenty-two percent of patients will have heart failure within 6 months of liver transplant [11]. The risk of heart failure goes down to 11% six months and beyond after liver transplant [11]. Increased heart failure risk is seen in older patients that are non-Hispanic and had poorer functional status prior to transplantation [12].

Heart failure after liver transplant can occur early or late after transplant. Early heart failure occurs within the first 30 days after transplant and late heart failure is greater than 30 days after transplant [4]. Close follow-up post-transplantation is necessary to ensure identification of symptoms immediately.

Heart failure in the early stages of liver transplantation relates to the post-operation cardiac stress and all the hemodynamic changes from surgery [13]. Early heart failure also can be related to decreased myocardial function of the heart [13]. Research shows that late heart failure from liver transplantation is most likely connected to other cardiovascular and metabolic risk factors [13].

The major cardiac adverse events that occur after liver transplantation are atrial fibrillation, heart failure, pulmonary embolism, stroke, myocardial infarction, and cardiac death [12]. Clinical manifestations depend on the presenting cardiac condition and can vary greatly. Also, presenting symptoms depend on the cardiac function of the patient pre-liver transplant.

Heart failure after liver transplant is associated with a high mortality [12]. Patients with the largest risk of heart failure and death are those that had prior history of atrial fibrillation and those with increased stroke risk factors [12].

15.3 The Role of Heart Failure in Liver Disease

Every condition that affects the right ventricle of the heart can cause burden on the liver related to backwards circulatory blood flow [3]. Reduction of right ventricular blood flow triggers liver congestion [3]. Many acute injuries to the heart can cause injury to the liver. Examples include myocardial infarction, acute decompensation of chronic heart failure, infection/sepsis, or pulmonary embolism [14]. Chronic heart issues can also lead to liver injury/disease, and the liver damage is related to chronic perfusion issues [14]. Examples of these chronic heart diseases that can lead to liver disease are heart failure, congenital heart disease, cor pulmonale, and several others [14]. One of the major risks of chronic right-sided heart failure is congestive hepatopathy. With acute heart failure, patients may experience cardiogenic ischemic hepatitis.

15.3.1 Congestive Hepatopathy

Congestive hepatopathy is a condition related to progressive liver dysfunction and a slow progression of liver damage [14], which leads to congestion of liver parenchyma [15]. Congestive hepatopathy occurs in up to 65% of patients with heart failure [16, 17] and is most often seen in those with severe heart failure, left ventricular assist devices (LVAD), congenital heart disease, and patients with Fontan circulation [4, 18].

There are three things that trigger congestive hepatopathy: blood inflow, blood outflow, and decreased oxygenation to the liver. Chronic decrease in hepatic blood inflow and outflow leads to congestion in the liver and volume overload [4, 5]. The deoxygenation leads to hypoxia of the liver and eventual liver failure [4, 5].

Patients suffering from congestive hepatopathy may complain of jaundice, right upper quadrant pain, early satiety, weight loss, and malaise [5, 19]. Physical exam findings most often include peripheral edema, ascites, jugular venous distension, hepatomegaly, and hepatojugular reflux [5, 19]. Hepatomegaly is seen in 90–95% of patients with congestive hepatopathy and can be as clinically significant as >5 cm below right costal margin [3]. Occasionally patients with congestive hepatopathy have a pulsatile liver related to increased blood volume in right side of the heart [3].

After surgical repair to resolve cardiac dysfunction, there is potential for chronic hepatopathy to lead to benign regenerative nodules, focal nodular hyperplasia (FNH), and/or malignant hepatocellular carcinoma (HCC) [14, 20]. Deciphering nodules versus normal enhancement on computed tomography (CT) is difficult for radiologists related to the chronic cardiac and liver dysfunction [20]. Therefore, close follow-up is imperative to ensure proper management and treatment for these patients.

15.3.2 Cardiogenic Ischemic Hepatitis

Cardiogenic ischemic hepatitis is a condition that occurs often in patients presenting with heart failure. There are many names in the literature surrounding this condition—cardiogenic ischemic hepatitis, acute cardiogenic liver injury (ACLI), hypoxic hepatitis, ischemic hepatitis, and shock liver. For the purposes of this chapter, the term cardiogenic ischemic hepatitis will be used.

Cardiogenic ischemic hepatitis occurs in roughly 20–30% of patients with acute heart failure [21]. This is seen most often following acute coronary events, cardiac arrythmias, and acute, severe hypotension and cardiogenic shock [4, 5].

The cause of cardiogenic ischemic hepatitis is the decrease in hepatic blood flow related to impaired cardiac output. Decreased hepatic perfusion can lead to hepatocellular dysfunction and necrosis of the liver [22]. Hepatic congestion and liver hypoperfusion are both needed to confirm this diagnosis.

Cardiogenic ischemic hepatitis is typically asymptomatic [4]. These patients occasionally will have acute hepatitis symptoms like nausea, vomiting, decreased

appetite, fatigue, and right upper quadrant abdominal pain [3, 23]. Increased symptom duration can lead to jaundice and decreased urinary output, potentially leading to a flapping tremor and/or hepatic coma [3, 5, 19, 23]. The flapping tremor in these patients is related to decreased hepatic function leading to inability to filter toxins. Ultrasound exam may show dilation of the inferior vena cava and suprahepatic veins resulting in liver congestion [5]. This condition, like many other liver conditions, may lead to issues with bleeding related to lack of liver coagulability [3, 4].

Mortality remains high for this condition related to the acuity and its effects on the entire patient [4]. Quick identification of the condition and perfusion restoration can improve patient outcomes [4]. Management will be discussed later in this chapter.

15.4 Approach to the Management of Liver Disease and Heart Failure

When managing patients with comorbid heart failure and liver disease, it is important to keep in mind the additive effects of the two disease states. Early recognition of each disease is important due to the complex interplay between the two. The severity of heart disease and fatty liver disease is worse in patients who have both disease states, and there is a higher prevalence of fatty liver disease in patients with heart failure compared with the general population [24]. One study demonstrated that patients with comorbid heart failure with reduced ejection fraction and nonalcoholic fatty liver disease (NAFLD) were younger, had higher body mass indexes (BMIs), and had more left ventricular changes compared to patients with normal liver morphology [25]. Additionally, patients with liver disease and heart failure are more likely to have a poorer prognosis and are at higher risk when undergoing cardiac surgeries [26]. Both pharmacological and nonpharmacological management techniques are needed to prevent the more severe disease progression that can be seen in patients with these two comorbidities.

15.4.1 Pharmacologic Management

There are a few general principles of drug metabolism that are important to consider when treating co-occurring liver disease and heart failure. The efficiency of hepatic metabolism is multifactorial, comprised of the functionality of the hepatocytes themselves, the blood supply to the liver, and the availability of plasma proteins capable of binding drugs [27]. Therefore, there are multiple mechanisms by which disease processes can impair hepatic metabolism. Liver function test abnormalities do not always correspond with alterations in metabolism, making it difficult to predict to what degree drug metabolism will be affected [27]. However, it has generally been found that mild to moderate liver disease does not impair metabolism significantly, and it is not until a patient is cirrhotic that medication doses need to be adjusted [27]. In cirrhosis, shunting of blood reduces drug elimination during the

first pass effect and cytochrome activity can be decreased; both can lead to increased serum concentrations of drugs [27]. Heart failure can additionally damage the liver due to venous congestion and decreased perfusion, which ultimately causes liver hypoxia and impacts hepatic metabolism of drugs [27]. Specific medication considerations as they pertain to liver disease and heart failure treatment will be discussed further below.

15.4.1.1 Nonalcoholic Fatty Liver Disease (NAFLD)

There are currently no approved medications specifically for the treatment of NAFLD. High-dose vitamin E can be used in more advanced fibrosis [28]. There are several other current or emerging drug therapies that are being studied for use in NAFLD. Diabetes medications, including pioglitazone, metformin, GLP1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors, are all being studied due to observed positive benefits in liver fibrosis or steatosis [28, 29]. In patients with comorbid heart failure, SGLT2 inhibitors could have the added benefit of reducing heart failure-associated risks. Conversely, though pioglitazone shows promise in treating NAFLD patients, it would be contraindicated in those with comorbid heart failure due to its risks of swelling and heart failure exacerbation [29]. There is additionally early research to suggest that use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) could slow progression of hepatic fibrosis [29], which would be advantageous in heart failure patients given that treatment with ACE inhibitors or ARBs is already part of the standard of care.

15.4.1.2 Heart Failure

The standard therapeutic agents used to treat heart failure with reduced ejection fraction include ACE inhibitors, ARBs, ARNIs, beta blockers, diuretics, SGLT2is, and aldosterone antagonists. Specific considerations for each will be discussed separately below.

ACE Inhibitors

ACE inhibitors are largely excreted by the kidneys and are not expected to be affected much by hepatic dysfunction [26]. However, many are prodrugs which require metabolism in the liver to form active metabolites. These include enalapril, ramipril, fosinopril, trandolapril, quinapril, benazepril, and moexipril [26, 27]. Hepatic impairment may decrease the bioavailability of the active metabolite and increase the prodrug concentration in the blood stream. Therefore, it is advised to start at the initial dose but titrate slowly in cirrhotic patients when administering the aforementioned prodrugs, with the exception of moexipril and trandolapril which require a dose reduction [27].

ARBs

Candesartan, losartan, and valsartan are currently the three ARBs with an approved indication for use in heart failure patients [30]. Of these, candesartan and losartan are both prodrugs and require a lower starting dose in cirrhosis [25, 26]. Telmisartan also requires a lower starting dose and slower titration [27].

ARNIs

Sacubitril/valsartan is now recommended in place of ACEs or ARBs for all HFrEF patients who can tolerate it due to its superior ability to reduce hospitalizations and mortality [31]. It requires a dose reduction for patients with moderate liver disease and is contraindicated for those with severe more advanced liver disease.

Beta Blockers

Bisoprolol, metoprolol succinate, and carvedilol are the three FDA-approved beta blockers for heart failure treatment. All of these are lipophilic beta blockers, which are predominantly metabolized by the liver and require a dose reduction in the setting of cirrhosis [26, 27]. Other commonly used lipophilic beta blockers requiring dose reduction include propranolol, timolol, and nebivolol [26, 27]. Nonselective beta blockers (such as nadolol, propranolol, timolol, and carvedilol) can further be of benefit in liver disease patients as the preferred treatment for portal hypertension and prevention of variceal bleeding [32]. There have been concerns raised about the use of nonselective beta blockers in cirrhotic patients with refractory ascites due to concerns for increased mortality. However, current evidence still supports their use in heart failure and in cirrhotic patients with portal hypertension, but it is recommended to start at a very low dose and titrate slowly, every 1–2 weeks [32]. Close monitoring to watch for signs of decreased organ perfusion and hypotension is advised [32]. Beta blockers may need to be temporarily discontinued in heart failure patients in the setting of ischemic hepatitis, as treatment focuses on restoration of blood flow to the liver typically through removal of negative inotropes and blood pressure reducing medications [5].

Diuretics

Use of diuretics in heart failure can be mutually beneficial in liver diseases by improving jaundice, ascites, and liver congestion [19]. Thiazide diuretics can be utilized in mild heart failure, though loop diuretics are typically the mainstay of therapy in heart failure patients. Thiazide diuretics may also be used for ascites management. Diuretics are typically excreted renally so there is no dose reduction in advanced liver disease. However, dehydration can cause hepatic encephalopathy in cirrhosis, so close monitoring of volume status is required to avoid diuretic-induced dehydration [27].

SGLT2 Inhibitors

The most recent heart failure guidelines have a new addition of SGLT2 inhibitors to the treatment regimen of patients with symptomatic chronic heart failure, even if they do not have comorbid diabetes [31]. There are no dose adjustments required for patients with comorbid liver disease, and in fact SGLT2 inhibitors show promise in improving liver fibrosis or steatosis [28, 29].

Aldosterone Antagonists

Spironolactone and eplerenone are common adjunct therapies in heart failure, especially in diuretic-resistant patients. Spironolactone is also highly effective for the treatment of ascites in liver disease [33]. However, the doses for these two

conditions may differ. Adjunct therapy in heart failure often involves spironolactone doses of 25–50 mg daily, whereas ascites treatment may require up to 400 mg daily for adequate diuresis [33].

Lipid-Lowering Agents

Patients with heart failure as well as liver disease commonly have comorbid hyperlipidemia. Pharmacological treatment with statins and ezetimibe is recommended to reduce the risk of cardiovascular events in these patients, though there is no known benefit in improving liver disease itself [29]. However, both classes of medications are contraindicated in severe hepatic disease and dose reduction may be required for more mild hepatic impairment [27]. Although not typically first-line agents, fibric acid derivatives may also commonly be used for adjunct lipid lowering therapy, but again would be contraindicated in severe liver disease [27].

Anticoagulant/Antiplatelet Therapy

Anticoagulant or antiplatelet therapy may be indicated in many patients with heart failure due to common comorbidities such as atrial fibrillation, coronary artery disease, or prior stroke. However, both heart failure and hepatic dysfunction are associated with elevated prothrombin levels leading to increased clotting times [19]. Furthermore, patients with cirrhosis have an increased risk of hemorrhage due to the high prevalence of esophageal varices [1]. Therefore, use of anticoagulants in these patients can be controversial, particularly with newer agents such as rivaroxaban or apixaban which are contraindicated in more advanced hepatic disease [19]. There is also concern for possible liver toxicity in all newer oral anticoagulants [3]. Warfarin is still commonly used in patients with heart failure and hepatic dysfunction requiring anticoagulation [19] though frequent INR monitoring is advised.

15.4.1.3 Congestive Hepatopathy

The primary treatment of congestive hepatopathy involves correcting the underlying heart disease which in turn alleviates the hepatic congestion. It is predominantly treated with diuretics to reduce fluid overload, which corrects the associated liver congestion, ascites, and jaundice [19]. ACE inhibitors and B blockers are also recommended as they are indicated in the treatment of symptomatic heart failure [5].

15.4.1.4 Cardiogenic Ischemic Hepatitis

Pharmacological management of cardiogenic ischemic hepatitis typically involves removing medications that contribute to decreased perfusion, predominantly negative inotropes such as B blockers [5]. Patients may also require the use of positive inotropes or vasopressors to return perfusion to the liver, such as milrinone or digoxin [5, 19]. Inotropic and vasopressor medications can generally be used without dose adjustment in the setting of hepatic impairment [27].

15.4.1.5 Post-Liver Transplant

Immunosuppressive therapies used after liver transplantation may have cardiac side effects. Tacrolimus has been shown to cause significant myocardial hypertrophy in some patients [3]. Corticosteroids such as prednisone can cause edema and heart

failure exacerbations. On the other hand, cyclosporine, sirolimus, and mycophenolate mofetil do not appear to cause significant cardiac issues [3].

15.4.2 Nonpharmacologic Management

15.4.2.1 Lifestyle Modifications

Lifestyle modifications are currently the mainstay of NAFLD. These modifications include diet, weight loss, exercise, smoking cessation, and alcohol reduction [28, 29]. Given that fatty liver disease tends to have many of the same risk factors as heart failure, including type 2 diabetes, obesity, hypertension, hyperlipidemia, and metabolic syndrome, the lifestyle modifications aimed at reducing liver disease tend to improve heart failure, as well [29].

Diet

Current evidence suggests that the Mediterranean diet or a low-glycemic index diet containing high fiber, few saturated fats, and few simple sugars are the best diets for improving hepatic steatosis [28, 29]. The Mediterranean diet has also repeatedly been shown to improve cardiovascular outcomes [34].

Exercise

Exercise regimens should include 150 min weekly of resistance training and moderate to high intensity aerobic exercise. This not only improves hepatic steatosis but also assists with weight loss, reduces insulin resistance, and improves lipid profiles, all of which improve cardiovascular outcomes [28, 29]. Aerobic exercise also improves exercise tolerance in heart failure patients [24].

Weight Loss

Patients with fatty liver disease are typically advised to lose 5–10% of total body weight to see improvements in NAFLD. There are times even more weight loss may be advised based on the degree of aminotransferase elevation or severity of histological change [28, 29]. Weight loss can help prevent the development of heart failure or improve exercise tolerance and reduce symptoms in those with preexisting heart failure [24, 35]. However, in patients with preexisting heart failure, there is a well-established obesity paradox in which obesity seems to provide a protective mechanism on heart failure outcomes. Obese patients have better prognoses and higher survival rates than those heart failure patients who lose weight or have lower BMI [29, 35]. There are currently unclear guidelines about weight loss recommendations for heart failure patients, which poses a challenge when trying to advise those with comorbid fatty liver disease. More research is needed in this area. In the interim, for those patients with preexisting heart failure, it is best to focus on dietary improvements rather than a specific weight reduction goal itself. If patients are more severely obese, a modest amount of weight reduction may be advisable for the sake of reducing heart failure-associated symptoms and improving quality of life [35].

15.5 Laboratory Monitoring and Diagnostics for Hepatic Complications in Heart Failure

15.5.1 Liver Function Tests

The pattern of liver function test elevations can be an important indicator of heart failure status and severity. Elevations in cholestatic markers including alkaline phosphatase, ϒ-glutamyl transpeptidase (GGT), and bilirubin are indicative of congestive hepatopathy, the venous liver congestion that results from poor right ventricular function [3, 19, 26]. These changes are more likely to be seen in chronic heart failure, and the degree of elevation corresponds to the severity of heart failure [3]. Sharp increases in aminotransferases (AST, ALT) and lactate dehydrogenase are more indicative of an abrupt decrease in cardiac output resulting in ischemic hepatitis. This is more likely due to acute decompensated heart failure, and levels typically improve within 7–10 days [10]. In the setting of acute heart failure with acute cardiogenic liver injury, elevated liver function tests at baseline are associated with higher mortality rates over the next 6 months [3]. Elevated bilirubin in particular is a strong predictor of cardiovascular death in heart failure patients [19].

15.5.2 Synthetic Function Tests

Liver synthetic function tests can also be affected in the setting of heart failure. Congestive hepatopathy can impair the liver's production of both clotting factors and albumin [26]. Prothrombin time may be increased, an important consideration prior to surgery or other medical procedures that carry a risk of bleeding. Albumin production may be decreased [19, 26]. Hypoalbuminemia is associated with poorer outcomes in heart failure patients, likely due to low albumin causing increased edema, platelet aggregation, inflammation, and oxidative stress [36].

15.5.3 Metabolic Markers

It is important to screen for underlying diabetes and dyslipidemia. These are commonly seen in both liver disease and cardiovascular disease, including heart failure. Many patients with NAFLD meet criteria for metabolic syndrome, which increases cardiovascular disease risk. Insulin resistance, diabetes, and dyslipidemia are all associated with more advanced disease and poorer outcomes in both liver and heart disease [29]. The typical lipid profile in NAFLD includes high triglycerides, high low-density lipoproteins, high very-low-density lipoprotein, and low high-density lipoproteins.

15.5.4 EKG

Fatty liver disease is commonly associated with several EKG disturbances, including atrial fibrillation, QT prolongation, or ventricular arrhythmias, which could lead to sudden cardiac death [3, 5]. Routine EKGs could be beneficial in determining those experiencing a prolonged QT interval, as this could impact dosing and selection of medications used to treat heart failure.

15.5.5 Echocardiogram

Fatty liver disease is commonly associated with several structural and functional changes on echocardiogram, including increased left ventricular mass, interatrial thickness, left atrial stiffness, and left ventricular diastolic dysfunction [29]. It is also common to find calcifications of the aortic and mitral valves in patients with fatty liver disease [29].

15.5.6 Risk Scores

There are a few different scoring systems that can be beneficial in clinical decision making and risk stratification for patients with coinciding heart failure and liver disease. All of these are noninvasive and utilize common laboratory values that the clinician could readily have available.

15.5.7 Fibrosis Score

The fibrosis score is used to estimate the amount of scarring on the liver. Although typically used to determine presence of advanced fibrosis, it can also predict cardiovascular risk [5]. A higher fibrosis score correlates to more frequent cardiovascular events and more advanced heart failure stages [37].

15.5.8 Model for End-Stage Liver Disease (MELD)

The MELD score and its affiliates (MELD-Na and MELD-XI) are risk calculators used to assess the severity of liver disease especially for transplant planning purposes. However, it can also be clinically useful in risk stratification when assessing mortality or disease progression in heart failure patients [26]. The MELD score is the most used clinical score among advanced heart failure patients and is an accurate predictor of mortality rates, bleeding risk, and high-risk surgical candidates [3].

15.5.9 Child-Pugh Score

The Child-Pugh score has historically been used to determine the prognosis of patients with advanced liver disease. It is calculated similarly to the MELD score and the two are often used in conjunction when determining candidates for liver transplantation. The Child-Pugh score has been subject to criticism due to its use of subjective data (ascites and encephalopathy). Nevertheless, it can be useful to calculate since hepatic dosing guidelines for medications often reference the Child-Pugh class, including medications used in heart failure treatment [38]. For example, Ivabradine, a newer medication used to treat symptomatic heart failure with reduced ejection fraction, is contraindicated in those with severe hepatic dysfunction falling into Child-Pugh Class C [26]. Entresto, which falls in the ARNI class of medications, also carries a contraindication for Child-Pugh Class C and dose reduction for Class B.

15.6 Case Study: Putting It All Together

15.6.1 Subjective

15.6.1.1 History of Presenting Illness (HPI)

JM is a 58-year-old male patient presenting to primary care provider with a chief complaint of progressive, right upper quadrant pain that has been occurring for 2 months. Pain is 6/10 on the pain scale, dull and tender to touch. Associated symptoms include: weight loss (5%), fatigue, decreased appetite. Over the past week, he noted progressive worsening of bilateral lower extremity edema and decreased exercise tolerance. Experiencing dyspnea and fatigue when performing activities of daily living (ADLs) such as bathing and brushing teeth. Describes orthopnea the past two nights. Noted changes in chronic conditions since last visit:

15.6.1.2 Chronic Conditions Changes Since Last Visit

- *Heart Failure with Reduced Ejection Fraction*—Seen by cardiology 4 months ago. Echocardiogram noting LVEF 35%, LVIDD 6.7 cm, right ventricle moderately dilated. Stable, NYHA class II symptoms at that time. Entresto was increased.
- *Dyslipidemia*—Managed by primary care provider. Total cholesterol and LDL drawn 3 months ago and within goal. Continuing diet modifications and exercise.
- *Hypertension*—Managed by cardiologist—compliant with medications. Patient does not check BP at home but denies chest pain, headaches, and dizziness. Reports shortness of breath over the past 4 months.
- *Type 2 Diabetes Mellitus, controlled, non-insulin dependent*—Managed by primary care provider—Hemoglobin A1c 3 months ago was 7.1. Complaint with medications. Checks glucose BID and numbers are within goal. Continues with dietary modifications and exercise.

- *Depression*—Managed by primary care provider—stable on current medications. Medications provide relief of depressive symptoms. Denies suicidal/homicidal ideation.

15.6.1.3 Past Medical History/Problem List

- Heart Failure with reduced ejection fraction (diagnosed in 2010)
- Dyslipidemia (Diagnosed 2006)
- Hypertension (Diagnosed 2006)
- Type 2 Diabetes Mellitus, controlled, non-insulin dependent (Diagnosed 2008)
- Obesity
- Depression (Diagnosed in 2008)
- *Surgeries*: Appendectomy at age 28, tonsillectomy at age 20
- *Immunizations*: Received two COVID vaccines (Pfizer)—last one 5 months ago

15.6.1.4 Family History

- *Father*—Deceased at age 65—Hypertension, dyslipidemia, myocardial infarction
- *Mother*—Deceased at age 68—Hypertension, stroke
- *Sister*—Alive—Hypertension, obese, history of breast cancer
- *Brother*—Deceased at age 50—Hypertension and fatal myocardial infarction at age 50
- *Son*—Alive—Obese, hypertension, depression

15.6.1.5 Social History

Patient lives with partner of 20 years in an apartment downtown. Patient is unemployed, on medical disability. Receives Medicaid. Has one child. Patient smokes cigarettes and has a 20-year pack/day tobacco history. Drinks alcohol four times a week, and totals 16–20 drinks/week. Denies illicit drug use. Drinks 2 cups of coffee/day.

15.6.1.6 Medications/Allergies

- Furosemide 80 mg bid
- Sacubitril/Valsartan 97 mg/103 mg BID
- Metoprolol succinate 100 mg QD
- Spironolactone 25 mg QD
- Sertraline 100 mg QD
- Bupropion XL 150 mg QD
- Metformin ER 1000mg BID
- Empagliflozin 10 mg by mouth daily
- Patient has no known drug allergies (NKDA)

15.6.1.7 Review of Systems (ROS)

Constitutional: Positive for fatigue and weight loss, Negative for fever, lightheadedness, and syncope.

Cardiovascular: Positive for chest tightness, swelling of legs and joint stiffness. Negative for chest pain and palpitations.

Respiratory: Positive for shortness of breath with exertion. Negative for cough and difficulty breathing.

Abdomen: Positive for upper quadrant abdominal pain, weight loss, and decreased appetite. Negative for vomiting, diarrhea, constipation, and blood in the stool.

15.6.2 Objective

Vital Signs Blood pressure 132/90, Heart rate 100, Respiratory Rate 22, Temperature 98.4 °F, Height 68 inches, Weight 235 pounds (down 12 pounds since last visit), BMI 35.7.

15.6.2.1 Physical Examination

General statement: JM is a 58-year-old African American male alert and oriented x3, cooperative and obese.

Neck: JVD elevated to 16 cm with head of bed elevated to 45°. Hepatojugular reflux is positive with moderate palpation of the liver.

Cardiovascular: Apical heart rate 100, rhythm regular. No murmurs, heaves, lifts or thrills present. 2+ bilateral edema in shin, ankles, and feet.

Respiratory: Tachypneic at rest, increased work of breathing, expiratory wheezes present bilaterally.

Abdomen: Normoactive bowel sounds in all four quadrants. Abdomen is distended with ascites and there is right upper quadrant pain to palpation. Murphy's sign is negative. Hepatomegaly noted. Pulsation is palpated in liver during exam.

15.6.2.2 Labs and Risk Scores

- *Comprehensive Metabolic Panel (CMP)*—serum alkaline phosphatase level 200 (elevated), aspartate aminotransferase 120 (elevated), alanine aminotransferase 125 (elevated)
- *Bilirubin*—2.7 (elevated)
- *Serum gamma-glutamyl transpeptidase (GGT)*—75 (elevated)
- *Albumin*—2.7 (decreased)
- *Prothrombin time*—20 seconds (elevated)
- Pro-B-type natriuretic peptide (BNP)—1200
- New York Heart Association (NYHA) Functional Classification III-IV
- *Child-Pugh* Score—Child-Pugh Class B
- *Fibrosis Score*—2 (Moderate Fibrosis)
- *Model for End State Liver Disease (MELD) Score*—12

15.6.3 Assessment

Differentials Diagnoses: Acute on Chronic Decompensated Heart Failure, Budd-Chiari syndrome, acute or chronic hepatitis, biliary obstruction, constrictive pericarditis, congestive hepatopathy, hepatic infiltrative disorders, and drug toxicity causing liver failure.

Final Diagnosis: Acute decompensated heart failure with hepatic congestion.

15.6.3.1 Plan

Mr. JM is experiencing NHYA Class III-IV symptoms in the setting of volume overload. Hospital admission is recommended for intravenous diuretics, possible hemodynamic monitoring, and further treatment and evaluation of concomitant heart failure and liver congestion.

15.6.3.2 Nonpharmacology

Labs ordered: Hepatitis panel including autoimmune hepatitis, iron and total iron binding capacity (to rule out hemochromatosis), alpha-1 antitrypsin, celiac panel, prothrombin time/international normalized ratio and thyroid-stimulating hormone.

Imaging: Right upper quadrant ultrasonography with Doppler studies of the portal and hepatic veins and hepatic artery, electrocardiogram, and echocardiography.

Diagnostic testing: Histologic examination of the liver is sometimes performed to look at level of liver fibrosis. It is crucial to weigh risks of this related to elevation in prothrombin time and potential to cause more harm [4].

Patient Education: JM should be educated on monitoring signs and symptoms of fluid volume overload in an effort to prevent acute decompensation in the future. This is particularly important as cardiac dysfunction causing congestive hepatopathy of the liver can lead to benign regenerative nodules, focal nodular hyperplasia (FNH), and/or malignant hepatocellular carcinoma (HCC). Referral to hepatologist should be considered. Additionally, the patient should prepare for potential diagnostic paracentesis looking for an increase in protein count in peritoneal fluid. Extensive education regarding the importance of refraining from alcohol should be advised given its cardio and liver toxic effects.

15.7 Clinical Pearls

Labs help to identify patients with congestive hepatopathy as there is generally mild hyperbilirubinemia with coinciding mild increase in alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase [5]. Patients with congestive hepatopathy may also have mild decrease in albumin levels. Hepatomegaly is seen in almost 99% of patients with congestive hepatopathy but only 25% of these patients will have ascites [3]. If a paracentesis is performed, seeing protein in ascitic fluid helps to differentiate congestive hepatology from other causes of cirrhosis [3]. Underlying heart failure needs to be corrected for patients to have symptomatic improvement. This may result in assessment of acute decompensated heart failure with likely invasive hemodynamic evaluation. In extreme cases it can include surgery, temporary left ventricular assistive device support (LVADs), or cardiac transplantation depending on the levels of severity of heart failure [5]. Therefore, it is imperative that the patient is safely diuresed and managed in the hospital acutely related to decompensation. They may need swift inpatient inotropic support if diuresed with no symptom improvement [4]. Prognosis is worse in patients with increased liver biomarkers with hypoalbuminemia [4]. If liver function does not

improve with heart failure management, patients are typically not a candidate for heart transplantation unless a combined liver and heart transplant is considered [4]. Lastly, heart failure patients who are volume overloaded with notable passive hepatic congestion may present with a chief complaint of "right upper quadrant pain," therefore, mimicking concerns for cholecystitis. After decongestion, the pain most often subsides. It is important to consider acute decompensated heart failure as a differential for a chief complaint of right upper quadrant pain.

15.8 Conclusion

Managing heart failure and liver disease is challenging related to all the cardiohepatic interactions [4]. Interprofessional management of these patients including primary care providers, hepatologists, and cardiologists is important for improved care and quality of life. Diagnosis and treatment of these conditions is generally related to the complexity of identification of the triggers of illness. Therefore, it is imperative that primary care providers have knowledge of the cardiohepatic interactions so patients can receive swifter diagnosis and improved care.

References

1. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clin Gastroenterol Hepatol. 2020;18(12):2650–66. https://doi.org/10.1016/j.cgh.2019.07.060.
2. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev. 2017;3(1):7–11. https://doi.org/10.15420/cfr.2016:25:2.
3. Correale M, Tarantino N, Petrucci R, Tricarico L, Laonigro I, Di Biase M, et al. Liver disease and heart failure: back and forth. Eur J Intern Med. 2018;48:25–34. https://doi.org/10.1016/j.ejim.2017.10.016.
4. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease. JACC Heart Fail. 2019;7(2):87–97. https://doi.org/10.1016/j.jchf.2018.10.007.
5. El Hadi H, Di Vincenzo A, Vettor R, Rossato M. Relationship between heart disease and liver disease: a two-way street. Cell. 2020;9:567. https://doi.org/10.3390/cells9030567.
6. Ruiz-del-Árbol L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol. 2015;21(41):11502. https://doi.org/10.3748/wjg.v21.i41.11502.
7. Wiese S, Hove JD, Bendtsen F, Møller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol. 2014;11(3):177–86. https://doi.org/10.1038/nrgastro.2013.210.
8. Møller S, Lee SS. Cirrhotic cardiomyopathy. J Hepatol. 2018;69(4):958–60. https://doi.org/10.1016/j.jhep.2018.01.006.
9. Stahl EP, Dhindsa DS, Lee SK, Sandesara PB, Chalasani NP, Sperling LS. Nonalcoholic fatty liver disease and the heart. J Am Coll Cardiol. 2019;73(8):948–63. https://doi.org/10.1016/j.jacc.2018.11.050.
10. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328–57. https://doi.org/10.1002/hep.29367.

11. Konerman MA, Fritze D, Weinberg RL, Sonnenday CJ, Sharma P. Incidence of and risk assessment for adverse cardiovascular outcomes after liver transplantation: a systematic review. Transplantation. 2017;101(7):1645–57. https://doi.org/10.1097/TP.0000000000001710.
12. VanWagner LB, Serper M, Kang R, Levitsky J, Hohmann S, Abecassis M, Skaro A, Lloyd-Jones DM. Factors associated with major adverse cardiovascular events after liver transplantation among a national sample. Am J Transplant. 2016 Sep;16(9):2684–94. https://doi.org/10.1111/ajt.13779.
13. Silvestre OM, Farias AQ, Bacal F. Early-onset and late-onset heart failure after liver transplantation. Liver Transpl. 2014;20:122. https://doi.org/10.1002/lt.23760.
14. de Gonzalez AK, Lefkowitch JH. Heart disease and the liver: pathologic evaluation. Gastroenterol Clin. 2017;46(2):421–35. https://doi.org/10.1016/j.gtc.2017.01.012.
15. Fortea JI, Puente Á, Cuadrado A, Huelin P, Pellón R, González Sánchez FJ, et al. Congestive hepatopathy. Int J Mol Sci. 2020;21(24):9420. https://doi.org/10.3390/ijms21249420.
16. Van Deursen VM, Damman K, Hillege HL, Van Beek AP, Van Veldhuisen DJ, Voors AA. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail. 2010;16(1):84–90. https://doi.org/10.1016/j.cardfail.2009.08.002.
17. Myers RP, Cerini R, Sayegh R, Moreau R, Degott C, Lebrec D, Lee SS. Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. Hepatology. 2003;37(2):393–400. https://doi.org/10.1053/jhep.2003.50062.
18. Asrani SK, Asrani NS, Freese DK, Phillips SD, Warnes CA, Heimbach J, Kamath PS. Congenital heart disease and the liver. Hepatology. 2012;56(3):1160–9. https://doi.org/10.1002/hep.25692.
19. Drăghici T, Negreanu L, Bratu OG, Tincu R, Socea B, Inacu MA, et al. Liver abnormalities in patients with heart failure. Arch Balk Med Union. 2018;53(1):76–81.
20. Hilscher MB, Wells ML, Kamath PS. Liver lesions in congestive hepatopathy. In: Evaluation and management of liver masses. Springer; 2020. p. 201–14. https://doi.org/10.1007/978-3-030-46699-2_9.
21. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioncel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann V. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2017 Jul;19(7):821–36. https://doi.org/10.1002/ejhf.872.
22. Cannon MV, van Gilst WH, de Boer RA. Emerging role of liver X receptors in cardiac pathophysiology and heart failure. Basic Res Cardiol. 2016;111(1):1–7. https://doi.org/10.1007/s00395-015-0520-7.
23. Fouad YM, Yehia R. Hepato-cardiac disorders. World J Hepatol. 2014;6(1):41. https://doi.org/10.4254/wjh.v6.i1.41.
24. Miller A, McNamara J, Hummel SL, Konerman MC, Tincopa MA. Prevalence and staging of non-alcoholic fatty liver disease among patients with heart failure with preserved ejection fraction. Sci Rep. 2020;10(1):12440. https://doi.org/10.1038/s41598-020-69013-y.
25. Zhang Z, Wang P, Guo F, Liu X, Luo T, Guan Y, et al. Chronic heart failure in patients with nonalcoholic fatty liver disease: prevalence, clinical features, and relevance. J Int Med Res. 2018;46(9):3959–69. https://doi.org/10.1177/0300060518782780.
26. Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. Circulation. 2016;133(17):1696–703. https://doi.org/10.1161/CIRCULATIONAHA.115.020894.
27. Sokol SI, Cheng A, Frishman WH, Kaza CS. Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. J Clin Pharmacol. 2000;40:11–30. https://doi.org/10.1177/00912700022008649.
28. Jeznack-Steinhagen A, Ostrowska J, Czerwonogrodzka-Senczyna A, Boniecka I, Shahnazaryan U, Kurylowicz A. Dietary and pharmacological treatment of nonalcoholic fatty liver disease. Medicine. 2019;55(5):166. https://doi.org/10.3390/medicina55050166.
29. Ismaiel A, Dumitrascu DL. Cardiovascular risk in fatty liver disease: the liver-heart axis – literature review. Front Med. 2019;6:202. https://doi.org/10.3389/fmed.2019.00202.

30. Dézsi CA. The different therapeutic choices with ARBs. Which one to give? When? Why? Am J Cardiovasc Drugs. 2016;16:255–66. https://doi.org/10.1007/s40256-016-0165-4.
31. Heidenreich P, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Am Coll Cardiol. 2022;79(17):e263–421. https://doi.org/10.1016/j.jacc.2021.12.012.
32. Rodrigues SG, Mendoza YP, Bosch J. Beta-blockers in cirrhosis: evidence-based indications and limitations. JHEP Rep. 2020;2(1):100063. https://doi.org/10.1016/j.jhepr.2019.12.001.
33. Qavi AH, Kamal R, Schrier RW. Clinical use of diuretics in heart failure, cirrhosis, and nephrotic syndrome. Int J Nephrol. 2015;2015:975934. https://doi.org/10.1155/2015/975934.
34. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. Circ Res. 2018;124(5):779–98. https://doi.org/10.1161/CIRCRESAHA.118.313348.
35. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. Prog Cardiovasc Dis. 2018;61(2):151–6. https://doi.org/10.1016/j.pcad.2018.05.005.
36. Arques S. Serum albumin and cardiovascular disease: state-of-the-art review. Ann Cardiol Angeiol. 2020;69(4):192–200. https://doi.org/10.1016/j.ancard.2020.07.012.
37. Takahashi T, Watanabe T, Shishido T, Watanabe K, Sugai T, Toshima T, et al. The impact of non-alcoholic fatty liver disease fibrosis score on cardiac prognosis in patients with chronic heart failure. Heart Vessel. 2018;33(7):733–9. https://doi.org/10.1007/s00380-017-1113-1.
38. Párraga LP, Bosch PV, Martínez-López I, Sánchez OD, Sotelo JM, Hernández MAC. Evaluation of pharmaceutical intervention in patients with hepatic insufficiency in a hospital setting. Gastroenterol Hepatol Open Access. 2018;9(6):241–7. https://doi.org/10.15406/ghoa.2018.09.00335.