INVITED REVIEW

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Cardiovascular dysfunction in patients with liver cirrhosis

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Abstract

Hyperdynamic syndrome is a well-known clinical condition found in patients with cirrhosis and portal hypertension, characterized by increased heart rate and cardiac output, and reduced systemic vascular resistance and arterial blood pressure. The leading cause of hyperdynamic circulation in cirrhotic patients is peripheral and splanchnic vasodilatation, due to an increased production/activity of vasodilator factors and decreased vascular reactivity to vasoconstrictors. The term "cirrhotic cardiomyopathy" describes impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in patients with cirrhosis without known cardiac disease. Underlying circulatory and cardiac dysfunctions are the main determinant in the development of hepatorenal syndrome in advanced cirrhosis. Moreover, the clinical consequences of cirrhosis-related cardiovascular dysfunction are evident during and after liver transplantation, and after transjugular intrahepatic portosystemic shunt insertion. Cardiovascular complications following these procedures are common, with pulmonary edema being the most common complication. Other complications include overt heart failure, arrhythmia, pulmonary hypertension, pericardial effusion, and cardiac thrombus formation. This review discusses the circulatory and cardiovascular dysfunctions in cirrhosis, examining the pathophysiologic and clinical implications in light of the most recent published literature.

Keywords Hyperdynamic syndrome, cirrhotic cardiomyopathy, cardiovascular dysfunction, cirrhosis

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Introduction

Hyperdynamic syndrome is a well-known clinical condition found in patients with cirrhosis and portal hypertension [1-3]. It is characterized by increased heart rate and cardiac output, and reduced systemic vascular resistance and arterial blood pressure [4]. The leading cause of hyperdynamic circulation in cirrhotic patients is peripheral and splanchnic vasodilatation, due to an increased production/activity of vasodilator factors (such as nitric oxide [NO], carbon monoxide [CO], and endogenous cannabinoids) and decreased vascular reactivity to vasoconstrictors [4-6].

Although the presence of cardiomyopathy in cirrhotic patients has been described since 1960s, it had been erroneously attributed to alcoholic cardiotoxicity [1,7,8]. Only in the last 2 decades has it been shown that cardiac dysfunction is also present in nonalcoholic cirrhosis. The term "cirrhotic cardiomyopathy" was introduced to describe impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in the absence of known cardiac disease [9-12].

The circulatory dysfunction and the abnormal activation of systemic and renal neurohormonal regulation in advanced cirrhosis are the main determinant in the development of the hepatorenal syndrome (HRS). However some studies suggested that underlying cardiac dysfunction precedes the development of HRS [13-16]. Cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) insertion are at high risk of developing cardiovascular complications. This may be the consequence of diastolic dysfunction, common feature in this patient population [17,18]. Furthermore, the clinical consequences of cirrhosis-related cardiovascular dysfunction are evident during and after liver transplantation (LT) [19], and this may be manifestation of occult cirrhotic cardiomyopathy [20]. These data point out the importance of a careful cardiac assessment of cirrhotic patients, but also suggest the need for further studies to identify specific diagnostic protocols in this patient population.

This review discusses the circulatory and cardiovascular dysfunction in cirrhosis, examining the pathophysiologic and clinical implications in the light of the most recent published literature. Hepatopulmonary syndrome has been the topic of recent comprehensive reviews and will not be discussed here [21,22].

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Conflict of Interest: None

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Hyperdynamic circulation

Kowalski and Abelmann [1] first documented in 1953 that cirrhosis is associated with a hyperdynamic circulatory syndrome, characterized by an increase in cardiac output and a decrease in peripheral vascular resistance. These findings were subsequently confirmed in several studies [2,3].

Frequently, cirrhotic patients display clinical signs such as palmar erythema, reddish skin, raised and bounding pulse, and low blood pressure, secondary to systemic vasodilatation [4]. Peripheral and splanchnic vasodilatation is the leading cause of hyperdynamic circulation and portal hypertension in advanced cirrhosis [4,5]. Initially, a reduction in systemic vascular resistance is compensated by an increase in cardiac output, and effective arterial blood volume remains in the normal range. In advanced stages of cirrhosis, a marked reduction in systemic vascular resistance cannot be compensated by a further increase in cardiac output, and this leads to underfilling of arterial circulation. At this stage, there is activation of vasoconstrictor systems such as renin-angiotensin, sympathetic nervous system, and antidiuretic hormone, which maintain effective arterial blood volume and arterial pressure [23]. On the other hand, these compensatory systems are the leading cause of sodium and water retention that lead to ascites formation with the disease progression [24]. Moreover, a prolonged activation of the aforementioned vasoconstrictor systems lead to severe renal vasoconstriction and reduced glomerular filtration rate, a condition that may escalate into a progressive renal insufficiency, namely HRS [23,25].

Pathogenetic mechanism

The precise mechanism leading to systemic vasodilatation in advanced cirrhosis is unclear, however, several humoral substances have been identified as possible mediators of peripheral vasodilatation and portal hypertension: especially NO, but also adrenomedullin, natriuretic peptides, cytokines, hydrogen sulphide, endothelins, and endocannabinoids [26].

NO has been recognized as the most important vasodilator molecule in the splanchnic and systemic circulation of patients with cirrhosis [27]. NO distribution differs in the splanchnic circulation of patients with cirrhosis: it is decreased in the intrahepatic microcirculation, where there is a predominance of vasoconstrictor molecules such as angiotensin II and endothelin 1, and is overproduced in the remaining part of the splanchnic circulation. The net result is a progressive increase in intrahepatic vascular resistance, and, at the same time, an increase in splanchnic vasodilatation [27]. Additionally, endothelial dysfunction, with reduced NO bioavailability and increased vasoconstrictor cyxlooxygenase-1-derived prostanoids is implicated in the pathogenesis of increased intrahepatic resistance [28]. The altered intestinal mucosal permeability and the portosystemic collaterals allow the transfer of a large amount of endotoxins that promote NO production [29]. Moreover, cytokines such as tumor necrosis factor-α, are considered other NO inducers [30].

Endocannabinoids are other factors that may play a role in the peripheral vasodilatation of cirrhotic patients [31]. They are lipid-like substances acting on two inhibitory G protein-coupled receptors, CB1 and CB2. CB1 receptors are upregulated in the vascular endothelium of cirrhotic rats, causing pronounced vasodilatation [32]. The administration of CB1 receptor antagonist was able to reverse the arterial hypotension and to increase the splanchnic vascular resistances in cirrhotic rats, leading to a concomitant decrease in the mesenteric arterial blood flow and portal pressure [32,33]. Additionally, Varga *et al* [34] showed that bacterial endotoxin stimulates endocannabinoid production in cirrhosis.

Studies in animal models and humans have shown that a decreased vascular reactivity to vasoconstrictors contributes to splanchnic arterial vasodilatation. Defects in the contractile signaling pathways in smooth muscle cells in response to vasoconstrictor stimulation contribute to vascular hyporesponsiveness to endogenous vasoconstrictors [6].

Moreover, recent studies have shown that renin-angiotensin system mediates mesenteric vasodilatation in cirrhosis through an alternative system in which angiotensin II is cleaved by the angiotensin-converting enzyme (ACE) 2 to angiotensin [1-7], which activates the G-protein coupled Mas receptor (MasR) [35]. In the splanchnic vessels of patients and rats with cirrhosis, increased levels of ACE2 appear to increase production of angiotensin [1-7], which leads to activation of MasR and splanchnic vasodilatation in rats. This mechanism could cause vascular hypocontractility in patients with cirrhosis, and might be a therapeutic target for portal hypertension [36].

Lastly, there may be a potential role of the central nervous system (CNS) in the pathogenesis of hyperdynamic circulation in cirrhosis. A marker protein (Fos) has been detected in the brainstem and hypothalamic cardiovascular-regulatory nuclei of rats following portal vein ligation; the blockade of CNS Fos expression resulted in eliminating the development of the hyperdynamic circulation [37].

Cirrhotic cardiomyopathy

The presence of cardiocirculatory dysfunction in liver cirrhosis has been described since 1960s but it was erroneously attributed to alcoholic cardiomyopathy [1,7,8]. Only in the last 2 decades has it been shown that cardiac dysfunction is also present in nonalcoholic cirrhosis and is characterized by depressed cardiac contractility in response to stimuli [9-11]. Thus, the term "cirrhotic cardiomyopathy" was introduced to describe this cardiac dysfunction in patients with cirrhosis [38-43]. Cirrhotic cardiomyopathy is defined as "cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in the absence of known cardiac disease" [12].

Systolic dysfunction

The left ventricular ejection fraction (LVEF), which reflects systolic function, has been found normal at rest in patients with cirrhosis [44-47]. Conversely, an attenuated LVEF has been shown after several stimuli such as exercise, sodium load or erect posture [44-46,48-50]. This can be attributed to a blunted heart rate response to stress, reduced myocardial reserve and impaired muscular oxygen extraction [44,51].

Diastolic dysfunction

A decreased preload reserve in response to various loading conditions has been reported in cirrhosis, both in human and in animal models [10,52]. Moreover various studies have demonstrated diastolic dysfunction in patients with ascites improved after paracentesis [48,49,53,54]. This diastolic dysfunction may be a consequence of cardiac hypertrophy, patchy fibrosis and subendothelial edema [4]. Determinants of a diastolic dysfunction on a Doppler echocardiogram are decreased E/A ratio (less than 1), which is the ratio of early to late atrial phases of ventricular filling. The E/A ratio is decreased in cirrhotic patients, especially in those with ascites [48,49,53,54].

However, a low E/A is highly preload-determined, and also a E/A <1 may be a normal age-related finding. Doppler tissue imaging measures the slow velocity high amplitude annular tissue motion (denoted by E') that is less affected by preload. An increase in the E/E' ratio has been used as a more sensitive measure of diastolic dysfunction [55].

Dyastolic dysfunction, with an impaired passive and active filling of the left ventricle during diastole, leads to an inability to adequately increase stroke volume in response to stimuli, and may be responsible for the development of heart failure. Thus, diastolic dysfunction may precede systolic dysfunction in cirrhosis, and may be responsible to the reported low physical activity seen in cirrhotic patients [56,57]. Additionally, diastolic dysfunction probably contributes to the pathogenesis of fluid retention in these patients [48,49].

Electrophysiological abnormalities

Prolonged QT interval on the electrocardiogram have been documented in cirrhosis, with a prevalence that exceeds 60% in patients with an advanced disease, and has been related with the severity of liver disease [58]. Moreover, these abnormalities disappear after LT [59-62].

Henriksen *et al* [63] found an electromechanical dissociation (dispersion between the onset of electrical systole and the mechanical systole) in patients with different degrees of severity of cirrhosis. Although these electrophysiological abnormalities may be associated with increased risk of ventricular arrhythmia and sudden cardiac death, these events are rare in cirrhosis, and their clinical significance in patients with cirrhosis is unclear. Studies in cirrhotic rats suggest that functional alterations of potassium channels in cardiac plasma membranes may be the main responsible of cardiac electrophysiological abnormalities [64,65]. The prolongation of the Q-T interval is partly reversible after β-blocker treatment [66]. However, β-blockers remain the cornerstone of therapy in patients with cirrhosis and portal hypertension [67], and the presence of electrophysiological abnormalities are not an indication/contraindication for their use.

Chronotropic incompetence

It consists of a defective cardiac response to physiological and pharmacological stimuli able to increase heart rate, and has long been recognized in cirrhosis [68]. The clinical importance of chronotropic incompetence in cirrhotics is unknown [62], however, recent studies suggest it may play a role in the pathophysiology of some cirrhosis complications, such paracentesis-induced circulatory dysfunction [69], renal failure precipitated by spontaneous bacterial peritonitis [15] and HRS [16].

Pathogenic mechanism

NO and endocannabinoids are endogenous substances involved in the pathogenesis of hyperdynamic circulation in cirrhosis [27,29-32]. Additionally, these substances have a negative inotropic effect in human and animal models, and the use of specific antagonist restored the myocardial contractile response in cirrhotic rats [70-73]. Thus, these substances may have a role in the pathogenesis of cirrhotic cardiomyopathy.

CO is a known vasodilalator that also has negative inotropic effects [74]. Liu *et al* [75] showed that hemoxygenase-CO pathway was augmented in ventricles of cirrhotic rats compared to controls, and hemoxygenase inhibition restored the contractility of papillary muscles in cirrhotic rats but not in controls. Based on these data the authors suggested that hemoxygenase-CO activation is involved in the pathogenesis of cirrhotic cardiomyopathy [75].

The catecholamine stimulation of β-adrenergic receptors leads to a number of intracellular effects resulting in intracellular calcium fluxes and cardiac muscle contraction [76]. In cirrhotic patients and animal model β-receptors density is reduced [11], and β-receptors signaling pathway is also impaired at different levels [77,78]. Contrary to β-1 and β-2 receptors, which are down-regulated in cirrhosis, β-3 receptors are normally expressed and are responsible for the unexpected negative inotropic effects of catecholamines. These receptors may serve to protect the myocardium against negative effects of excessive catecholamine stimulation [14,79]. However, in some stress conditions such as infections or hemorrhage, when a compensatory cardiac reserve is needeeds to maintain a sufficient perfusion of vital organs, β-3 adrenoceptor activation may cause deleterious myocardial dysfunction and may be involved in the chronotropic incompetence seen in cirrhosis, decreasing the cardiac output [14].

Membrane fluidity, the mobility of lipid moieties in the lipid bilayer of the plasma membrane, determines important cellular biochemical and biophysical properties [80]. The fluidity of plasma membrane is impaired in heart cells and others tissues in patients with cirrhosis, and this leads to abnormal biochemical and biophysical functions, with negative effects on β-receptor signaling pathway [77,80,81].

Adrenal insufficiency is another condition possibly involved in the cardiocirculatory dysfunction observed in advanced cirrhosis [82,83], although the prevalence of adrenal insufficiency reported in the literature has been largely overestimated when the serum total cortisol was used [84,85].

Clinical consequences of cardiovascular dysfunction in cirrhosis

Some studies suggested that underlying cardiac dysfunction in advanced cirrhosis, namely cirrhotic cardiomyopathy, is an important determinant in the pathogenesis of HRS [13-16]. HRS is a functional renal failure present in approximately 20% of advanced cirrhotics that confers a worse prognosis [24]. The main determinants in the development of HRS are the circulatory dysfunction and the abnormal activation of systemic and renal neurohormonal regulation in advanced cirrhosis. The effective central blood volume is reduced in advanced cirrhosis due to arterial splanchnic vasodilatation, reduced systemic vascular resistance, and arterial blood pressure. Consequently, there is an abnormal activation of potent vasoconstricting systems such as sympathetic nervous system, renin-angiotensin-aldosterone system, and non-osmotic release of vasopressin. This leads to the development of hyperdynamic circulation with an increased heart rate and cardiac output [4]. However, some studies suggested that underlying cardiac dysfunction precedes the development of HRS [13-16].

Ruiz-del-Arbol *et al* reported a lower cardiac output in patients with cirrhosis who developed renal failure during a course of spontaneous bacterial peritonitis compared to those without renal failure. Moreover, after resolution of the infections, those patients with renal failure had an even lower cardiac output [15]. In another study from the same group assessing 66 patients with cirrhosis and refractory ascites, a low baseline cardiac output was associated with the development of HRS [16]. In 24 patients with advanced cirrhosis, a low cardiac index (ratio between cardiac output from left ventricle in 1 min and body surface area) was associated with lower glomerular filtration rate and higher plasma levels of creatinine [13]. Moreover, patients with suppressed cardiac function had higher probability of developing HRS type 1 within 3 months [13]. These data support the association between cardiac dysfunction and renal failure in cirrhosis, the so-called "cardio-renal syndrome" [14,86,87].

TIPS insertion leads to significant hemodynamic changes, with a sudden increase in the preload, that may rapidly worsen the hyperdynamic circulatory state of cirrhotic patients [18,88]. Multiple cardiovascular complications such as arrhythmias, heart failure, myocardial ischemia, and acute pulmonary edema have been reported following TIPS insertion [17]. This may be the consequence of diastolic dysfunction, a common feature in this patient population [17,18]. In a recent study, E/A ratio <1, an indicator of diastolic dysfunction, was predictive of slow ascites clearance and death after TIPS [89]. This study confirms previous data showing a high mortality rate in patients with an E/A ratio <1 [90]. These data demonstrate that TIPS candidates are at high risk of developing cardiovascular complications, thus deserving a careful assessment of cardiac function prior to TIPS insertion.

The clinical consequences of cirrhosis-related cardiovascular dysfunction are evident during and after LT, because the hemodynamic system is further compromised by the effect of anesthesia, mechanical ventilation, and surgical clamping, with a significant reduction in the cardiac output [19]. Ripoll *et al* [20] investigated the cardiac response during LT in 209 cirrhotic patients. Abnormal cardiac response was observed in 47 (22.5%) patients after reperfusion, and this was related to a longer postoperative intubation time. The authors suggested that the abnormal cardiac response observed during LT is a manifestation of occult cirrhotic cardiomyopathy [20].

Cardiovascular complications following LT are common, with pulmonary edema being the most common complication. Other complications include overt heart failure, arrhythmia, pulmonary hypertension, pericardial effusion, and cardiac thrombus formation [19,91,92].

In a recent study, Fouad *et al* [19] reviewed 197 patients who underwent LT to identify predictors of cardiac complications within 6 months after transplantation. By multivariate analysis, after adjusting for age and sex, independent predictors were adverse intraoperative cardiovascular events, history of cardiac disease, and model for end-stage liver disease score. Conversely, none of the pre-LT investigations (chest X-ray, electrocardiogram, echocardiography, coronary angiography, pulmonary arterial pressure, and 2-methoxy isobutyl isonitrile scan) predicted complications. In another study, two-dimensional and dobutamine stress echocardiography, used to predict the development of adverse cardiac events following LT, showed a low predictive value [93].

These data point out the importance of a careful cardiac assessment in LT candidates, but also suggest the need for further studies to identify standardized diagnostic protocols and clear prognostic factors in this patient population.

Coronary artery disease (CAD) in patients undergoing LT

In the past it was believed that cirrhosis of the liver had a protective role for CAD, and this was supported by some studies reporting a low prevalence of atherosclerosis in patients with cirrhosis [94-96]. These observations were motivated by a theoretical protective role of some common features in cirrhotic patients: reduced circulating low-density lipoproteins and total cholesterol as a result of abnormal synthetic liver function [97], decreased vascular resistance and low blood pressure [98], and high levels of circulating estrogens [96].

However, recent cohort studies assessing cirrhotic candidates for LT have reveled a high prevalence of asymptomatic CAD in these patients. Sixty-five LT candidates without known CAD underwent multidetector computed tomography coronary angiography: 58% had mild CAD and

34% had moderate to severe CAD [99]. In another study [100], the prevalence of coronary artery calcification, a novel and independent predictor of cardiovascular risk, was assessed by thoracic computed tomography scans in 147 consecutive patients undergoing assessment for LT: moderate disease was identified in 37.6% of patients, with 19.8% classified as a high-risk group. Nearly all the cardiovascular disease was occult as few were known to have CAD. Moreover, Tiukinhoy-Laing *et al* [101] reported a prevalence of moderate or severe CAD of 26% in 161 patients LT candidates assessed with coronary angiography.

Conventional cardiovascular risk factors have become common in patients with liver cirrhosis thanks to increased survival rates, and this explains the reported high prevalence of CAD in this population. In particular some risk factors such as age >60 years, male gender, history of CAD, dyslipidemia, smoking and diabetes mellitus are independent risk factors for CAD in cirrhotic candidates for LT [101,102]. Other risk factors for CAD have been assessed (renal failure, C-reactive protein) but they need to be more extensively evaluated [103]. Moreover, nonalcoholic fatty liver disease (NAFLD), an important cause of liver disease, is an independent risk factor for cardiovascular events [104-106].

In a recent retrospective case-control study comparing patients with nonalcoholic steatohepatitis (NASH) and alcoholic cirrhosis, NASH was more frequently associated with cardiovascular events after LT compared with alcoholic cirrhotic patients [107].

The presence of CAD is the major contributor of the post-LT outcomes, and cardiovascular complications are the main cause of non-graft-related mortality after LT [108,109]. In a study assessing 32 patients with CAD who underwent LT, patients with significant CAD (stenosis ≥70%) had an overall all-cause mortality rate of 50% and morbidity rate of 81%. Half of these deaths occurred in the first 35 days after LT as a direct consequence of CAD, and this high mortality rate occurred irrespective of the treatment modality for CAD [109]. In another study, among patients who survived 3 years after LT, cardiovascular disease accounted for 21% of the total deaths, and was the third most common cause of death after recurrent primary liver disease and malignancy [110].

All these data highlight the need for a rigorous cardiovascular risk assessment in LT candidates. However, there are currently no specific guidelines in this patient population, and clinicians use general guidelines for the preoperative assessment before non cardiac surgery [111,112]. It has been suggested that patients with advanced liver disease have a different risk-factor profile for CAD than general population, thus new prospective studies are needed to identify more specific scores for these patients [113].

An initial cardiovascular risk-factor assessment is followed by noninvasive functional testing to identify the presence of CAD. This is currently another gray area, as superiority of a test compared to others has not been established, and data in the literature are conflicting. Dobutamine stress echocardiography (DSE) has been advocated as the assessment tool of choice in these patients [112,114]. However, several studies have shown that DSE has a poor performance to predict outcomes in patients with cirrhosis [93,115-117]. The high prevalence of β-blocker use in patients with advanced cirrhosis, which limits the achievements of the target heart rates during the test, may be responsible of a high prevalence of nondiagnostic tests [117]. Other emerging techniques for coronary artery and myocardial functional assessment, such as computed tomography coronary artery calcification scoring and cardiac magnetic resonance imaging may be useful to improve the identification of CAD in advanced cirrhotic patients in the waiting list for LT, but further studies are needed to evaluate their diagnostic performance in this population [118].

At this time, there is no strong evidence for or against routine cardiac screening of asymptomatic transplantation candidates. Conversely, noninvasive stress testing should be considered in LT candidates with multiple (3 or more) CAD risk factors regardless of functional status [119]. Moreover, it is reasonable to perform resting echocardiography for the purpose of identifying pulmonary hypertension and/or intrapulmonary arteriovenous shunt [119].

Last, for patients with positive or equivocal initial non-invasive test, and for patients initially assessed to be at high or intermediate risk for CAD, proceeding directly to coronary angiography is the preferable option, once any coagulopathy is corrected [120].

Cardiovascular diseases in patients with NAFLD

NAFLD is highly prevalent diseases in the general adult population, with a prevalence of 15-30% and increase steadily to 70-90% in obesity and type 2 diabetes [121], representing the most common cause of chronic liver disease and LT [122].

In recent epidemiological studies, cardiovascular disease was found to be the major cause of death in subjects with NAFLD, with liver disease being the third cause of death [123]. The association between NAFLD and cardiovascular diseases represents an important matter of debate. Given the shared features between NAFLD, metabolic syndrome (MS) and traditional cardiovascular risk factors, it remains controversial whether NAFLD is merely a marker or an independent factor involved in the pathogenesis of cardiovascular events.

Recently, some studies were performed to evaluate and clarify the nature of the association between NAFLD and the risk of incident cardiovascular outcomes. In the Valpolicella Heart Diabetes Study [124], the presence of ultrasound-diagnosed NAFLD in a large cohort of type 2 diabetic patients was associated with an increased incidence of cardiovascular events, independently of a broad number of confounding factors. Almost identical results were reported in a community-based cohort of 1,637 non-diabetic individuals [125].

A recent study from a Danish National Registry reported that 28% of NAFLD patients died during the study period and the leading causes of death were related to cardiovascular disease and cancer [126]. Wong *et al* [127] enrolled 612 consecutive patients with ultrasound-diagnosed fatty liver. All patients underwent a coronary angiogram. Significant CAD, defined as ≥50% stenosis in at least one coronary artery,

was present in 84.6% of those with fatty liver, confirming the association between NAFLD and CAD. In addition, in a multiple regression analysis fatty liver remained independently associated with CAD.

The lack of diagnostic uniformity and the difficulty in accurately quantifying the severity of NAFLD in the various published studies make interpretation of results challenging and sometimes contradictory. Despite these limitations, the majority of the published data suggest an association between NAFLD and cardiovascular outcomes.

In addition, a large body of evidence supports the relationship between NAFLD and intermediate markers of atherosclerosis, independently of the broad spectrum of risk factors of MS. In a large observational study, the histological severity of NAFLD predicted carotid intima media thickness independently of classical risk factors, homeostasis model assessment (HOMA)-estimated insulin resistance and components of MS [128]. Villanova *et al* [129] showed that non-diabetic patients with NAFLD had a significant decrease in brachial artery endothelial flow-mediated vasodilatation when compared with matched healthy controls, and this was correlated to histological features of NAFLD, independently of age, sex, body mass index (BMI), HOMA-insulin resistance and other MS components. Lee *et al* [130] demonstrated that the presence of more severe degree of fatty liver disease added incremental value beyond traditional cardiovascular risk factors in the predicting coronary artery calcification.

Furthermore, with the development of NASH, cardiovascular mortality increases at least two-fold [131]. As shown by Targher *et al* [132], NASH seems to predict a more atherogenic risk profile: in patients with biopsy-proven NASH plasma level of hs-CRP was significantly higher compared to non-obese healthy subjects or overweight patients without NASH. Another study showed that NAFLD patients had an increased concentration of ultrasensitive CRP independently of other metabolic factors [133]. Recently, several cytokines and chemokines (interleukin [IL]-8, IL-6, monocyte chemotactic protein 1, chemokine receptor type 2) have also been involved in atherosclerosis and obesity. Another important marker of atherosclerosis is myeloperoxidase (MPO), an enzyme released by activated leukocytes, elevated in vulnerable plaques. MPO has been shown to be a good predictor of the risk of myocardial infarction and major adverse cardiac events. In patients with NASH, MPO levels were found increased compared with those of similar BMI and without NASH [134].

The presence of a procoagulant imbalance in patients with NAFLD has been suggested on the basis of the inflammatory state associated with this condition and on epidemiological studies [135]. Recently, Tripodi *et al* [136] confirmed this hypothesis in a study involving 113 patients with varying histological liver damage (32 with steatosis, 51 with steatohepatitis, 30 with metabolic-cirrhosis), 54 with alcoholic/viral cirrhosis and 179 controls. The authors found a procoagulant imbalance, resulting from increased factor VIII and reduced protein C, progressing from the less severe (steatosis) to the most severe (metabolic-cirrhosis) form of NAFLD. This imbalance might play a role in the risk of cardiovascular events and liver-fibrosis linked with NAFLD.

These data suggest that NAFLD plays a direct role in CAD pathogenesis, and all NAFLD patients need an overall assessment of CAD risk and the comprehensive management of atherosclerotic risk factors.

Concluding remarks

Liver cirrhosis is a systemic disease with widespread functional consequences affecting almost any other organ including the cardiovascular system. Some systemic complications of cirrhosis, such as HRS, acute and chronic encephalopathy, hepatopulmonary syndrome, are well-defined and specific guidelines have been developed for their diagnosis and treatment. Cardiovascular dysfunction in patients with liver cirrhosis has been documented since 1960 [2,3], although only recently has it been well-characterized and defined [9-12].

In the majority of cases, cardiocirculatory dysfunction develops as subclinical condition during the natural course of liver disease, manifesting only in certain clinical situations. For example cirrhotic cardiomyopathy is an important determinant in the pathogenesis of HRS [13-16]. Moreover, pre-existing diastolic dysfunction in cirrhotic patients causes cardiovascular complications after TIPS insertion [17,18,88]. Recent cohort studies have shown a high prevalence of asymptomatic CAD in cirrhotic patients candidates for LT [99-101]. The presence of CAD is the major contributor of the post-LT outcomes, and cardiovascular complications are the main cause of non-graft-related mortality after LT [108,109]. Moreover NAFLD, an important cause of liver disease, is an independent risk factor for cardiovascular events [104-106].

All these data highlight the need for a rigorous cardiovascular risk assessment in patients with liver cirrhosis. It has been suggested that patients with advanced liver disease have a different risk-factor profile for cardiovascular disease than the general population [113]. However, there are currently no specific guidelines for the diagnosis and treatment of cardiovascular disease in this patient population. Thus, new prospective studies are needed to identify more specific criteria and standardized procedure for cardiovascular assessment and treatment of cardiocirculatory dysfunction in patients with liver cirrhosis.

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