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Xiu-Xia Song, Vice Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

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REVIEW

Redox therapeutics in hepatic ischemia reperfusion injury

Rakesh P Patel, John D Lang, Alvin B Smith, Jack H Crawford

Rakesh P Patel, Department of Pathology, Center for Free Radical Biology, University of Alabama at Birmingham, Birmingham, AL 35294, United States
John D Lang, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, WA 98108, United States
Alvin B Smith, Department of Anesthesiology, University of Alabama Birmingham, Birmingham, AL 35249, United States
Jack H Crawford, Division of Cardiothoracic Anesthesia, Department of Anesthesiology, University of Alabama Birmingham, Birmingham, AL 35249, United States
Author contributions: All authors contributed equally to the design of the review; Patel RP and Crawford JH wrote the review; Smith AB designed and developed the figure; all authors contributed to critical revision and editing of the article.
Correspondence to: Jack H Crawford, MD, PhD, Professor, Division of Cardiothoracic Anesthesia, Department of Anesthesiology, University of Alabama Birmingham, 619 19th Street South, JT 845, Birmingham, AL 35249, United States. dunston@uab.edu
Telephone: +1-205-9347424 Fax: +1-205-9963195
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Abstract

Ischemia-reperfusion plays a major role in the injury experienced by the liver during transplantation. Much work has been done recently investigating the role of redox species in hepatic ischemia-reperfusion. As animal models are better characterized and developed, and more insights are gained into the pathophysiology of hepatic ischemia reperfusion injury in humans the questions into exactly how oxidants participate in this injury are becoming more refined. These questions include effects of cellular location, timing of injury, and ability of therapeutics to access this site are increasing our appreciation of the complexity of ischemia reperfusion and improving attempts to ameliorate its effects. In this review, we aim to discuss the various methods to alter redox chemistry during ischemia reperfusion injury and future prospects for preventing organ injury during hepatic ischemia reperfusion.

Key words: Ischemia; Reperfusion; Pre-conditioning; Nitrite

Core tip: Reactive oxygen and nitrogen species play a central role in the pathology of ischemia-reperfusion injury. In this review we discuss the efforts of many groups to trial therapeutics to ameliorate this damage in animal models of disease as well as clinical trials in humans. The failure of some trials has served to highlight the complexity of timing and compartmentalization of Ischemia Reperfusion injury. Finally, we discuss the emerging potential of replenishing nitric oxide by nitrite therapy and the uniquely broad therapeutic profile of nitrite.

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INTRODUCTION

Ischemia reperfusion injury (IRI) identified in animal models in the mid-70's was not a widely used clinical term until the mid-80's[1-3]. Ischemia reperfusion is a process whereby the initial damage caused to tissue by compromised blood flow (and associated deficit in oxygen and nutrient delivery) is then compounded by additional and more severe injury caused by restoration of blood flow (*i.e.*, reperfusion). Multiple participants play a role in the post ischemic stress that is caused by restoration of blood flow and oxidant formation, the interplay of these participants form the initial layer of complexity to the problem of IRI. An excellent review by Jaeschke and

Woolbright discusses in greater detail the cellular and molecular participants in post ischemic stress of IRI[4]. Adding to this complexity is the multiple and diverse situations in which IRI occurs in the clinic which we posit likely leads to unique signatures of IRI in different diseases. In this review we discuss IRI that occurs in liver transplantation and how our understanding of these redox mechanisms may be critical as we attempt to define and implement strategies aimed at expanding donation pools by utilizing marginal donors[5]. The term marginal donor refers to grafts from donors of old age, steatosis, viral infection or other known insults to the liver graft. The added complexity resulting from each distinct clinical scenario has required further development of our scientific models to more closely mimic the problem[6]. These models have revealed a more prominent role for IRI when marginal grafts are used. The goal of this review is to provide the reader a brief review of the pathophysiology of IRI and focus the discussion on attempts to ameliorate IRI and how these therapeutics are suggesting a direction forward for clinical strategies.

One emerging candidate for the inhibition of mitochondrial dysfunction and restoration of nitric oxide bioactivity during ischemia reperfusion injury is the Nitrite anion. Emphasis on nitrite within this review will discuss the unique profile of *in vivo* nitrite to address the multiple insults of IRI injury.

IRI

During the ischemic phase of injury liver tissue is left with anaerobic metabolism to keep up with the demand of various cellular processes for high energy phosphates. Eventually the supply of high energy phosphates becomes inadequate resulting in disruption of cellular homeostasis. Primarily disruption of Na^+/K^+ ATPase function results in loss of membrane gradients which then allows for Ca^{2+} influx to the cell. Further production of reactive oxygen and nitrogen species (ROS, RNS), H^+ and toxic metabolites amplify injury and attract water into the cell and the resultant edema further impairs cellular function. As cell death begins within the hepatocytes, nearby endothelial cells and Kupffer cells begin to express adhesion molecules and chemokines, that recruit neutrophils to the site of injury and amplify tissue injury[7]. Below we discuss individual cell types implicated in liver IRI during transplantation and their respective roles in controlling the redox milieu (Figure 1).

Kupffer cells

Kupffer cells are perhaps the most important producer of ROS during the ischemic stress that occurs during the cold preservation of transplantation. A general lack of appreciation of the details of the hepatic IRI led to studies providing more detail into the timing and compartmentalization of IRI. The observation that glutathione was oxidized in the extracellular space but not within the hepatocyte drew attention to leukocytes. Given that very few neutrophils had infiltrated the liver during the early phase of ischemia focus was directed at the resident macrophages of the liver, the Kupffer cells, as possible mediators of glutathione oxidation[8,9]. Given that circulating leukocytes have not begun to infiltrate the liver in the early phase of ischemia and that donor blood is largely flushed from the liver during the initiation of cold preservation it is likely that the role of Kupffer cells in ROS production is relatively more important during the IRI experienced by the transplanted organ. The main ROS generated by Kupffer cells has been demonstrated to be the superoxide anion radical, and selective inhibition of Kupffer cells has been shown to ameliorate IRI further emphasizing the role of ROS derived from these cells[8,10,11]. Targeting the Kupffer cells clinically is challenging given their multiple roles in normal liver function and defense. However, this work reveals the clinical relevance of inhibiting ROS within the more accessible extracellular or vascular space.

Neutrophils

As Kupffer cells contribute to the early ischemic phase, neutrophils infiltrate and cause much of the damage after reperfusion. Cytokines and chemokines produced by the activated Kupffer cells initiate expression of the cellular adhesion molecules such as ICAM-1 and VCAM-1. Neutrophils become activated, adhere, and begin to infiltrate the hepatic tissue. Once activated neutrophils are capable of producing large amounts of superoxide, hydrogen peroxide, and hypochlorous acid[2,12]. These ROS are then capable of injuring the hepatocyte with the mitochondria being principal targets[13,14].

Mitochondria

Mitochondria play a central and complex role in IRI as both sources and targets of reactive oxygen species (ROS). Mitochondria produce ROS such as the superoxide anion as a result of electron leak during normal respiration. This process is enhanced during ischemia leading to decreased ATP production and organelle dysfunction[15]. Ultimately, mitochondria become central to the fate of the cell as opening of the mitochondrial permeability transition pore (MPT) instantly short circuits the membrane potential resulting in the cessation of ATP production and necrosis ensues[16]. Interestingly, whilst opening of the MPT may occur if the ischemic phase is long enough, it has also been shown that the MPT opening can be triggered by oxidant stress that ensues with the restoration of oxygen supply thereby supporting the model of IRI in that the tissue injury is amplified during the post ischemic stress phase[14].

ANTI-OXIDANT BASED THERAPIES TO INHIBIT IRI

As described above, elucidation of the mediators, timing, and location of IRI has proven complex and presented many potential targets for therapy. Indeed further experiments to evaluate the role of many therapeutics within

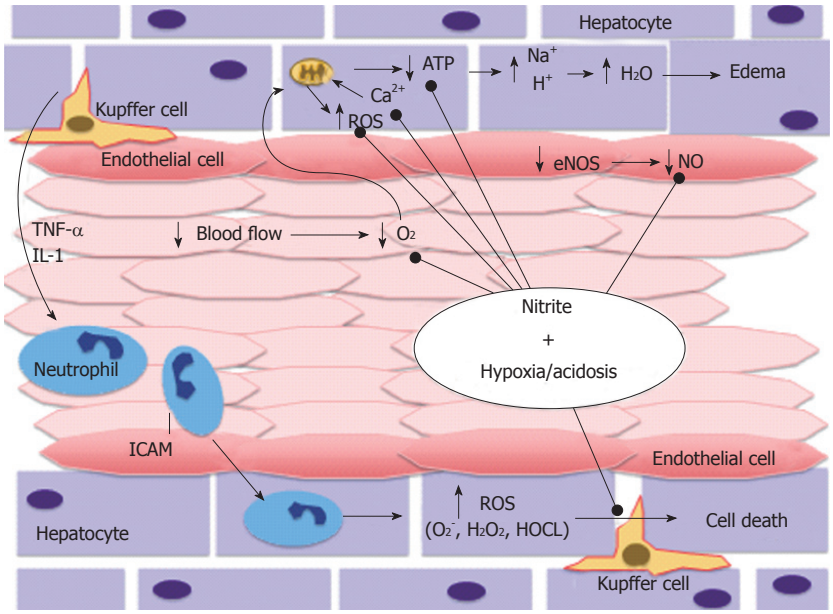

Figure 1 Ischemia initiates injury leading to reactive oxygen species formation from mitochondria and Kupffer cells. Restoration of blood flow introduces neutrophils and substrate that further amplify injury. Nitrite reduction in the setting of hypoxia and acidosis restores nitric oxide bioavailability and augments mitochondrial tolerance to ischemia if administered prior to injury. ROS: Reactive oxygen species; ATP: Adenosine triphosphate; TNF: Tumor necrosis factor; IL: Interleukin; ICAM: Intercellular adhesion molecule; O_2^-: Superoxide anion; H_2O_2: Hydrogen peroxide; HOCL: Hypochlorous acid.

animal models of IRI have displayed promise[6]. Further appreciation for the complexities of IRI within humans will develop as we attempt to intervene with therapies in clinical trials. Further, attempts to expand organ donation pools to decrease mortality within the waiting list for organ transplantation will result in a greater need to optimize graft function by inhibiting IRI. The following will discuss several potential therapies of relevance to ROS and RNS during IRI and their translational potential.

Ischemic preconditioning

Since initial observations that exposure of organs to brief periods of non-lethal ischemia provides protection from injury against a subsequent lethal ischemic event[17], many studies have established the concept of ischemic preconditioning (IP) in multiple organs[18-20] and across various species, including humans[18,21,22]. Unlike many pathologies characterized by a period of ischemia, liver transplantation presents an ideal model for therapies such as ischemic preconditioning as liver is exposed to a defined, scheduled, and relatively controlled period of cold ischemia.

Animal models of IP have shown that IRI can be inhibited by a defined therapy period of multiple[3-5], brief (5-10 min) bouts of ischemia followed by a reperfusion phase of equal time. As alluded to above although organ transplantation may represent an ideal model for IP it also emphasizes that the greatest limitation to IP in other human diseases, such as myocardial ischemia, is the inability to predict when the injury may occur and provide the therapeutic IP. This limitation has led to the search for the mechanism and mediators of IP in hopes of duplicating its effects pharmacologically. Interestingly, this research has led to the finding that the effects of IP are not completely limited to the timing or location of the ischemic therapy in order to provide a protective effect and have led to the advent of ischemic post conditioning[23] and remote ischemic preconditioning[24].

The hypotheses to explain the phenomena of ischemic conditioning generally fall into the general categories of IP causing changes directly on the organ subjected to the repeated IP therapy or that a humoral factor is produced by the tissue undergoing IP that then provides a systemic effect of protection. Given the advent of remote IP the evidence would suggest the latter mechanism predominates. Further, blood taken from rabbits that have undergone preconditioning confer their protective effects during myocardial infarction in rabbits that have not undergone a preconditioning phase[25]. Mechanistic studies have revealed that adenosine, bradykinin, or perhaps other circulating factors signal through G-protein coupled receptors[26]. This initiates a signaling cascade involving activation of protein kinase C[27], heat shock factor 1[28], and mitogen-activated protein kinase[29]. Activation of these receptors during preconditioning result in up regulation of multiple systems capable of attenuating IRI including superoxide dismutase, heat shock proteins, and eNOS[30-32]. Interestingly, the mild oxidation associated with the sub-lethal insult of IP as opposed to the hypoxia itself has been shown to confer protection against a subsequent lethal insult. Specifically, inducing a mild oxidative insult of infusing a peroxide analog into the portal vein of a mouse protected the liver from a subsequent ischemic insult enforcing the concept that timing and amount of exposure to oxidants results in either protection by inducing anti-oxidant de-

fenses, or overwhelm the cell and initiate cell death[33].

Attempts to translate preconditioning whether pre-, post-, or remote into human disease has had mixed results[34]. In part this is due to variance in the research and clinical models such as the timing of preconditioning. Mechanistic studies into IP have led to many potential candidates to confer the protective effects of IP pharmacologically. Some of these molecules will be discussed further below and include redox active effectors. Ongoing work in humans will further assess the clinical relevance of IP on liver transplantation outcomes[35].

Volatile anesthetics

Further evidence to support the principle of providing a pharmacologic agent that imparts the benefits of ischemic preconditioning is the finding that volatile anesthetics impart a similar profile of protection against ischemia reperfusion injury in the heart[36]. Termed anesthetic preconditioning, this phenomenon has been reproduced in multiple species and by multiple volatile anesthetics. Mechanistically, it appears that anesthetic preconditioning does closely parallel ischemic preconditioning and interestingly *via* ROS species induces a minute stress that activates similar pathways of ischemic preconditioning within target cells. The net effect is the up regulation of anti-oxidant systems such as heme oxygenase, and eNOS that help protect the cell from an ensuing IRI[37,38]. Human studies have revealed that patients preconditioned with sevoflurane experienced a reduction in peak transaminase levels, an improvement in clinical outcomes, and enhanced benefit in those with steatotic livers. Interestingly, iNOS mRNA was significantly increased in the preconditioned group suggesting a role for NO although further investigation into mechanism or eNOS expression was not performed[39]. As the role of nitric oxide in IRI and protection is more complex a detailed discussion is saved for a later sub-section.

Glutathione/NAC

Glutathione (GSH) is an important intracellular anti-oxidant and reductant found in high concentrations within hepatocytes. The protective role of glutathione and its importance in intracellular detoxification is emphasized by the model of glutathione oxidation and depletion found in acetaminophen overdose. Glutathione may react directly with oxidants such as peroxynitrite and hydrogen peroxide, but also provides reducing equivalents to maintain catalytic antioxidant systems (*e.g.*, glutathione peroxidase) that provide protection against these ROS and RNS in intracellular compartments[40,41]. Additionally, hepatocytes export glutathione and thereby detoxify the important ROS produced by Kupffer cells within the vascular space as described above during the early phases of IRI. GSH can either be administered itself or reduced GSH levels can be replenished by N-acetylcysteine (NAC) administration. Both GSH and NAC have been shown to reduce ROS production and oxidant stress after IRI[42,43]. Additionally, clinical trials of NAC and GSH have shown a reduction in biochemical markers of liver injury. However, few have reported differences in clinical outcomes associated with GSH or NAC infusion[44]. It should be noted that GSH or NAC therapy is limited in that non-specific effects are likely, and neither target oxidants in specific compartments. Emerging and exciting recent findings indicate that targeted expression of antioxidants for example in the mitochondria may result in more effective and safer strategies[45].

α-Tocopherol

α-Tocopherol is an orally administered analogue of vitamin E that limits lipid peroxidation. In general, α-tocopherol therapy studies have led to mixed results. In IRI of the liver, pre-treatment of α-Tocopherol in mice was shown to be protective. In humans, α-Tocopherol had no effect on biomarkers of hepatic damage after hepatic ischemia; however, patients in the α-Tocopherol treatment group had a reduction in ICU stay. Clearly, the implications on ICU length of stay are complex but suggest the potential for α-Tocopherol in human liver transplantation remains and require further testing.

Allopurinol

Xanthine oxidase has long been considered one of the major producers of ROS during IRI largely due to evidence of the protective effect of the xanthine oxidase inhibitor, allopurinol[46]. However, multiple studies have demonstrated the limited contribution of xanthine oxidase mediated generation of ROS to the post ischemic stress of IRI. These findings are further supported by the dose and length of pretreatment required to convey the protective effects of allopurinol relative to the much smaller dose and time demonstrated to effectively inhibit xanthine oxidase[47,48]. Additionally, the length of time required (d) for pretreatment with allopurinol to be effective will limit its potential clinically due to the limited lead time a patient has from notification until transplantation due to the nature of organ donation.

Superoxide dismutase

One of the problems with targeting ROS in IRI is the separation of intracellular and extracellular sources of the oxidant stress during IRI as well of the timing of ROS generation within these locations. Generally, Kupffer cells produce ROS early within the ischemic phase that injures intracellular targets within the hepatocytes. Later, during the reperfusion phase previously damaged and dysfunctional mitochondria in addition to infiltrating neutrophils contribute to the oxidant stress within the intra and extracellular spaces. This delineation of timing and location was emphasized by the failure of one of the early attempts of scavenging free radicals as a means to ameliorate IRI. In these studies catalase and superoxide dismutase were administered intravenously either in combination or alone[49]. This study found only partial protection from IRI implicating a significant role for other ROS or highlighting the weakness that this therapy

cannot target the intracellular effects of ROS. Subsequent studies have utilized carbohydrate modifications of these enzymes or gene delivery to up regulate the intracellular activity of these enzymes and have shown potential benefit and cause for further investigation[50,51].

Augmentation of endogenous nitric oxide and application of exogenous nitric oxide and Nitrite

Nitric oxide (NO) produced at low levels by endothelial nitric oxide synthase (eNOS) is associated with protection against IRI *via* multiple possible mechanisms including preventing leukocyte adhesion and limiting reactive oxygen species production by mitochondria. Moreover, deficits in eNOS-derived NO have been documented in numerous inflammatory disorders and IRI, although how eNOS activity is altered in human liver transplantation remains to be clearly defined[52,53]. Consistent with protective effects of eNOS are gene therapy studies that show overexpression of this enzyme in the liver protects against IRI in mice[54].

An alternate strategy to gene therapy is to augment NO using NO-repletion strategies. Many NO-donors exist but suffer from a lack of compartmentalized release that can result in unwanted effects (*e.g.*, hypotension)[55]. Recent studies are beginning to address this limitation. As alluded to above, targeting drugs to the mitochondria is now a possibility. This has also been demonstrated with NO, with a mitochondrial targeted S-nitrosothiol showing protection against IRI in the heart[56,57] in part by limiting ROS production in this organelle. The potential for this strategy in liver transplantation remains to be tested. In addition, recent studies have shown that nitrite administration can replete NO-signaling in areas of ischemia[58]. The underlying concept is that nitrite will only be reduced to NO by ischemia sensitive mechanisms and thus only produce NO in the environments where needed and avoid unwanted systemic effects (Figure 1). This concept has been validated in numerous experimental models, including hepatic IRI and lung and liver transplantation providing a rationale for testing in humans[59-64]. Supporting this rationale is the protective effects of inhaled NO in preventing IRI and improving graft function in liver transplant patients[52]; the protective effects of inhaled NO was posited to be mediated by increased circulating nitrite levels. In addition to a therapy that can be administered during the ischemic phase, nitrite may also be a candidate therapeutic to mimic IP exemplified by studies showing nitrite administration to normal rats, resulting in protection against myocardial and hepatic IRI 24#h thereafter *via* mechanisms that involved limiting mitochondrial dysfunction during the IRI period[61].

CONCLUSION

Further appreciation of the time course and mediators of IRI has led to the discovery of many potential therapeutics. Each of these faces the hurdle of increased complexity and other unknowns when trying to translate to the pathology seen in human disease. Take for instance the IRI of liver transplantation and the question of when best to administer a proposed therapeutic to: the donor, the graft after harvest, the graft during flushing prior to reperfusion, or after reperfusion. Now, clinical trials must utilize the best data available to choose timing of administration and the most valuable targets to investigate whether the therapy is working by the proposed mechanism. These studies will provide the mechanistic insights currently needed into the IRI of human pathology.

Additionally, the demand for a better understanding of IRI is increasing as we try to reduce the significant wait list mortality caused by demand outpacing supply. This push is causing a closer look at marginal grafts deemed as such because they are steatotic or come from donors of advanced age. These conditions are important to the field of IRI as many of the therapeutics outlined above show an enhanced benefit in steatotic livers. In order to optimize these grafts system changes are occurring within the organ donation network primarily to reduce cold ischemic times associated with transportation. These proposed changes will result in donors being transported to specialized centers more experienced with organ harvest which should minimize organ harvest time and as the recipient will be located at the same medical center this will significantly limit cold ischemic time. Importantly, the advent of donation centers will also create an opportunity to further study these processes. As our clinical trials are often controlled for safety by regulatory boards it has been logistically difficult to administer a therapeutic to a donor that will conceivably affect multiple recipients at multiple institutions. Although donation centers do not remove all logistical barriers of such studies they will create more opportunities to address IRI prior to the ischemic phase and certainly allow for tissue collection to improve our understanding of the human disease.

Given the outlined complexity of IRI it seems that the ideal candidate therapeutic will function by multiple pathways. By preventing ROS production, scavenging ROS in the vascular space and preventing the intracellular damage and mitochondrial dysfunction caused by ROS in the reperfusion phase we may envision an ideal therapeutic against IRI. It is unlikely a single candidate will fulfill the multitude of needs of the ideal therapeutic but as we gain further information on the mechanisms of human IRI it will be possible to identify a combination of therapeutics to best ameliorate the effects of IRI.

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REVIEW

Complementary and alternative medications in hepatitis C infection

Dina L Halegoua-De Marzio, Jonathan M Fenkel

Dina L Halegoua-De Marzio, Jonathan M Fenkel, Division of Gastroenterology and Hepatology, Thomas Jefferson University Hospital, Philadelphia, PA 19107, United States
Author contributions: Halegoua-De Marzio DL and Fenkel JM both outlined, researched the topics, and wrote the manuscript.
Correspondence to: **Jonathan M Fenkel, MD,** Division of Gastroenterology and Hepatology, Thomas Jefferson University Hospital, 132 S. 10th Street, Suite 480, Main Building, Philadelphia, PA 19107,
United States. jonathan.fenkel@jefferson.edu
Telephone: +1-215-9558900 Fax: +1-215-5032146
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Abstract

Chronic hepatitis C (CHC) infection affects almost 3% of the global population and can lead to cirrhosis, liver failure, and hepatocellular carcinoma in a significant number of those infected. Until recently, the only treatments available were pegylated interferon and ribavirin, which traditionally were not very effective and have considerable side effects. For this reason, interest in complementary and alternative medications (CAM) in the management of hepatitis C has been investigated. Some CAM has demonstrated therapeutic potential in chronic hepatitis C treatment. Unfortunately, some CAM has been shown to have the potential to cause drug-induced liver injury. This article will review and evaluate many of the natural molecules that interact with the hepatitis C virus (HCV) life cycle and discuss their potential use and safety in HCV therapy, as well as highlight some important interactions between medical and complementary treatments.

Key words: Hepatitis C infection; Natural molecules; Direct acting antivirals; Hepatotoxicity; Herbal treatments

Core tip: Over the last 10 years there has been a substantial increase in reports of natural compounds displaying anti-viral activity against hepatitis C. At this time, there is no firm evidence supporting complementary and alternative medications for hepatitis C virus infection. Due to a limited number of trials and small numbers of subjects included in them, it is not possible to fully evaluate the risk of adverse events connected with the use of these products.

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INTRODUCTION

Hepatitis C virus (HCV) infection affects an estimated 180 million people globally and is a leading cause of chronic hepatitis, cirrhosis, and liver cancer[1,2]. To prevent the complications of chronic hepatitis C (CHC), the goal of therapy is complete viral eradication. For the past decade, a combination of pegylated interferon-α (peg-IFN) and ribavirin was used to treat CHC with disappointing viral eradication rates. These rates were particularly suboptimal in patients with genotype 1 HCV, which is responsible for approximately 60% of worldwide infections[3]. Sustained virological response (SVR) rates for genotype 1 HCV are approximately 40% following 48 wk of peg-IFN/ribavirin and are even lower in patients with HIV co-infection, high baseline viral load, advanced fibrosis, or those of African descent[4-7].

The life cycle of HCV can be divided into three major steps: (1) entry of the virus into its target cells by receptor-mediated endocytosis; (2) cytoplasmic and mem-

brane-associated replication of the RNA genome; and (3) assembly and release of the progeny virions[8]. In recent years, there has been improvement in SVR rates with the development and approval of the first HCV-specific direct-acting antiviral agents (DAAs), namely boceprevir and telaprevir[9,10]. In contrast to the non-specific antiviral activity of peg-IFN and ribavirin, DAA are designed to inhibit viral proteins involved in the HCV life cycle. Still, the first DAAs require coadministration with peg-IFN and ribavirin, and many patients remain intolerant to treatment-associated side effects, including fevers, influenza-like symptoms, headache, cytopenias, fatigue, anorexia, rash, and depressive symptoms.

CAM is being used increasingly across the globe for many chronic diseases[11,12]. The Cochrane Library included nearly 50 systematic reviews of complementary medicine interventions as of 2003[13]. Many people turn to CAM when conventional medicine fails, or they believe strongly in its effectiveness. During the last few years, a substantial increase of reports on natural compounds displaying an anti-HCV activity has been published. There is data that some of these medicinal herbs might have therapeutic potential in CHC, or may alleviate side effects of conventional therapy[13]. CAM use is common among people with CHC. A survey of 1145 participants in the National Institutes of Health (NIH)-supported HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) trial found that 23% of the participants used herbal products[14]. Although sometimes thought by the public to be safer then conventional therapy, there are many reports about liver toxicity and other adverse events from some herbal products[11,15]. The aim of this review is to evaluate the efficacy and safety of treating HCV infection using complementary and alternative medicine.

MEDICINAL HERBAL AND DIETARY SUPPLEMENTS WITH ANTI-HCV ACTIVITY

Silymarin

An extract of the milk thistle plant, silymarin *(Silybum marianum*), has been used to treat chronic liver disease since the time of the ancient Greeks[16]. Owing to its purported hepatoprotective properties, it is the most commonly used herbal product by individuals with chronic liver disease in the United States[16,17]. A recent publication from the HALT-C study group indicated that 33% of patients with CHC and cirrhosis reported current or past use of silymarin[14]. A follow-up study found silymarin use among CHC patients was associated with reduced progression from fibrosis to cirrhosis, but had no impact on clinical outcomes[16].

The major active component of silymarin, silibinin (a mixture of the two diastereoisomers silybin A and silybin B), is thought to be responsible for silymarin's hepatoprotective properties[18]. Silymarin appears to inhibit HCV infection at two or more different levels: (1) it inhibits HCV replication in cell culture; and (2) it displays anti-inflammatory and immunomodulatory actions that may contribute to its hepatoprotective effect[19,20]. The inhibition of HCV replication has been attributed to inhibitory action on the NS5B RNA-dependent RNA polymerase.

Clinical studies that have evaluated milk thistle for a variety of liver diseases have yielded inconsistent results and low bioavailability of oral silymarin components[21]. Studies with Ⅳ silibinin have shown substantial antiviral effect against HCV in liver transplant recipients, and even in nonresponders with good safety outcomes[22-24]. Although oral administration of silymarin is not effective for the treatment of HCV, intravenous silibinin formulation may represent a future potential therapeutic option.

Green tea extract

Green tea, made from the unfermented leaves of *Camellia sinensis*, is comprised of several polyphenolic compounds called catechins, and can be concentrated into a green tea extract (GTE). Epigallocatechin-3-gallate (EGCG) is the most abundant and potent catechin contained within GTE, comprising typically approximately 40% of the total polyphenol content[25]. EGCG is a potent inhibitor of HCV entry in primary human hepatocytes independent of the genotype, by blocking virus attachment. This novel inhibitor may provide a new approach to prevent HCV infection, especially in the setting of liver transplantation of chronically infected HCV patients[26,27]. Beyond its antiviral effect on HCV, EGCG may have potential use as a chemopreventative agent for hepatocellular cancer as EGCG may inhibit cancer cell growth. This mechanism of action is thought to be due to tyrosine kinase inhibition and modulation of target gene expression associated with induction of apoptosis and cell cycle arrest in cancer cells[28-34].

GTE is a common ingredient in several dietary supplements, some of which have been withdrawn from the market due to safety concerns. An example of this is *Exolise* (Arkopharma, France), a weight loss supplement containing high EGCG levels that was withdrawn from the market in April 2003 due to 13 cases of attributable liver injury[35]. Between 1966 and 2008, 216 case reports of toxicity with green tea extracts were identified by the United States Pharmacopeia, of which 34 were concerning for liver toxicity[36]. Recent animal studies with high doses of GTE and EGCG have described dose-dependent hepatotoxicity resulting in severe morbidity and mortality[37]. However, chronic moderate to high dose daily GTE and EGCG use in healthy human volunteers, and selected patients with cirrhosis, was safe and did not impair liver function[38-40]. Although GTE may be very useful in further treatment of CHC and prevention of HCC, its hepatotoxic potential must be acknowledged and monitored carefully in future studies.

Naringenin

HCV associates with β-lipoproteins [very low density lipoprotein (vLDL) and low-density lipoprotein (LDL)]

circulating in blood[41]. In addition, HCV replication can be up-regulated by fatty acids and inhibited by statins; this suggests an interaction between HCV, cholesterol, and lipid metabolism[42]. Recent research has found that of HCV secretion is dependent on both apolipoprotein B (ApoB) expression and vLDL assembly in a chromosomally integrated complementary DNA (cDNA) model of HCV secretion[43].

Naringenin is the predominant flavanone present in the grapefruit and is responsible for its bitter taste. Naringenin has been shown to reduce cholesterol levels both *in vitro* and *in vivo*[44,45]. Furthermore, naringenin inhibits ApoB secretion by reducing the activity and the expression of the microsomal triglyceride transfer protein (MTP) and the acyl-coenzyme A cholesterol acyltransferase 2 (ACAT)[44,46]. Due to the close link between HCV assembly/secretion and lipoprotein metabolism, there has been extensive study on the impact of naringenin on the secretion of HCV particles[43]. A dose-dependent decrease of core protein, HCV-positive strand RNA, infectious particles, and ApoB has been observed in the supernatant of infected primary hepatocytes in culture after naringenin treatment[43]. Overall, naringenin blocked the assembly of intracellular infectious viral particles without affecting intracellular levels of the viral RNA or protein. Although still at the cell culture phase, naringenin may offer new insight into a promising and novel HCV therapeutic target.

Glycyrrhizin

Glycyrrhizin, a natural compound extracted from the roots of *Glycyrrhiza glabra*, has been used for more than 20 years as a treatment for chronic hepatitis[47]. It has been used for many centuries in traditional Chinese medicine as an anti-allergic agent. Because of its sweet taste it is also used as a food additive, for example in beverages and licorice[48]. In an attempt to use glycyrrhizin as a treatment for "allergic" hepatitis it was found to lower the transaminases. In a study by Suzuki *et al*[49] in 1977, plasma transaminases activity improved significantly with glycyrrhizin in patients with chronic liver disease compared to a placebo group.

The mechanism by which glycyrrhizin improves the biochemistry and histology in liver disease is unknown. It is thought to have anti-inflammatory, antioxidant and immunomodulatory activities. Due to this there has been much interest in use of glycyrrhizin in CHC. In the only randomized clinical trial of glycyrrhizin, ALT levels declined modestly during treatment, compared with placebo, but this was not sustained after cessation of treatment and there was no significant effect on HCV RNA levels[50]. In the another trial, statistically significant differences in liver enzyme levels, but not viral loads, between treatment groups were identified during treatment, however, again no sustained response occurred at follow-up[51]. Use of glycyrrhizin is not without side effects. It has been found to cause pseudo-aldosteronism, manifested by sodium retention, hypokalemia and hypertension[52]. Cardiac arrhythmia and acute rhabdomyolysis due to severe hypokalemia caused by excess licorice consumption have also been reported[52-54].

Oxymatrine

Oxymatrine is the major alkaloid extract from the root of *sophora flavescens*, a deciduous shrub native to China, Japan, South Korea and Russia. It is reported to have antiviral activity against HCV in cell cultures and in animal studies[55-57]. Clinical studies have shown that oxymatrine has some hepatoprotective activity in alcohol toxicity and hepatitis B infection, but not carbon tetrachloride, acetaminophen or cadmium chloride-induced acute hepatitis[58,59]. Oxymatrine is considered to be an antifibrotic, likely through inhibition of lipid peroxidation[60-62]. In a study of HCV-infected subjects randomized subjects to receive either an intramuscular injection of oxymatrine 600 mg/d or other support products such as oral vitamins 47% of the treated cases had complete HCV viral suppression after 3 mo, compared with only 5% in the control group[61]. No serious adverse events were reported. The treated group had significantly more ALT normalizations than the control group in the first 2 mo, but this improvement waned by the end of the third month of treatment. While treatment with oxymatrine holds promise, it is difficult to draw conclusions from the small studies currently available.

Traditional chinese herbal medications

The primary goal of Chinese traditional medicine is to create wholeness and harmony within a person, allowing the mind/body/spirit to heal itself. There have been several randomized clinical trials of traditional Chinese medicine in the treatment of hepatitis C, however, the methodological quality of these studies is generally considered poor[63-70]. In two trials of herbal formulations in combination with interferon-alfa, there was a trend toward greater clearance of HCV RNA and ALT normalization with the combination treatment compared with patients receiving monotherapy[63,64]. In the only placebo-controlled trial of solo therapy with traditional Chinese medicine, a significant reduction in ALT levels during treatment occurred, though no virologic effect was identified[69]. Detailed descriptions of adverse events were not provided for most of these trials. The safety of these medicines is unclear due to the individualized nature of many of the herbal compounds involved, the large number of different herbs in each formulation, and the relatively small number of subjects within each clinical trial.

Vitamin D

The traditional role of Vitamin D (Vit D) was thought to be based upon its interaction in calcium homeostasis, *via* regulation of intestinal calcium absorption and of bone health. However, over the last several years Vit D has been shown to have a much more complex role in many other host functions, including its interaction with

chronic hepatitis C. 25-OH Vit D is made in the liver *via* cytochrome P450 (CYP27A1) activated hydroxylation of Vit D, brought into the body either by intestinal absorption or endogenous synthesis through sun-exposed skin. It is then converted to 1.25 OH Vit D (calcitriol) in the kidneys, the most active form, where it becomes available to bind to Vit D receptors throughout the body[71,72].

A growing body of clinical evidence has demonstrated an increased prevalence of Vit D deficiency in patients with CHC. As such, Vit D supplementation has been proposed as an adjunct to current standard regimens for treatment of hepatitis C[72]. One study found that mean 25-OH Vit D serum levels were significantly lower in CHC (25 μg/L) than in the controls (43 μg/L)[73]. Importantly, low Vit D has been linked to increased fibrosis and impaired sustained virologic response (SVR) in IFN-based therapy[71]. One clinical trial demonstrated that the addition of Vit D to the standard IFN plus ribavirin treatment significantly increased SVR in patients with genotype 1 CHC[74]. Regarding the underlying molecular mechanisms, an *in vitro* study showed that Vit D remarkably inhibits HCV production in Huh7.5 hepatoma cells[75]. These cells express Vit D hydroxylases and can eventually generate calcitriol. Notably, treatment with calcitriol resulted in HCV inhibition through induction of IFN-beta. Overall, 25-OH Vit D levels appear to be an important prognostic marker in helping determine the likelihood of SVR. 25-OH Vit D levels should be checked routinely before HCV treatment and supplementation provided to deficient patients, in an effort to enhance treatment response.

Antioxidants

Antioxidants are one of the most common dietary supplements taken by patients with CHC[14]. The use of these supplements is based on the fact that oxidative stress has been attributed to both host inflammatory processes and induction by viral proteins. By increasing antioxidants, one may be able to decrease oxidative stress and therefore decrease liver injury[76]. Existence of oxidative stress in CHC is well documented, as oxidized protein and nucleic acid markers are increased and antioxidant levels are decreased[77-80]. Studies have shown levels of oxidative stress markers to correlate with disease severity, HCV RNA, iron overload, and insulin sensitivity[78,79]. Oxidative stress has also been shown to be an early event in carcinogenesis and is a risk factor for development of HCC in patients with chronic HCV[81].

Multiple trials have shown antioxidants, such as Vitamin E and N-acetyl cysteine, only lead to small reductions in ALT after chronic administration in some instances[82-93]. Further, the decrease in ALT levels in most studies is marginal and is not sustained after stopping the treatment, raising the question of their clinical significance. No study has shown an improvement in outcome. In addition, no study has shown clear benefit of antioxidants as adjuvant to interferon based therapy of HCV. At the doses studied, these antioxidants appear to be well-tolerated, with no specific adverse events reported in any of the trials. However, very large oral doses of *N*-acetyl cysteine are commonly associated with nausea and vomiting and intravenous administration of *N*-acetyl cysteine can result in anaphylactoid reactions, which may be more common in patients with chronic liver disease[94]. Therefore, evidence supporting use of antioxidants as useful therapeutic agents in CHC is lacking.

HERBAL SUPPLEMENTS AND DRUG INDUCED LIVER INJURY IN CHRONIC HCV

Drug-related hepatotoxicity is a serious health problem, with broad implications for patients, healthcare providers, the pharmaceutical industry and governmental regulatory agencies. The Drug Induced Liver Injury Network (DILIN), a federally funded consortium of 12 centers in the United States, recently reported the preliminary results of its prospective study[94]. Dietary supplements were implicated in 9% of reported DILI cases. This may be potentially related to increasing use of herbal or dietary supplements in the US population. The importance of these supplements as a cause of DILI is further underscored by a retrospective Japanese study, in which 10% of 879 cases of single agent DILI from 1997 to 2006 were attributed to dietary supplements and 7% to Chinese herbal drugs[95].

In general, chronic liver diseases such as HCV infection are thought to be associated with an increased incidence of hepatotoxicity induced by several specific drugs. Furthermore, patients with underlying liver disease potentially have worse outcomes than healthy individuals if they do develop DILI[96]. For example, the presence of underlying CHC has been shown to increase the risk of DILI caused by the antituberculosis drugs isoniazid and rifampin, as well as ibuprofen and methimazole[15,97,98]. Due to this, patients with chronic hepatitis C should be counseled and screened by physicians on potential risks associated with herbal medications.

DRUG-CAM INTERACTIONS

Another major area of awareness when patients are considering using CAM is whether or not drug-CAM interactions may exist that could impact the medical therapy. This issue is becoming even more complicated with the addition of new medications for the treatment of CHC infection such as simeprevir and sofosbuvir approved for use in the U.S. in December 2013. St. John's wort (*Hypericum perforatum*), a common CAM used for the treatment of depression, is an inducer of cytochrome P450 3A4[99]. This cytochrome is also the primary metabolizer of many medications, including the HCV protease inhibitors: telaprevir, boceprevir, and simeprevir. Additionally, St. John's wort is a potent intestinal P-gp inducer and may lead to a reduced therapeutic effect of

Table 1 Herbal supplements to discontinue and/or avoid while taking hepatitis C virus treatment

Herbal Product	Effect
Milk thistle (*Silybum marianum*)	Concomitant use of milk thistle may result in increased plasma concentrations of simeprevir
St. John's wort (*Hypericum perforatum*)	Concomitant use of St. John's wort may result in decreased plasma concentrations of telaprevir, boceprevir, simeprevir and sofosbuvir

the HCV nucleotide polymerase inhibitor sofosbuvir[100]. Concomitant use of St. John's wort and these HCV treatments is contraindicated and can lead to treatment failure by reducing blood concentrations. Additionally, concomitant use of milk thistle use is contraindicated with simeprevir. This combination may increase levels of simeprevir by milk thistle CYP3A inhibition leading to possible toxicity[101] (Table 1). Garlic extracts, grapefruit juice, and germander also have cytochrome P450 3A4 interactions[102].

CONCLUSION

Many human studies have shown improvements in subjective symptoms and liver biochemistries in HCV patients with CAM, but there is no convincing data to suggest a definite histological and/or virologic improvement with any of the herbal agents currently available. Vit D seems to have the best available data as adjunctive therapy to antiviral medications in patients with Vit D deficiency. Poorly designed studies, heterogeneous patient populations, lack of standardized preparations, and poorly defined nonobjective end points may partly explain the conflicting reports in the literature.

The safety profiles of the interventions discussed within this review are encouraging at the doses studied. However, the long-term safety for use in the treatment of hepatitis C, either alone or in combination with conventional medicines, has not been established. Comparative and placebo-controlled trials suggest that patients experience no more adverse events with these interventions than with placebo or comparative medications, although short-term clinical trials are not designed to detect rare or delayed adverse events. Physicians need to be cognizant of known or occult use of CAM by their patients because hepatotoxicity and drug interactions may occur with many herbal medications, and may occur more frequently in patients with chronic liver disease.

There is an undoubted need for further research into the treatment of hepatitis C, and this review has identified several promising compounds, including Vit D, silymarin, oxymatrine, naringenin, and GTE. Some or all of these may be integral components of future HCV management.

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REVIEW

Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment

Rolf Teschke, Albrecht Wolff, Christian Frenzel, Alexander Schwarzenboeck, Johannes Schulze, Axel Eickhoff

Rolf Teschke, Alexander Schwarzenboeck, Axel Eickhoff, Department of Internal Medicine Ⅱ, Klinikum Hanau, Academic Teaching Hospital of the Medical Faculty of the Goethe University of Frankfurt/Main, D-63450 Hanau, Germany
Albrecht Wolff, Department of Internal Medicine Ⅱ, Division of Gastroenterology, Hepatology and Infectious Diseases, Friedrich Schiller University Jena, D-07743 Jena, Germany
Christian Frenzel, Department of Medicine Ⅰ, University Medical Center Hamburg Eppendorf, 20246 Hamburg, Germany
Johannes Schulze, Institute of Industrial, Environmental and Social Medicine, Medical Faculty, Goethe University, 60590 Frankfurt/Main, Germany
Author contributions: Teschke R and Eickhoff A provided substantial contributions to the conception and design; Wolff A, Frenzel C and Schwarzenboeck A contributed to the literature search and acquisition of relevant literature; Teschke R, Schulze J and Eickhoff A contributed to analysis and interpretation of the data; Teschke R contributed to drafting the article; Wolff A, Frenzel C, Schwarzenboeck A, Schulze J and Eickhoff A contributed to revising it critically for important intellectual content; all the authors contributed to final approval of the version to be published.
Correspondence to: Rolf Teschke, MD, Professor of Medicine, Department of Internal Medicine Ⅱ, Klinikum Hanau, Academic Teaching Hospital of the Medical Faculty of the Goethe University of Frankfurt/Main, Leimenstrasse 20, D-63450 Hanau, Germany. rolf.teschke@gmx.de
Telephone: +49-6181-21859 Fax: +49-6181-2964211
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Abstract

Causality assessment of suspected drug induced liver injury (DILI) and herb induced liver injury (HILI) is hampered by the lack of a standardized approach to be used by attending physicians and at various subsequent evaluating levels. The aim of this review was to analyze the suitability of the liver specific Council for International Organizations of Medical Sciences (CIOMS) scale as a standard tool for causality assessment in DILI and HILI cases. PubMed database was searched for the following terms: drug induced liver injury; herb induced liver injury; DILI causality assessment; and HILI causality assessment. The strength of the CIOMS lies in its potential as a standardized scale for DILI and HILI causality assessment. Other advantages include its liver specificity and its validation for hepatotoxicity with excellent sensitivity, specificity and predictive validity, based on cases with a positive reexposure test. This scale allows prospective collection of all relevant data required for a valid causality assessment. It does not require expert knowledge in hepatotoxicity and its results may subsequently be refined. Weaknesses of the CIOMS scale include the limited exclusion of alternative causes and qualitatively graded risk factors. In conclusion, CIOMS appears to be suitable as a standard scale for attending physicians, regulatory agencies, expert panels and other scientists to provide a standardized, reproducible causality assessment in suspected DILI and HILI cases, applicable primarily at all assessing levels involved.

Key words: Drug induced liver injury; Drug hepatotoxicity; Herb induced liver injury; Herbal hepatotoxicity; Causality assessment

Core tip: We propose that the attending physicians caring for patients with assumed drug induced liver injury and herb induced liver injury should use the Council for International Organizations of Medical Sciences (CIOMS) scale for causality assessment. This approach includes the option of subsequent refinement of the CIOMS based results by expert panels and regulatory agencies. The use of the CIOMS scale as an identical

tool for all involved parties will allow early and prospective collection of all relevant data required for a valid causality assessment in clinical hepatology.

Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. *World J Hepatol* 2014; 6(1): 17-32 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i1/17.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i1.17

INTRODUCTION

Drug induced liver injury (DILI) and herb induced liver injury (HILI) are complex diseases and often overdiagnosed[1-5]. An expert review of suspected DILI reports from primary and secondary care physicians to the UK Committee on the Safety of Medicine revealed that 47.1% of the cases were not DILI and that the misdiagnoses delayed arriving at the correct diagnoses, possibly worsening patient outcome[1]. Misdiagnosis was a common phenomenon in other DILI studies[2-4], including publications in which DILI was initially assumed, but hepatitis E virus infection later on evolved as the correct diagnosis[2,3]. Similarly, in a recent assessment of initially suspected HILI, correct diagnoses were missed in 278/573 cases, corresponding to 48.5%[5]. Given these frequencies because of insufficient case assessment, DILI and HILI represent major issues for physicians who care for patients with these diseases.

Physicians commonly are confronted with a wealth of published data about hepatic adverse drug and herb reactions and may use this information for evaluating the cases of their patients. Reviews addressed general aspects of DILI[6,7] or HILI[4,8-10], whereas other reports focused on various basic features like clinical course, prognosis, alternative causes, case definition and phenotype standardization[5,11-17]. They suggest a similar or identical clinical presentation of DILI and HILI, raising the question of whether HILI needs a separate term. However, major differences exist between DILI and HILI; DILI is caused by a single chemically characterized drug, whereas HILI is triggered by a chemical mixture constituted of the herbal extract, which often lacks the benefit of regulatory surveillance. Herbal product quality varies and is a major issue in HILI, adding to the complexity in evaluating causality for herbs. This may explain why HILI is considered as a poorly defined entity, is a neglected disease, and requires special attention.

Potential genetic risk factors and biomarkers, including micro-RNA, are presently being investigated to explain DILI and HILI disease[18-20]. These data provide promising clinical and scientific results but currently contribute little to diagnose DILI or HILI correctly and in time, or to exclude alternative causes. Recognizing that the best approach is still not available in clinical practice, the physician needs a pragmatic guideline to quickly evaluate suspicious cases and reach a conclusive diagnosis. This is at present best achieved by the combination of clinical judgement and a liver specific causality assessment algorithm like the CIOMS (Council for International Organizations of Medical Sciences) scale[21,22], as has been summarized recently[10,14,23-25]. For DILI and HILI case reports, the CIOMS scale based on international consensus meetings[21,22,26,27] is the commonly applied method to assess causality[4,5,10,14,23,24,28,29]. In clinical practice, causality assessment of suspected hepatotoxicity is hampered by the lack of a standardized approach, which is applicable to all levels of causality assessment[4,14,24] and requires simplicity of the assessment method rather than complexity to evaluate DILI and HILI cases.

This review analyzes the suitability of the liver specific CIOMS scale for causality assessment in DILI and HILI cases as a standard for attending physicians, regulatory agencies, expert panels and the scientific community. It focuses on the characteristic features of the CIOMS scale, discusses strengths and weaknesses, and suggests approaches for the clinician who lacks a standby panel of DILI or HILI experts.

The PubMed database was searched for the following terms: drug induced liver injury; herb induced liver injury; DILI causality assessment; and HILI causality assessment. The literature search was done on June 4, 2013. Several hundreds of records were initially obtained, depending of the term used. The first 50 publications of each search were analyzed in depth for suitability in the analysis of the CIOMS scale quality, with numerous duplicated reports found in each category. The final compilation of evaluated publications consists of original papers, case series, case reports, consensus reports and review articles. All relevant reports were included in the reference list to be presented in this review. Analyzed reports were published between 1977 and 2013, preferentially within the last decade.

GENERAL ASPECTS

The liver specific and quantitative CIOMS scale was conceptualized and developed in consensus meetings organized at the request of the Council for International Organizations of Medical Sciences (CIOMS), with details published in 1993[21,22]. This CIOMS scale represented a breakthrough in DILI causality assessment methods and extended, specified and quantified the preceding qualitative RUCAM (Roussel Uclaf Causality Assessment Method) of 1988[26] and qualitative CIOMS method of 1990[27]. The basis for the CIOMS scale was provided by eight experts in hepatology from 6 countries and included J P Benhamou (France), J Bircher (Germany), G Danan (France), W C Maddrey (United States), J Neuberger (United Kingdom), F Orlandi (Italy), N Tygstrup (Denmark) and H J Zimmerman (United States)[21]. This expert panel evaluated DILI cases for case characteris-

tics, hepatotoxicity criteria, liver injury pattern and reexposure criteria, standardized DILI case assessment with specific, quantitative items[21], and the experts validated their method with established positive reexposure DILI case results[22]. The CIOMS scale was developed for assessment of a single drug containing a synthetic product and may be used for a single herb containing multiple chemical constituents, but does not allow causality attribution to a specific constituent. The scale is a learning system and not immutable; room for improvement and refinement of the CIOMS scale has been outlined[29], with modifications of the CIOMS scale based on improved diagnostic instruments[14].

STRENGTHS

Prospective use

Its prospective application enables the CIOMS scale to provide an early causality grading for patients with suspected DILI or HILI; its results can be adapted further to diagnostic and therapeutic measures. This scale is easily used as a bedside tool at a time the disease is developing (Tables 1 and 2). Results do not depend on expert opinion and are quickly available for trained physicians to decide whether DILI and/or HILI should be considered as relevant differential diagnoses due to their clinical experience. Assessment is best started on the day of suspecting DILI or HILI, with a continuous update of the required data and a change in the diagnostic and therapeutic concept if needed. Finally, a complete data set for presentation to regulatory agencies, expert panels and eventually for publication is obtained[24,30-33], including a checklist with additional data helpful in overall case evaluation and causality assessment (Table 3). Therefore, the CIOMS scale should be considered as a standard for causality assessment of DILI and HILI, both for the attending physician and later evaluation stages. Using one single assessment method at all evaluating levels allows comparison of different assessment outcomes.

Liver specificity

Liver specificity is a hallmark of the CIOMS scale, in contrast to liver unspecific causality assessment methods or ad hoc approaches[4,24]. The CIOMS items are specially tailored to liver injury and not applicable to liver unrelated adverse drug reactions[24]. All current core elements of hepatotoxicity are considered in the CIOMS scale (Tables 1 and 2): time to onset of increased liver values or symptoms from the beginning and cessation of the drug/herb; course of liver enzymes after cessation; risk factors such as alcohol, age and pregnancy; comedication with other drugs/herbs; search for alternative causes, previously known drug/herb hepatotoxicity; and response to unintentional reexposure[21-25] based on specific criteria (Table 4). The individual items are transparent and facilitate quick and precise answers.

The CIOMS scale is structured and all its items undergo quantitative rather than qualitative assessment and scoring (Tables 1 and 2)[4,5,10,14,21,23,24,29]. Each item is weighted with specific scores based on the answer. The sum of the individual scores gives a final score that may range from -9 to +14 points, allowing for sufficient discrimination. The final score provides causality levels for the individual synthetic drug or herb as highly probable, probable, possible, unlikely or excluded (Tables 1 and 2)[12,24,30-32].

Hepatotoxicity definition

The international CIOMS expert panel defined liver injury in its consensus report as increased alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) activities of at least 2N, with N as the upper limit of normal[21]. Conversely, the consensus of the international DILI Expert Working Group with participants from Europe, the United States and Japan raised the ALT cut off point to 5N or 3N if total bilirubin values exceeded 2N and considered the 2N of ALP as an appropriate definition criterion[14]. Whereas the DILI Expert Working Group recommendations were based on expert opinion alone[14], those of the CIOMS expert panel were derived from both expert opinion and assessment of reference reexposure DILI cases[21,22].

Raising the ALT cut off to 5N increases the specificity of the hepatotoxicity causality assessment[24], eliminates false positive cases and substantiates hepatotoxicity causality at a higher level of probability[16,24]. The lower threshold of ALT > 2N will include multiple cases with nonspecific enzyme increases and requires more stringent exclusion of causes unrelated to drug(s) and herb(s)[24]. Also for low threshold N values, the inclusion rate of alternative diagnoses must be higher; false positive fulfilment of a hepatotoxicity definition results in high numbers of misattributed cases due to overdiagnosing and overreporting[8,12,17,24,34-48]. This phenomenon is illustrated in a recent HILI study where initial ALT values were available in only 8/22 cases (36%), including 3 cases with a range of 50-69 U/L serum activity[36]. None withstanding, regulatory assessment attributed a possible causality for the incriminated herb to all 22 cases[36,42]. In other spontaneous case collections, initial ALT values were available in 5/24 cases (21%)[35], 19/22 cases (86%)[37], 12/15 cases (80%)[38], and 7/13 cases (54%)[39]. The corresponding figures for ALT in published case reports of HILI were 16/16 cases (100%)[35], 21/21 cases (100%)[32], and 5/8 cases (63%)[33]. ALT values were included in DILI reports for amoxicillin/clavulanic acid, troglitazone, pioglitazone and montelukast in 11% to 88% of the cases, which were not further scored for causality by the Drug Induced Liver Injury Network (DILIN)[6]. ALT underreporting is therefore an issue for both DILI and HILI.

Other arguments merit further considerations. An ALT cut off point of 5N may not be applicable to some types of chronic liver injury like methotrexate liver fibrosis or nodular regenerative hyperplasia; misinterpretation is also possible in some forms of acute liver injury by mitochondrial toxicity in cases of valproate or

Table 1 Council for International Organizations of Medical Sciences scale for the hepatocellular type of injury and cholestatic or mixed type of injury in drug induced liver injury and herb induced liver injury cases

Items for hepatocellular injury	Score	Result
1 Time to onset from the beginning of the drug/herb		
5-90 d (rechallenge: 1-15 d)	2	-
< 5 or > 90 d (rechallenge: > 15 d)	1	-
Alternative: Time to onset from cessation of the drug/herb		
≤ 15 d (except for slowly metabolized chemicals: > 15 d)	1	-
2 Course of ALT after cessation of the drug/herb		
Percentage difference between ALT peak and N		
Decrease ≥ 50 % within 8 d	3	-
Decrease ≥ 50 % within 30 d	2	-
No information or continued drug/herb use	0	-
Decrease ≥ 50 % after the 30th day	0	-
Decrease < 50 % after the 30th day or recurrent increase	-2	-
3 Risk factors		
Alcohol use (drinks/d: > 2 for women, > 3 for men)	1	-
Alcohol use (drinks/d: ≤ 2 for women, ≤ 3 for men)	0	-
Age ≥ 55 yr	1	-
Age < 55 yr	0	-
4 Concomitant drug(s) or herbs(s)		
None or no information	0	-
Concomitant drug or herb with incompatible time to onset	0	-
Concomitant drug or herb with compatible or suggestive time to onset	-1	-
Concomitant drug or herb known as hepatotoxin and with compatible or suggestive time to onset	-2	-
Concomitant drug or herb with evidence for its role in this case (positive rechallenge or validated test)	-3	-
5 Search for non drug/herb causes	Tick if negative	-
Group Ⅰ (6 causes)		
Anti-HAV-IgM	□	-
HBsAg, anti-HBc-IgM, HBV-DNA	□	-
Anti-HCV, HCV-RNA	□	-
Hepatobiliary sonography/colour doppler sonography of liver vessels/endosonography/CT/MRC	□	-
Alcoholism (AST/ALT ≥ 2)	□	-
Acute recent hypotension history (particularly if underlying heart disease)	□	-
Group Ⅱ (6 causes)		
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases	□	-
Infection suggested by PCR and titer change for CMV (anti-CMV-IgM, anti-CMV-IgG)	□	-
EBV (anti-EBV-IgM, anti-EBV-IgG)	□	-
HEV (anti-HEV-IgM, anti-HEV-IgG)	□	-
HSV (anti-HSV-IgM, anti-HSV-IgG)	□	-
VZV (anti-VZV-IgM, anti-VZV-IgG)	□	-
Evaluation of group Ⅰ and Ⅱ		
All causes-groups Ⅰ and Ⅱ - reasonably ruled out	2	-
The 6 causes of group Ⅰ ruled out	1	-
5 or 4 causes of group Ⅰ ruled out	0	-
Less than 4 causes of group Ⅰ ruled out	-2	-
Non drug or herb cause highly probable	-3	-
6 Previous information on hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	2	-
Reaction published but unlabelled	1	-
Reaction unknown	0	-
7 Response to unintentional readministration		
Doubling of ALT with the drug/herb alone, provided ALT below 5N before reexposure	3	-
Doubling of ALT with the drug(s) and herb(s) already given at the time of first reaction	1	-
Increase of ALT but less than N in the same conditions as for the first administration	-2	-
Other situations	0	-
Total score for patient		

The CIOMS scale is based on the original CIOMS scale[21] and was adapted from previous modifications[4,14,23,24,44,45]. The above items specifically refer to the hepatocellular type of injury rather than to the cholestatic or mixed type (shown in Table 2). Regarding risk factor of alcohol use, 1 drink commonly contains about 10 g ethanol and details were discussed recently[14,44,45]. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; CT: Computer tomography; DILI: Drug induced liver injury; EBV: Epstein Barr virus; HAV: Hepatitis A virus; HBc: Hepatitis B core; HBsAg: Hepatitis B antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HILI: Herb induced liver injury; HSV: Herpes simplex virus; MRC: Magnetic resonance cholangiography; N: Upper limit of the normal range; VZV: Varicella zoster virus. Total score and resulting causality grading: ≤ 0: Excluded; 1-2: Unlikely; 3-5: Possible; 6-8: Probable; ≥ 9: Highly probable.

fialuridine hepatotoxicity[14]. Aspartate aminotransferase (AST) activities may be used instead if ALT activities are unavailable[14,44,45] and other pathologies for AST increases are excluded[14]. ALP increases should be paral-

Table 2 Council for International Organizations of Medical Sciences scale for the cholestatic or mixed type of injury and cholestatic or mixed type of injury in drug induced liver injury and herb induced liver injury cases

Items for cholestatic or mixed injury	Score	Result
1 Time to onset from the beginning of the drug/herb		
5-90 d (rechallenge: 1-90 d)	2	-
< 5 or > 90 d (rechallenge: > 90 d)	1	-
Alternative: Time to onset from cessation of the drug/herb		
≤ 30 d (except for slowly metabolized chemicals: > 30 d)	1	-
2 Course of ALP after cessation of the drug/herb		
Percentage difference between ALP peak and N		
Decrease ≥ 50 % within 180 d	2	-
Decrease < 50 % within 180 d	1	-
No information, persistence, increase, or continued drug/herb use	0	-
3 Risk factors		
Alcohol use (drinks/d: > 2 for women, > 3 for men) or pregnancy	1	-
Alcohol use (drinks/d: ≤ 2 for women, ≤ 3 for men)	0	-
Age ≥ 55 yr	1	-
Age < 55 yr	0	-
4 Concomitant drug(s) or herbs(s)		
None or no information	0	-
Concomitant drug or herb with incompatible time to onset	0	-
Concomitant drug or herb with compatible or suggestive time to onset	-1	-
Concomitant drug or herb known as hepatotoxin and with compatible or suggestive time to onset	-2	-
Concomitant drug or herb with evidence for its role in this case (positive rechallenge or validated test)	-3	-
5 Search for non drug/herb causes	Tick if negative	-
Group Ⅰ (6 causes)		
Anti-HAV-IgM	□	-
HBsAg, anti-HBc-IgM, HBV-DNA	□	-
Anti-HCV, HCV-RNA	□	-
Hepatobiliary sonography/colour doppler sonography of liver vessels/endosonography/CT/MRC	□	-
Alcoholism (AST/ALT ≥ 2)	□	-
Acute recent hypotension history (particularly if underlying heart disease)	□	-
Group Ⅱ (6 causes)		
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases	□	-
Infection suggested by PCR and titer change for CMV (anti-CMV-IgM, anti-CMV-IgG)	□	-
EBV (anti-EBV-IgM, anti-EBV-IgG)	□	-
HEV (anti-HEV-IgM, anti-HEV-IgG)	□	-
HSV (anti-HSV-IgM, anti-HSV-IgG)	□	-
VZV (anti-VZV-IgM, anti-VZV-IgG)	□	-
Evaluation of group Ⅰ and Ⅱ		
All causes-groups Ⅰ and Ⅱ - reasonably ruled out	2	-
The 6 causes of group Ⅰ ruled out	1	-
5 or 4 causes of group Ⅰ ruled out	0	-
Less than 4 causes of group Ⅰ ruled out	-2	-
Non drug or herb cause highly probable	-3	-
6 Previous information on hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	2	-
Reaction published but unlabelled	1	-
Reaction unknown	0	-
7 Response to unintentional readministration		
Doubling of ALP with the drug/herb alone, provided ALP below 5N before reexposure	3	-
Doubling of ALP with the drug(s) and herb(s) already given at the time of first reaction	1	-
Increase of ALP but less than N in the same conditions as for the first administration	-2	-
Other situations	0	-
Total score for patient		

The CIOMS scale presented in this table is designed specifically for the cholestatic or mixed type of liver injury rather than for the hepatocellular type, which differs in a few items and is presented separately in Table 1. Additional details and abbreviations are provided in the legend of Table 1. Abbreviation: ALP, Alkaline phosphatase. Total score with resulting causality grading: ≤ 0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥ 9, highly probable.

leled by γ-glutamyltranspeptidase (γGT) to rule out isolated increases of ALP activities due to bone rather than hepatobiliary disease. However, γGT alone is not an appropriate parameter for liver cell injury[14,36], contrary to published claims[42]. In addition, isolated hyperbilirubinemia is not DILI or HILI specific and may be caused by Gilbert's syndrome[1,14].

Liver injury pattern

The CIOMS scale takes into account divergent laboratory constellations of the liver injury pattern in the hepatocellular and the cholestatic type of liver injury and

Table 3 Data checklist for drug induced liver injury and herb induced liver injury diagnosis assessment

Items to be assessed	Information obtained			Individual result
	Yes	No	Partial	
Brand name with batch number and expiration date	□	□	□	-
Indication of drug/herb use	□	□	□	-
Begin of symptoms leading to drug/herb treatment	□	□	□	-
Daily dose	□	□	□	-
Application form of drug/herb product	□	□	□	-
Exact date of drug/herb start	□	□	□	-
Exact date of drug/herb end	□	□	□	-
Exact dates of emerging new symptoms after drug/herb start in chronological order	□	□	□	-
Exact date of initially increased liver values	□	□	□	-
Time frame of challenge	□	□	□	-
Time frame of latency period	□	□	□	-
Time frame of dechallenge	□	□	□	-
Verification of temporal association	□	□	□	-
Exclusion of temporal association	□	□	□	-
Gender, age, body weight, height, BMI	□	□	□	-
Ethnicity, profession	□	□	□	-
Preexisting general diseases with past medical history and actual assessment	□	□	□	-
Preexisting liver diseases with past medical history and actual assessment regarding	□	□	□	-
Risk factors such as age and alcohol	□	□	□	-
Alcohol use with quantification	□	□	□	-
Comedication by synthetic drugs, herbal drugs, herbal and other dietary supplements with all details of product, daily dose, exact dates of start and end of use, indication	□	□	□	-
ALT value initially including exact date and normal range	□	□	□	-
ALT values during dechallenge at least on days 8 and 30, and later on, with exact dates	□	□	□	-
ALT values during dechallenge to exclude a second peak, with exact dates	□	□	□	-
ALT normalization with exact date and actual value	□	□	□	
ALP value initially including exact date and normal range	□	□	□	-
ALP values during dechallenge at least on days 8 and 30, and later on, with exact dates	□	□	□	-
ALP values during dechallenge to exclude a second peak, with exact dates	□	□	□	-
ALP normalization with exact date and actual value	□	□	□	-
AST value initially including normal range	□	□	□	-
Laboratory criteria for hepatotoxicity	□	□	□	-
Laboratory criteria for injury pattern	□	□	□	-
Liver and biliary tract imaging including hepatobiliary sonography, CT, MRT, MRC	□	□	□	-
Color Doppler sonography of liver vessels	□	□	□	-
Unintended reexposure	□	□	□	-
Known hepatotoxicity caused by the drug/herb	□	□	□	-
Other possible causes, consideration and exclusion	□	□	□	-
Hepatitis A - Anti-HAV-IgM	□	□	□	-
Hepatitis B - HBsAg, anti-HBc-IgM, HBV-DNA	□	□	□	-
Hepatitis C - Anti-HCV, HCV-RNA	□	□	□	-
Hepatitis E - Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	□	□	□	-
Cytomegalovirus (CMV) - CMV-PCR, titer change for anti-CMV-IgM and anti-CMV-IgG	□	□	□	-
Epstein Barr virus (EBV) - EBV-PCR, titer change for anti-EBV-IgM and anti-EBV-IgG	□	□	□	-
Herpes simplex virus (HSV) - HSV-PCR, titer change for anti-HSV-IgM and anti-HSV-IgG	□	□	□	-
Varicella zoster virus (VZV) - VZV-PCR, titer change for anti-VZV-IgM and anti-VZV-IgG	□	□	□	-
Other virus infections - specific serology of Adenovirus, coxsackie-B-Virus, echovirus, measles virus, rubella virus, flavivirus, arenavirus, filovirus, parvovirus, HIV, and others	□	□	□	-
Other infectious diseases - specific assessment of bacteria (such as campylobacter, coxiella, leptospirosis, listeria, salmonella, treponema pallidum), fungi, parasites, worms, tropical diseases, and others	□	□	□	-
Autoimmune hepatitis (AIH) type Ⅰ - Gamma globulins, ANA, SMA, AAA, SLA/LP	□	□	□	-
Autoimmune hepatitis (AIH) type Ⅱ - Gamma globulins, anti-LKM-1 (CYP 2D6), anti-LKM-2 (CYP 2C9), anti-LKM-3	□	□	□	-
Primary biliary cirrhosis (PBC) - AMA, anti PDH-E2	□	□	□	-
Primary sclerosing cholangitis (PSC) - p-ANCA, MRC	□	□	□	-
Autoimmune cholangitis (AIC) - ANA, SMA	□	□	□	-
Overlap syndromes - see AIH, PBC, PSC, and AIC	□	□	□	-
Non alcoholic steatohepatitis (NASH) - BMI, insulin resistance, hepatomegaly, echogenicity of the liver	□	□	□	-
Alcoholic liver disease (ALD) - patient's history, clinical and laboratory assessment, sonography	□	□	□	-
Drug/herb induced liver injury - patient's history, clinical and laboratory assessment, sonography, use of the CIOMS scale	□	□	□	-
Toxin Screening - cocaine, ecstasy and other amphetamines	□	□	□	-
Rare intoxications - toxin screening for household and occupational toxins	□	□	□	-
Hereditary hemochromatosis - serum ferritin, total iron-binding capacity, genotyping for C2824 and H63D mutation, hepatic iron content	□	□	□	-

Wilson's disease - copper excretion (24 h urine), ceruloplasmin in serum, free copper in serum, coombs-negative hemolytic anemia, hepatic copper content, Kayser-Fleischer-Ring, neurologic-psychiatric work-up, genotyping	□	□	□	-
Porphyria - corphobilinogen in urine, total porphyrines in urine	□	□	□	-
α1 - antitrypsin deficiency - α1- Antitrypsin in serum	□	□	□	-
Biliary diseases - clinical and laboratory assessment, hepatobiliary sonography, endosonography, CT, MRT, MRC	□	□	□	-
Pancreatic diseases - clinical and laboratory assessment, sonography, CT, MRT	□	□	□	-
Celiac disease - TTG antibodies, endomysium antibodies, duodenal biopsy	□	□	□	-
Anorexia nervosa - clinical context	□	□	□	-
Parenteral nutrition - clinical context	□	□	□	-
Cardiopulmonary diseases with shock liver (cardiac hepatopathy, ischemic hepatitis) - cardiopulmonary assessment of congestive heart disease, myocardial infarction, cardiomyopathy, cardiac valvular dysfunction, pulmonary embolism, pericardial diseases, arrhythmia, hemorrhagic shock, and various other conditions	□	□	□	-
Addison's disease - plasma cortisol	□	□	□	-
Thyroid diseases - TSH basal, T4, T3	□	□	□	-
Grand mal seizures - clinical context of epileptic seizure (duration > 30 min)	□	□	□	-
Heat stroke - shock, hyperthermia	□	□	□	-
Polytrauma - shock, liver injury	□	□	□	-
Systemic diseases - specific assessment of M. Boeck, amyloidosis, lymphoma, other malignant tumors, sepsis, and others	□	□	□	-
Graft *vs* host disease - clinical context	□	□	□	-
Other diseases - clinical context	□	□	□	-

This checklist is far from complete and considered as a reminder for the physician. Some listed liver diseases like AIH require a liver biopsy to establish the diagnosis. Few elements are not directed to causality assessment but are important for overall case evaluation. AAA: Anti-actin antibodies; AMA: Antimitochondrial antibodies; ANA: Antinuclear antibodies; BMI: Body mass index; CT: Computed tomography; CYP: Cytochrome P450; HAV: Hepatitis A virus; HBc: Hepatitis B core; HBsAg: Hepatitis B antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HILI: Herb induced liver injury; HIV: Human immunodeficiency virus; LKM: Liver kidney microsomes; LP: Liver-pancreas antigen; MRC: Magnetic resonance cholangiography; MRT: Magnetic resonance tomography; p-ANCA: Perinuclear antineutrophil cytoplasmatic antibodies; PDH: Pyruvate dehydrogenase; PCR: Polymerase chain reaction; SLA: Soluble liver antigen; SMA: Smooth muscle antibodies; TSH: Thyroid stimulating hormone; TTG: Tissue transglutaminase.

Table 4 Conditions of unintentional reexposure tests in drug induced liver injury and herb induced liver injury cases

Reexposure test result	Hepatocellular type of liver injury		Cholestatic or mixed type of liver injury	
	ALTb	ALTr	ALPb	ALPr
Positive	< 5N	⩾ 2ALTb	< 5N	⩾ 2ALPb
Negative	< 5N	< 2ALTb	< 5N	< 2ALPb
Negative	⩾ 5N	⩾ 2ALTb	⩾ 5N	⩾ 2ALPb
Negative	⩾ 5N	< 2ALTb	⩾ 5N	< 2ALPb
Negative	⩾ 5N	NA	⩾ 5N	NA
Uninterpretable	< 5N	NA	< 5N	NA
Uninterpretable	NA	NA	NA	NA

Conditions and criteria for an unintentional reexposure test are described in previous reports[4,21,22,24,26,27]. **Accordingly, required data for the hepatocellular type of liver injury are the ALT levels just before reexposure, designed as baseline ALT or ALTb, and the ALT levels during reexposure, designed as ALTr. Response to reexposure is positive, if both criteria are met: first, ALTb is below 5N with N as the upper limit of the normal value, and second ALTr ⩾ 2ALTb. Other variations lead to negative or uninterpretable results. For the cholestatic or mixed type of liver injury, corresponding values of ALP are to be used rather than of ALT. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; NA: Not available.**

therefore provides two different subscales[21,23,24] for the hepatocellular type of injury (Table 1) and for the cholestatic or mixed type (Table 2). These types are differentiated by the ratio R, calculated as the ALT/ALP activity measured at the time liver injury is suspected, with both activities expressed as multiples of N[21,24]. Injury is hepatocellular, if only ALT > 2N, alternatively if R ⩾ 5; cholestatic injury is assumed, if only ALP > 2N or R ⩽ 2; mixed damage is prevalent, if ALT > 2N and ALP is increased, with R > 2 and R < 5[21,23,24]. Of note, R may vary during the later course of the liver injury independent from the initial attribution of damage type.

Time to onset from the beginning of the drug/herb

Clear challenge criteria are defined with a time frame between beginning of the drug/herb use as the first day of intake and the onset of increased liver enzymes or symptoms at the time of ongoing use, with a high score for 5-90 d and a lower one for < 5 d or > 90 d (Tables 1 and 2). If drug/herb use has been terminated prior to the onset of challenge criteria, then this specific condition must be considered and scored exclusively. Scoring is only possible when the onset occurs within 15 d after cessation for the hepatocellular injury (Table 1) or 30 d for the cholestatic or mixed type (Table 2), a longer interval commonly excludes causality (Tables 1 and 2). An exemption is provided for slowly metabolized chemicals like amiodarone, leflunomide and clavulanate[44,45]; no definitive time frame can be provided in these cases due to varying half lives. The time frame of challenge and latency period were neither specified nor individually scored by other causality assessment methods[4,24], including the DILIN method[49,50].

Course of liver enzymes after cessation of the drug/herb

Precise dechallenge criteria are cornerstones of the CIOMS scale and facilitate causality assessment (Tables 1 and 2). In analogy to the periods mentioned, the physician can easily determine relevant future time points for repeated liver enzyme tests. When dechallenge data are missing in retrospective analyses, the CIOMS scale considers this and provides 0, but not negative points, so

Table 5 Frequency of risk factors of alcohol and age among herb induced liver injury patients

HILI study cohort	Total study cases (*n*)	Cases scored with risk factors (*n*)			Total cases scored with risk factors *n* (%)	Cases with references
		Alcohol	Age	Alcohol + Age		
Kava	26	0	6	1	7 (26.9)	Cases 2, 4, 10, 17, 20, 24, 26[12]
Kava	5	0	3	0	3 (60.0)	Cases 1-3[46]
Ayurvedic herbs	1	0	1	0	1 (100.0)	Case 1[30]
Black cohosh	4	2	1	0	3 (75.0)	Cases 2, 3, 4[47]
Black cohosh	9	1	1	0	2 (22.2)	Cases 4, 9[48]
Black cohosh	22	4	2	0	6 (27.3)	Cases 2, 8, 10, 16, 17, 21[36]
Greater Celandine	22	1	9	0	10 (45.5)	Cases 3, 5, 8, 11, 14-18, 21[37]
Greater Celandine	21	0	7	0	7 (33.5)	Cases 4,9, 11, 16-18, 20[32]
Pelargonium sidoides	15	0	3	0	3 (20.0)	Cases 1, 7, 14[38]
Pelargonium sidoides	13	0	7	0	7 (53.9)	Cases 2, 3, 5, 8, 9, 11, 13[39]
Herbalife	8	0	3	0	3 (37.5)	Cases 1, 2, 4[33]
Total	146	8	43	1	52 (35.6)	

The study cohort consisted of 146 herb induced liver injury patients patients assessed for the frequency of the risk factors alcohol and age ⩾ 55 years. In 52/146 cases (35.6%), risk factors were evident.

that the overall score may still present a probable causality level. Of note, the dechallenge time frame was not specifically considered or scored by the DILIN method[49,50] or by virtually any of the other methods[4,24].

Risk factors

The consensus report of the international CIOMS expert panel considered alcohol and age ⩾ 55 years as risk factors each scoring +1 point (Tables 1 and 2)[21], as suggested by DILI cases with positive reexposure[21,22]. The international DILI Expert Working Group specified alcohol intake of > 2 drinks per day (> 14 units/week) in women and > 3 drinks per day (21 units/week) in men as the lower threshold for alcohol intake as a risk factor (Tables 1 and 2)[14]. This limit is in line with the recommendations of NIH LiverTox equalling 1 drink to 10 g ethanol[44,45].

The impact of including alcohol as a risk factor on the overall CIOMS scoring was negligible as only 9/146 patients (6%) of a HILI study cohort were allotted an alcohol related scoring point (Table 5)[12,30,32,36-39,46-48]. In these 9 patients, CIOMS causality grading was changed in only one case (patient 16) and unchanged in the other 8 cases (patients 2, 13, 14, 17, 20, 21, 22, 32) (Table 6). In the single case (patient 16), alcohol as risk factor raised the overall CIOMS scoring from 0 to +01 point, *i.e.*, from excluded to unlikely causality (Table 6). Therefore, alcohol per se as risk factor upgrades the CIOMS causality level in virtually none of the cases in this study cohort.

Age ⩾ 55 years was as a risk factor in 44/146 cases (30%) of the analyzed HILI study cohort (Table 5)[12,30,32,36-39,46-48]. In 35/44 patients, the overall CIOMS causality grading remained unchanged whether or not age as a risk factor was included in the CIOMS scale scoring (Table 6). Deletion of age as a risk factor reduced the overall CIOMS grading by one causality level in 9/44 patients, *i.e.*, from unlikely to excluded in 5 cases (patients 1, 3, 15, 42, 43), from highly probable to probable in 1 case (patient 23), and from probable to possible in 3 cases (patients 9, 25, 34). Therefore, within this cohort the risk factor age upgraded the causality levels only marginally, which appears to have no clinical relevance. Overall, age as a risk factor has a limited impact on the final causality gradings by the CIOMS scale.

Risk factors are not considered and/or not scored by various other methods[4,24,49,50], including the DILIN method[49,50]. Conversely, the international DILI Expert Group also accepts the risk factors defined in the CIOMS scale, with modified specifications and limitations, if risk factors for hepatotoxicity are present in addition to those listed in the CIOMS algorithm[14].

Concomitant drug(s) and herbs(s)

Concomitant drugs and herbs are individually assessed for temporal association and hepatotoxic potency (Tables 1 and 2). For reasons of comparison and transparency, each comedicated drug or herb requires a separate analysis by the complete CIOMS scale. This is feasible and easily tabulated (Table 7)[30,47,48]. In patients with multiple drug or herb intakes, causality should be attributed primarily to the product with the highest score.

Search for non drug/herb causes

In this section, the CIOMS scale considers the clinically most relevant alternative causes (Tables 1 and 2). There is no difference in alternative causes made between the two types of liver injury, avoiding the need of subsequent reassessment, if the laboratory based typology changes during the clinical course[45]. Complications of underlying disease(s) are exemplified, such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis and sclerosing cholangitis and genetic liver diseases (Tables 1 and 2), in accordance with recent suggestions[45]. Other rare alternative causes are included in a checklist of differential diagnoses as a reminder for the clinician in case of unclear clinical diagnosis (Table 3)[24].

To improve its performance when used as an investigational tool, criteria for competing liver injury causes have been proposed for the CIOMS scale[14,29,44,45,49,50]

Table 6 Changes of the Council for International Organizations of Medical Sciences gradings with considering the risk factors

HILI study	Scored risk		CIOMS assessment with RF	CIOMS assessment without RF	Grading change	Cases with references
	Alcohol	Age	Score/grading	Score/grading		
Kava	0	+	+1/Unlikely	0/Excluded	↓	Case 2[12]
Kava	+	+	-1/Excluded	-3/Excluded	0	Case 4[12]
Kava	0	+	+1/Unlikely	0/Excluded	↓	Case 10[12]
Kava	0	+	-1/Excluded	-2/Excluded	0	Case 17[12]
Kava	0	+	+8/Probable	+7/Probable	0	Case 20[12]
Kava	0	+	-1/Excluded	-2/Excluded	0	Case 24[12]
Kava	0	+	-1/Excluded	-2/Excluded	0	Case 26[12]
Kava	0	+	+5/Possible	+4/Possible	0	Case 1[46]
Kava	0	+	+6/Probable	+5/Possible	↓	Case 2[46]
Kava	0	+	+8/Probable	+7/Probable	0	Case 3[46]
Ayurvedic herbs	0	+	+8/Probable	+7/Probable	0	Case 1[30]
Black cohosh	0	+	-2/Excluded	-3/Excluded	0	Case 1[47]
Black cohosh	+	0	-2/Excluded	-3/Excluded	0	Case 2[47]
Black cohosh	+	0	-3/Excluded	-4/Excluded	0	Case 3[47]
Black cohosh	0	+	+1/Unlikely	0/Excluded	↓	Cases 4[48]
Black cohosh	+	0	+1/Unlikely	0/Excluded	↓	Case 9[48]
Black cohosh	+	0	-1/Excluded	2/Excluded	0	Case 2[36]
Black cohosh	0	+	-1/Excluded	-2/Excluded	0	Case 8[36]
Black cohosh	0	+	-1/Excluded	-2/Excluded	0	Case 10[36]
Black cohosh	+	0	0/Excluded	-1/Excluded	0	Case 16[36]
Black cohosh	+	0	0/Excluded	-1/Excluded	0	Case 17[36]
Black cohosh	+	0	-2/Excluded	-3/Excluded	0	Case 21[36]
Greater Celandine	0	+	+9/Highly probable	+8/Probable	↓	Case 2[37]
Greater Celandine	0	+	+10/Highly probable	+9/Highly probable	0	Case 5[37]
Greater Celandine	0	+	+6/Probable	+5/Possible	↓	Case 8[37]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 11[37]
Greater Celandine	0	+	+8/Probable	+7/Probable	0	Case 14[37]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 15[37]
Greater Celandine	0	+	-1/Excluded	-2/Excluded	0	Case 16[37]
Greater Celandine	0	+	+8/Probable	+7/Probable	0	Case 17[37]
Greater Celandine	0	+	0/Excluded	-1/Excluded	0	Case 18[37]
Greater Celandine	+	0	+4/Possible	+3/Possible	0	Case 21[37]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 4[32]
Greater Celandine	0	+	+6/Probable	+5/Possible	↓	Case 9[32]
Greater Celandine	0	+	+3/Possible	+2/Possible	0	Case 11[32]
Greater Celandine	0	+	+7/Probable	+6/Probable	0	Case 16[32]
Greater Celandine	0	+	+7/Probable	+6/Probable	0	Case 17[32]
Greater Celandine	0	+	+5/Possible	+4/Possible	0	Case 18[32]
Greater Celandine	0	+	+7/Probable	+6/Probable	0	Case 20[32]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 1[38]
Pelargonium sidoides	0	+	+2/Unlikely	+1/Unlikely	0	Case 7[38]
Pelargonium sidoides	0	+	+1/Unlikely	0/Excluded	↓	Case 14[38]
Pelargonium sidoides	0	+	+1/Unlikely	0/Excluded	↓	Case 2[39]
Pelargonium sidoides	0	+	+4/Possible	+3/Possible	0	Case 3[39]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 5[39]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 8[39]
Pelargonium sidoides	0	+	+2/Unlikely	+1/Unlikely	0	Case 9[39]
Pelargonium sidoides	0	+	+2/Unlikely	+1/Unlikely	0	Case 11[39]
Pelargonium sidoides	0	+	0/Excluded	-1/Excluded	0	Case 13[39]
Herbalife	0	+	+7/Probable	+6/Probable	0	Case 1[33]
Herbalife	0	+	+2/Unlikely	+1/Unlikely	0	Case 2[33]
Herbalife	0	+	+2/Unlikely	+1/Unlikely	0	Case 4[33]

Based on details described in Table 5, in all 52 patients with evident risks factors of alcohol, age ⩾ 55 years, or both, scores and Council for International Organizations of Medical Sciences (CIOMS) gradings with risk factors were compared with conditions without risk factor consideration. In 9 patients, there was a CIOMS downgrading when risk factors would not have been considered. RF: Risk factor.

and were included in the updated CIOMS scale (Tables 1 and 2)[24]. This update ensures correct diagnosis of alternative causes but was limited to details of hepatitis serology and hepatobiliary sonography, as specified by the current knowledge in the field and adapted to actual diagnostic methods[23,24]. The update of the original CIOMS scale substantially improved specificity, *i.e.*, exclusion of alternative causes by hepatitis serology. HBsAg and HBV-DNA quantification were added to distinguish HBV infection from immunization, as was hepatitis C virus (HCV)-RNA to correctly assess HCV infections. Also, clinical and/or biological parameters for cytomegalovirus (CMV), Epstein Barr virus (EBV) or herpes simplex virus (HSV) infection were vague or

Table 7 Council for International Organizations of Medical Sciences scale as an example with items required for causality assessment in a patient with herb induced liver injury by four different Indian Ayurvedic herbs

Items for hepatocellular injury	Possible score	Psoralea corylifolia	Acacia catechu	Eclipta alba	Vetivexia zizaniodis
1 Time to onset from the beginning of the herb 5-90 d (rechallenge: 1-15 d)	2				
< 5 or > 90 d (rechallenge: > 15 d)	1	1	1	1	1
Alternative: Time to onset from cessation of the herb					
≤ 15 d (except for slowly metabolized herbal chemicals: > 15 d)	1				
2 Course of ALT after cessation of the herb					
Percentage difference between ALT peak and N					
Decrease ≥ 50% within 8 d	3	3	3	3	3
Decrease ≥ 50% within 30 d	2				
No information or continued herbal use	0				
Decrease ≥ 50% after the 30th day	0				
Decrease < 50% after the 30th day or recurrent increase	-2				
3 Risk factors					
Alcohol use (drinks/d: > 2 for women, > 3 for men)	1				
Alcohol use (drinks/d: ≤ 2 for women, ≤ 3 for men)	0	0	0	0	0
Age ≥ 55 yr	1	1	1	1	1
Age < 55 yr	0				
4 Concomitant herbs(s) and drug(s)					
None or no information	0				
Concomitant herb or drug with incompatible time to onset	0				
Concomitant herb or drug with compatible or suggestive time to onset	-1	-1			
Concomitant herb or drug known as hepatotoxin and with compatible or suggestive time to onset	-2		-2	-2	-2
Concomitant herb or drug with evidence for its role in this case (positive rechallenge or validated test)	-3				
5 Search for non herb causes					
Group Ⅰ (6 causes)					
Anti-HAV-IgM		-	-	-	-
HBsAg, anti-HBc-IgM, HBV-DNA		-	-	-	-
Anti-HCV, HCV-RNA		-	-	-	-
Hepatobiliary sonography/colour Doppler sonography of liver vessels/ endosonography/CT/MRC		-	-	-	-
Alcoholism (AST/ ALT ≥ 2)		-	-	-	-
Acute recent hypotension history (particularly if underlying heart disease)		-	-	-	-
Group Ⅱ (6 causes)					
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases		-	-	-	-
Infection suggested by PCR and titre change for		-	-	-	-
CMV (anti-CMV-IgM, anti-CMV-IgG)		-	-	-	-
EBV (anti-EBV-IgM, anti-EBV-IgG)		-	-	-	-
HEV (anti-HEV-IgM, anti-HEV-IgG)		-	-	-	-
HSV (anti-HSV-IgM, anti-HSV-IgG)		-	-	-	-
VZV (anti-VZV-IgM, anti-VZV-IgG)		-	-	-	-
Evaluation of group Ⅰ and Ⅱ					
All causes-groups Ⅰ and Ⅱ - reasonably ruled out	2	2	2	2	2
The 6 causes of group Ⅰ ruled out	1				
5 or 4 causes of group Ⅰ ruled out	0				
Less than 4 causes of group Ⅰ ruled out	-2				
Non herb cause highly probable	-3				
6 Previous information on hepatotoxicity of the herb					
Reaction labelled in the product characteristics	2				
Reaction published but unlabelled	1	1			
Reaction unknown	0		0	0	0
7 Response to unintentional readministration					
Doubling of ALT with the herb alone, provided ALT below 5N before reexposure	3				
Doubling of ALT with the herb(s) and drug(s) already given at the time of first reaction	1				
Increase of ALT but less than N in the same conditions as for the first administration	-2				
Other situations	0				
Total score for each individual herb used by the patient		7	5	5	5

The data of the patient with severe hepatotoxicity by four different Indian Ayurvedic herbs are derived from a published report[30], using the CIOMS scale for the hepatocellular type of liver injury (Table 1). The symbol of - signifies that this particular item has been evaluated and no abnormality was found. For the four herbs, the total score was either +7 (probable causality) or +5 (possible causality). Abbreviations see legend to Table 1.

unknown at the time of compilation[21] but specified in the updated CIOMS scale; also included and specified were infections by hepatitis E virus (HEV) and varicella zoster virus (VZV) (Tables 1 and 2)[24]. Specific diagnostic criteria include polymerase chain reaction detection and titer changes of the respective antibodies (IgM, IgG) for CMV, EBV, HEV, HSV and VZV infections. Hepatobiliary sonography was supplemented by color Doppler sonography, including assessments of the liver vessels, endosonography, computed tomography (CT) and magnetic resonance cholangiography (MRC), if these tests were indicated clinically (Tables 1 and 2). For comparison and method validation, causality has been evaluated in 101 hepatotoxicity cases by both the original and updated CIOMS scales, with identical causality results published in 6 studies[32,33,36-39]. Therefore, the updated CIOMS scale was validated and there is no need for further validation of the updated CIOMS scale versus the original CIOMS scale.

Previous information on hepatotoxicity of the drug/herb

Hepatotoxicity listed in the product information sheet must be checked; in addition, a quick literature search in PubMed will be sufficient to determine whether the observed reaction has been published before. Appropriate information may also be obtained from the NIH LiverTox database[44,45].

Response to unintentional readministration

To classify an unintentional reexposure test as positive, few criteria are required (Tables 1 and 2), as specified (Table 4)[21,22,24,26,27]. Although reexposure is an important domain, probable causality gradings with the CIOMS scale are achievable even in the absence of a reexposure (Table 7)[12,17,30-32,37].

Scoring system

Each item of the CIOMS scale receives an individual score and the sum of the individual scores provides the final score for the patient (Tables 1 and 2). With +14 down to -9 points, there is a wide range of the final scores, leading to the following causality levels: $\leqslant$ 0 points, excluded causality; 1-2, unlikely; 3-5, possible; 6-8, probable; and $\geqslant$ 9, highly probable (Tables 1 and 2)[21].

Sensitivity, specificity and predictive value

Cases with positive reexposure tests were proposed for validation of the CIOMS scale and used as gold standard[22]. Articles from two databanks were compiled with liver injury confirmed by a positive rechallenge. The mandatory information for inclusion in this series contained the type of liver injury, time interval between administration of the drug and occurrence of the reaction, and results of the positive response to readministration of the drug, in accordance with the conclusions of the International Consensus Meeting on drug induced liver injuries. For the final validation, 49 cases and 28 controls were assessed, as described in detail[22]. Most importantly, the discriminative power of the score was quantified in terms of sensitivity, specificity and predictive values. The cut off point was offset to maximize the combined sensitivity and specificity. Using +5 points as the cut off, sensitivity was 86%, specificity 89%, positive predictive value 93%, and negative predictive value 78% for the CIOMS causality assessment. In another study with 81 cases and 46 controls, sensitivity was 78% and specificity 100% for the CIOMS scale[51], confirming the validation of the CIOMS scale.

The interrater reliability of CIOMS assessment was good by one group[52] but mediocre by the DILIN group[49]. In the latter report, however, 40 cases going back to 1994 were studied. Uncertainties arose from numerous missing, incomplete or outdated medical reports and charts, especially for older cases. In particular, there were high rates (28%) of preexisting liver diseases like chronic hepatitis C virus infection, hemochromatosis and unspecified cirrhosis. Liver sonography was reported in 26/40 cases and found abnormal in 15/26 (58%). These data were nevertheless described as "best-case scenario"[49]. Considering these limitations and numerous confounding variables, poor case data quality likely results in mediocre assessment quality, including low interrater reliability[49]. Moreover, problematic data presentation by the principal assessor to external reviewers may have influenced the results as the external reviewers received only a subset of the case report forms and had no access to the original data of the cases[49]. Of interest, no proof has been provided that an expert group opinion improves the CIOMS assessment evaluation, at least according to recent comments and studies[11,49]. In another study comparing the CIOMS scale with the DILIN method, there was considerable interobserver variability in both methods[50].

Usage frequency

The CIOMS scale for hepatotoxicity assessment in its original or updated form[4,5,10,14,23,24,28,29] has been extensively used in epidemiological studies, clinical trials, case reports, case series, regulatory analyses and genotyping studies[4]. Additional efforts are still needed to reevaluate causality in most HILI reports for 60 different herbs and herbal products[53]. CIOMS based results were published by the DILIN group[49,50] and by the European Medicines Agency (EMA)[54]. Individual studies[10,16,55,56], the NIH LiverTox[44,45], the international DILI Expert Working Group[14], the Spanish Group for the Study of Drug-Induced Liver Disease[29], and the Hong Kong Herb-Induced Liver Injury Network (HK-HILIN)[57] provided further support for the CIOMS scale.

Among various causality assessment methods, the original and updated CIOMS scales were the preferred tools in cases of DILI[28] and HILI (Table 8)[5], seen for 573 cases from 23 HILI reports evaluating alternative causes[12,32,34,36-39,42,43,47,48,54,57-67].

Transparency

CIOMS based assessments should be reported or published as an original data set suitable for subsequent and independent assessments, rather than as final scores and

Table 8 Compilation of causality assessment methods used in suspected herb induced liver injury cases

Herbs/Herbal products	Ad hoc (*n*)	WHO (*n*)	CIOMS (*n*)	Naranjo (*n*)	DILIN (*n*)	KL (*n*)	Ref.
Kava	20						BfArM[58]
Kava		30					Denham *et al*[59]
Kava	20						Teschke *et al*[60]
Kava			36				Stickel *et al*[61]
Kava		80					Schmidt *et al*[62]
Greater Celandine	23						BfArM[63]
Black cohosh			31				EMA[54]
Herbalife products		12					Elinav *et al*[64]
Herbalife products		12					Schoepfer *et al*[65]
Kava			26				Teschke *et al*[12]
Black cohosh				30			Mahady *et al*[42]
Green tea				34			Sarma *et al*[43]
Black cohosh			4				Teschke *et al*[47]
Black cohosh			9				Teschke *et al*[48]
Kava			31				Teschke[34]
Hydroxycut					17		Fong *et al*[66]
Black cohosh			22				Teschke *et al*[36]
Greater Celandine			22				Teschke *et al*[37]
Herbalife products						20	Manso *et al*[67]
Various herbs			45				Chau *et al*[57]
Greater Celandine			21				Teschke *et al*[32]
Pelargonium sidoides			15				Teschke *et al*[38]
Pelargonium sidoides			13				Teschke *et al*[39]
Sum (*n*)	63	134	275	64	17	20	
Sum (percent)	11.00%	23.40%	48.00%	11.20%	3.00%	3.40%	

The data are derived from a study evaluating alternative causes in suspected HILI cases (n = 573) comprising the study cohort[5]. For the 275 CIOMS cases, causality assessment was performed with the updated CIOMS scale the original CIOMS scale, or both. Ad hoc: ad hoc approach; CIOMS: Council for International Organizations of Medical Sciences scale; DILIN: Drug Induced Liver Injury Network method; KL: Karch and Lasagna method; Naranjo: Naranjo scale; WHO: World Health Organization method.

corresponding causality levels, to improve data transparency. Scientists, editors and reviewers should strive to obtain appropriate CIOMS based details for all DILI and HILI case reports. This can easily be achieved since the CIOMS scale provides all items in tabulated form for each individual case (Tables 1, 2 and 7). These forms may be communicated as a spontaneous report to regulatory agencies and expert panels or presented for publication to scientific journals as a case report[24,30,31] or case series[12,24,32]. This tabulation is a good basis for further regulatory or scientific assessments and discussions. For regulatory and expert based assessments, there is no need for other causality assessment algorithms to be used subsequently since CIOMS based data are also amenable to regulatory and expert panel evaluations.

Comparison to precursor scales

The CIOMS scale resulted from intensive expert discussions[21], integrating medical progress and improving the initial qualitative RUCAM[26] and the qualitative CIOMS method[27]. The qualitative RUCAM represented the first objective attempt to assess causality in drug induced liver injury and considered some characteristic features of liver injury, but it had a qualitative rather than a quantitative approach[26]. As an improved version of the qualitative RUCAM[26], the qualitative CIOMS method differentiated the hepatocellular, the cholestatic and the mixed type of liver injury[27]. However, both the qualitative RUCAM[26] and the qualitative CIOMS method[27] were not quantitative, as opposed to the current quantitative CIOMS scale[21] that is now the preferred tool[24].

Other liver specific methods

The scale of Maria and Victorino (MV)[68] was developed to improve upon the CIOMS scale by deleting laboratory items and adding clinical elements, along with simplifying and changing the relative weight of elements in their algorithm[23,44,45]. No data are available for specificity, sensitivity, positive and negative predictive values for the MV scale[68]. Compared to the original CIOMS scale[21], the MV scale[68] showed shortcomings and the results are not equivalent, causing major concern[10,14,23,24,29,44,45,69-71]. This may explain why the MV scale was used in a few DILI studies[1,72,73], but not in 38 other publications of DILI cases[28] or in 23 publications of HILI cases[5]. The MV scale is not commonly recommended for assessing causality in assumed DILI and HILI cases and is certainly no substitute for the CIOMS scale[24].

The TTK scale[25], named for the first three authors Takikawa, Takamori, Kumagi *et al*[74], is a modification of the CIOMS scale[21] with different evaluations of the chronology, exclusion of comedication, inclusion of the drug lymphocyte stimulation test (DLST) and of eosinophilia in their assessment system[74,75]. The TTK scale is widely used in Japan[74], as recently reviewed[75]. In other countries, this scale is not or rarely

considered[5,10,14,24,28,29,44,45,76]. Limited access and lack of standardization have prevented general clinical use of the DLST and consequently TTK scale applications outside Japan[29]; this may be due to methodological difficulties with false positive and false negative cases in the DLST[25,75]. For clinicians, the TTK scale cannot replace the CIOMS scale[25].

The DILIN method provided by the DILIN group requires an expert panel[3,6,11,24,44,45,49,50,77,78], in contrast to the CIOMS scale[21,24]. Consequently, the DILIN method is of limited availability to physicians in need of early results for therapeutic decisions[24]. In particular, the DILIN method is not an appropriate substitute for the CIOMS scale, nor are other expert panel based approaches[24]. This includes the novel Causality Assessment Tool (CAT) specifically designed for herbs and dietary supplements (HDS), which was presented as an abstract[15]. As opposed to CIOMS based results with transparent data presentation (Table 7)[12,30,32,36-39,47,48,71], publications based on the DILIN method lack transparency for individual cases regarding assessed and scored items since only final causality levels are published without details and thereby open for discussions, not allowing valid conclusions[3,6,11,49,50,77,78]. The DILIN method also lacks data on specificity, sensitivity and predictive values, as an expert opinion based method no items can be validated. Individual weighing and scoring of items remain undisclosed and undiscussed, hampering thorough analysis of assessment results by the DILIN method.

Liver unspecific methods

In contrast to the liver specific core elements of the original and updated CIOMS scale (Tables 1 and 2)[4,21-24], numerous causality algorithms are liver unspecific[4,24,76,79,80], including the Naranjo scale[81], the World Health Organization (WHO) global introspection method as the WHO method in short[82], and the KL method of Karg and Lasagna[83]. Particularly intensive discussions focused on the Naranjo scale[4,24,25,84-87], the WHO method[4,24,84,87], and the KL method[24,25]. All these methods are obsolete for causality assessment of assumed hepatotoxicity as they lack liver specificity and do not consider hepatotoxicity characteristics.

WEAKNESSES

Retrospective use

Retrospective analysis of case data is problematic and may require some assistance evaluating the CIOMS items[14,44,45]; unselected and sometimes undefined, low quality data have to be adapted into a structured algorithm like the CIOMS scale. Therefore, physicians should prospectively use the CIOMS scale, which then may provide complete case data (Table 7)[30].

Dechallenge criteria

Missing ALT dechallenge data are factored as 0 points given (Table 1); this condition has been interpreted as a limitation of the CIOMS scale[14]. Retrospective studies commonly lack dechallenge results[6,12,32,34-39] which are included in prospective evaluations (Table 7)[30]. CIOMS performs inaccurately in acute liver failure and liver transplantation if liver values are not available within 30 d after cessation of the incriminated drug or herb. Under these circumstances, 0 but not negative points are credited due to lacking ALT data (Tables 1 and 2).

Risk factors

The CIOMS scale includes only the risk factors of alcohol and age $\geqslant$ 55 years[21]. Diabetes, metabolic syndrome, sex, ethnicity and body mass index[14], as well as genetic predisposition[29], are also proposed as potential risk factors; the lack of inclusion in the CIOMS scale has been considered as a limitation[14,29]. However, these factors have not been validated as risk factors; their inclusion into the CIOMS scale requires evidence as independent contributors and a subsequent new validation.

Alternative causes

It may be argued that rare alternative causes were not listed in the CIOMS scale (Tables 1 and 2) but this shortcoming was compensated for by the checklist for numerous rare liver diseases as a reminder for the clinician (Table 3)[24].

Previous information on hepatotoxicity of drug/herb

Safety labels are available for both synthetic and herbal drugs but rarely for other herbal products. This shortcoming of the CIOMS scale may be compensated by a thorough search for prior publications of hepatotoxicity by herbal products; published reports provide an even higher scoring than information obtained only from safety labels.

CONCLUSION

The major strength of the CIOMS is its potential as a standard scale for DILI and HILI causality assessment by attending physicians, regulatory agencies, expert panels and the scientific community. Other advantages include its liver specificity and its validation for hepatotoxicity cases, with excellent sensitivity, specificity and predictive validity based on results obtained from cases with a positive reexposure test. This scale will allow the physician treating patients with suspected DILI and HILI an early preliminary result of the likelihood, facilitates timely and prospective collection of all relevant data required for a subsequent valid causality assessment, does not require an expert panel, and has the option of subsequent refinement by regulatory agencies, expert panels and the scientific community. With the CIOMS scale, an identical causality assessment algorithm can used by all evaluating parties, which facilitates the overall procedure of causality association. Minor weaknesses of the CIOMS scale include the limited exclusion of alternative causes and the handling of poor case data in

retrospectively rather than prospectively assessed cases.

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REVIEW

Fatty liver in childhood

Yesim Ozturk, Ozlem Bekem Soylu

Yesim Ozturk, Department of Pediatrics, Division of Pediatric Gastroenterology, Dokuz Eylul University School of Medicine, Inciralti, 35340 İzmir, Turkey
Ozlem Bekem Soylu, Hepatology and Nutrition Unit, Department of Paediatric Gastroenterology, Behcet Uz Children's Disease and Pediatric Surgery Training and Research Hospital, Alsancak, 35340 İzmir, Turkey
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Correspondence to: Yesim Ozturk, MD, PhD, Professor, Department of Pediatrics, Division of Pediatric Gastroenterology, Dokuz Eylul University School of Medicine, Inciralti, Cumhuriyet Blv No.144, 35340 İzmir, Turkey. yesimzaferozturk@gmail.com
Telephone: +90-232-4126106 Fax: +90-232-4126106
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Abstract

Fatty liver is a growing health problem worldwide. It might evolve to nonalcoholic steatohepatitis, cirrhosis and cause hepatocellular carcinoma. This disease, which has increased because of eating habits, changes in food content and lifestyle, affects people from childhood. The most important risk factors are obesity and insulin resistance. Besides these factors, gender, ethnicity, genetic predisposition and some medical problems are also important. Cirrhosis in children is rare but is reported. Nonalcoholic fatty liver disease (NAFLD) has no specific symptoms or signs but should be considered in obese children. NAFLD does not have a proven treatment. Weight loss with family based treatments is the most acceptable management. Exercise and an applicable diet with low glycemic index and appropriate calorie intake are preferred. Drugs are promising but not sufficient in children for today.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Children; Obesity; Metabolic syndrome; Insulin resistance; Chronic liver disease

Core tip: Nonalcoholic fatty liver disease (NAFLD) consists of steatosis in liver, steatohepatitis and cirrhosis. Histological type 2 pattern (macrovesicular steatosis with portal inflammation and/or fibrosis, generally without evidence of cellular injury or lobular inflammation) is seen differently in children than in adults. The most important risk factors are obesity and insulin resistance, as well as gender, ethnicity, genetic predisposition and some medical problems. Progression to cirrhosis in children is rare but possible. NAFLD does not have a proven treatment. Losing weight and increasing physical activity provide improvement in histological and biochemical findings in fatty liver. Drugs are used in specific situations. More research is needed for drug therapy.

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INTRODUCTION

Fat is stored as triglyceride (TG) in human liver. Steatosis is defined as fat accumulation in hepatocytes and is seen in many liver diseases[1-3].

Nonalcoholic fatty liver disease (NAFLD) defines the spectrum of histological changes in liver in which macrovesicular steatosis is outstanding[3]. NAFLD includes simple hepatic steatosis due to obesity and/or insulin resistance, nonalcoholic steatohepatitis (NASH) and cirrhosis. Hepatosteatosis usually limits itself but it may advance to NASH. NASH differs from simple steatosis by hepatocyte damage, inflammatory infiltrate and collagen deposition[4-6].

In many ways, the NASH pattern and characteristics differ between children and adults[7]. In adults, common features are the combination of macrovesicular steatosis with ballooning degeneration and lobular inflammation

with or without pericellular fibrosis localized primarily in acinar zone 3 (type 1). Pediatric NASH is characterized by macrovesicular steatosis with portal inflammation and/or fibrosis, generally without evidence of cellular injury or lobular inflammation (Type 2). Type 1 and type 2 NASH are distinct subtypes of pediatric NAFLD associated with different clinical demographic and possible pathophysiological features. In children with NAFLD aged 2-18 years, 51% is type 2 and 17% is type 1. In most of the children with extensive fibrosis, type 2 pattern is demonstrated[8]. These children are younger and more obese compared to children displaying type 1 pattern. Type 2 NASH is more common in boys than girls. Asian, Native American race and those of Hispanic ethnicity predominantly demonstrate type 2. Among children with type 2 NASH, it is not known whether the pattern evolves into a more characteristically adult type 1 pattern as the children grow older[9].

There has been an increase in NAFLD frequency in the last 30 years[1,8-11]. Nowadays, NAFLD is the most common form of liver disease in children[7]. A chronic obesity associated condition, NAFLD can lead to cirrhosis and liver failure over time[8]. It is also an independent risk factor for cardiovascular disease and liver cancer[9]. Studies have demonstrated differences in NAFLD prevalence rates across race/ethnicity, gender and weight status[12-14].

EPIDEMIOLOGY

In developed countries, hepatosteatosis is seen in 20%-30% of an unselected population[15]. The prevalence of NAFLD in Hong Kong Chinese is 27.3%. Around 4% of patients with fatty liver in the community had advanced fibrosis, as estimated by transient elastography[16].

The frequency of NASH is considered to be 2%-3%. It is reported that 10%-29% of NASH cases develop cirrhosis in 10 years[17]. Cirrhosis may progress to liver cancer. Hepatocellular carcinoma may occur in 4%-27% of the individuals with NASH-induced cirrhosis[18-20].

Since childhood obesity became epidemic in developed countries, NAFLD became the most common cause of chronic liver disease in pediatrics[7].

In fact, the true NAFLD prevalence in children is unknown. A population based autopsy study reported that 13% of children and adolescents are affected with NAFLD, 23% of the subjects with NAFLD had evidence for steatohepatitis, whereas bridging fibrosis or cirrhosis was observed in 9% of the children with NASH. Overweight and obese children accounted for 81% of all of the cases of NAFLD. A male-to-female ratio was 2: 1[7,20-23].

It is suggested that NAFLD prevalence increases with age, with a mean age at diagnosis between 11 and 13 years[24]. This tendency is explained by adolescent hormonal changes which result in an increase in serum insulin levels and fat accumulation in the liver[25,26].

Obesity and insulin resistance are the most common risk factors for NAFLD. However, differing amounts of fat accumulation in individuals with similar adipose tissue suggests that other factors are also responsible. Gender, ethnicity and genetic predisposition are emphasized[27-35].

The prognosis of children with NAFLD is still unknown. Patients with simple steatosis may still develop NASH and fibrosis progression. It is reported that weight reduction is associated with non-progressive disease in adult patients[28]. It is suggested that long term survival of NAFLD pediatric patients is shorter than non-affected patients[29].

PATHOGENESIS

Triglycerides are preferred as storage nutrients in cells to regulate the changes between intake and usage. Triglycerides supply high calories. Additionally, because they are not dissolved in water, they might be stored intracellularly in high amounts without causing any colloidal or osmotic problems. Triglycerides are basic material stocks of adipocytes and are not accumulated in other cells, except in unusual situations. Steatosis in liver is not an adaptive process; indeed it may cause severe chronic problems[1].

Fat droplets should be seen in at least 5% of hepatocytes in order to be named as steatosis. Another definition is TG deposition in the liver above 95th percentile or more than 55 mg per gram of liver tissue in a healthy lean person[2].

Hepatosteatosis might be seen in two different types; macrovesicular and microvesicular. In macrovesicular steatosis, one or a few lipid droplets are present, filling the total hepatocyte. These lipid droplets propel the nucleus to the edge. In microvesicular type, multiple small lipid droplets are seen, giving a foamy appearance[3].

Microvesicular steatosis might be seen in Reye syndrome, salicylate, sodium valproate or ethanol intake, fulminant hepatitis D, mitochondrial fatty acid beta oxidation defects and urea cycle disorders. In these disorders, liver function tests are usually affected and the patient is comatose. If the patient survives, permanent damage will not occur in the liver. Macrovesicular type occurs in alcoholic liver disease, obesity, diabetes, kwashiorkor, AIDS, total parenteral nutrition therapy, phosphorus intoxication and steroid treatment[3].

High concentration of serum saturated free fatty acids is important in the pathogenesis of steatosis. This high concentration of saturated free fatty acids creates hepatotoxic impulse. Besides, esterification of these free fatty acids into TGs is a process of detoxification. The balance between TG deposition and removal is disrupted. There are three sources of fatty acids causing TG deposition in liver: from diet, 15%; *de-novo* synthesis (carbohydrates from diet), 26%; and adipose tissue circulating, 59%[1,5].

Twenty percent of the fat present in the systemic circulation (100 g/d) is taken by the liver. Daily intake of

TGs from diet (approximately 20g/d) and free fatty acids from adipose tissue (approximately 20 g/d) enter the liver as TG[1,36]. There has been an increase in NAFLD frequency in the last 30 years. It is considered that this is due to changes in the amount and content of food. Changes in food composition cause steatosis in liver. Generally, carbohydrates and fructose play the most important role in this issue. Fructose influences the dietary carbons to move to liver and participate in lipogenesis. Despite glucose, fructose is almost totally taken from the systemic circulation. Fructose is phosphorylated at C1 instead of C6 and because of this it cannot be used in glycogen synthesis. Instead, fructose is changed to glyceraldehyde-3-phosphate, which provides substrate for *de-novo* lipogenesis. Yearly fructose intake of the population is increasing day by day and consequently NAFLD incidence is rising[1,37]. As the adipose tissue increases in obesity, death receptors in adipose tissue and apoptosis pathway are activated. Increase in adipocyte death causes more macrophage migration. Insulin resistance and hepatosteatosis occur as a result. Approaches blocking apoptosis of adipose cells are considered to improve complications related to obesity, including NAFLD. Lipoapoptosis is related to AST/ALT > 1 and liver fibrosis[38-40].

Insulin stimulates fatty acid production while preventing glucose production in the liver. As insulin resistance develops in the liver, the effect of insulin on preventing glucose production diminishes. However, the effect of insulin on stimulating fat synthesis in the liver is preserved. When the insulin level decreases with therapy, steatosis in the liver also decreases. Additionally, high insulin levels increase hepatotoxicity by preventing FFA oxidation[41].

It is suggested that NAFLD pathogenesis is multifactorial with many factors affecting disease development and progression. The "multiple-hit" hypothesis is currently the established pathogenetic model[42]. At the onset, NAFLD is characterized by fat accumulation in the liver and insulin resistance, influenced by genetic susceptibility, epigenetic mechanisms, a sedentary lifestyle and hypercaloric diets[43]. Hepatic fat accumulation leads to exacerbating insulin resistance by interfering with phosphorylation of insulin receptor substrates[44]. Free fatty acid accumulation and insulin resistance predispose the fatty liver, including oxidative stress, inflammatory cytokines, stellate cells activation and mitochondrial disturbance, which lead to inflammation, necrosis and fibrosis[45]. A changing of gut microbiota and excess gut permeability increase liver exposure to gut-derived bacterial products in NAFLD. These products stimulate innate immune receptors and trigger liver inflammation and fibrogenesis[46].

Hepatic progenitor cell activation is correlated with fibrosis and NASH progression[47]. Adiponectin, leptin, resistin and tumor necrosis factor-alpha are also thought to be involved in the progression of steatosis to NASH. Adipocytes or inflammatory cells infiltrating the adipose tissue in insulin resistance are responsible for adipocytokine secretion. Leptin may activate hepatic stellate cells. The expansion of adipose tissue, especially visceral fat, is associated with a decrease in the release of insulin-sensitizing and anti-inflammatory cytokines and an increase in the release of pro-inflammatory molecules[48]. Tumor necrosis factor-α and interleukine-6 levels are elevated in the liver and blood of NASH patients. These cytokines are involved in Kupffer and hepatic stellate cell activation in myofibroblasts[49]. NAFLD results from the relationship between multiple organs, including adipose tissue, liver, gut and the pancreas[50,51].

CLINICAL FINDINGS

Most of the cases are asymptomatic but nonspecific symptoms like abdominal pain may be present[30]. The most common admission reason is slightly elevated transaminases or coincidentally noticed hepatomegaly. Multiple diseases like Wilson's disease, drug-induced liver injury and autoimmune hepatitis should be excluded before a diagnosis of NAFLD[30,31].

Obesity is distinctive[7-15,31]. In adults, 10%-75% of fatty liver occurs with insulin resistant type 2 diabetes. Fatty liver is defined in poorly regulated type 1 diabetes (Mauriac syndrome) in children. Children with typical NAFLD have insulin resistance with hyperinsulinemia but they are euglycemic. Type 2 diabetes mellitus is present in 5.5% of NASH cases[15,32]. Acanthosis nigricans, defined as hyperplasia of pigmented skin cells, is an important physical examination seen with insulin resistance. This can be found in more than 50% of children with NASH. Family story is important in NAFLD because familial clustering is common[33-35].

Obesity is reported, especially after ALL chemotherapy, hypothalamic dysfunction or hypothalamic surgery. Even NAFLD progressing to cirrhosis is defined in these children. NAFLD is also seen in Prader-Willi syndrome. Besides these, fatty liver may be seen concurrently with some inborn errors of metabolism and genetic diseases. Insulin resistance, obesity, type 2 DM and NAFLD progressing to cirrhosis may be seen in Alström syndrome. Liver fibrosis is reported in Turner's syndrome. Also, in lipodystrophy, cases are present with cirrhosis with liver transplantation[35,52].

LABORATORY FINDINGS

In NAFLD, serum aminotransferases are moderately high with ALT being higher than AST. Increase in AST and reversing of the AST/ALT ratio in NAFLD predicts a bad prognosis. Raised ALT and GGT levels, especially if they are within normal ranges, are found to be related to hepatic steatosis evaluated by USG or magnetic resonance imaging. Therefore, changing the normal ranges is being discussed. Serum GGT > 96.5 U/L is a marker of advanced fibrosis. Serum bilirubin levels are normal or near normal. Biochemical findings of cholestasis are

not present[32-57]. Serum IgG and nonspecific tissue autoantibodies imply autoimmunity. Mostly, the anti-smooth muscle antibody is positive at low titer[52-54].

The other markers synthesized in liver, like sex hormone binding globulin, ferritin and plasminogen activating inhibitor-1, may be used in the diagnosis of NAFLD[54]. Homocysteine levels may increase in steatohepatitis. High hyaluronic acid levels are the most powerful independent marker of severe fibrosis and distinguishes steatosis and NASH[15,55-57]. Laminin and ELF (enhanced liver fibrosis) scores may also be used. Low adiponectin with low adipokines are important in NASH diagnosis. A combination of serum adiponectin, homoeostasis model assessment of insulin resistance (HOMA-IR) and type Ⅳ collagen 7S, at cut-off limits of $\leqslant$ 4.0 μg/mL, $\geqslant$ 3.0 and $\geqslant$ 5.0 ng/mL respectively, was shown to have a sensitivity of 94% and specificity of 74% for identifying early NASH[58]. Cut-off values of HOMA-IR for insulin resistance are higher than in adults. When an obese patient loses weight, normal ALT decreases more and a decrease in HOMA-IR also occurs with insulin resistance.

Hypoadiponectinemia and high tumor necrosis factor-alpha levels were found to be related to NAFLD[59-71]. However, adiponectin and tumor necrosis factor-alpha gene polymorphism were not shown to be associated with NAFLD or significant fibrosis in Chinese people[72].

Urea, electrolytes, thyroid function tests, glucose, HbA1c and serum lipids should be controlled. The most common lipid disorder is hypertriglyceridemia. Autoantibodies, immunoglobulins, viral markers for hepatitis B, hepatitis C, cytomegalovirus and Ebstein-Barr virus are important in excluding chronic liver diseases. Chronic hepatitis C, Wilson's disease, cystic fibrosis and drug intoxication (*e.g.*, methotrexate) should especially be excluded[72].

Steatosis may be diagnosed by ultrasound, computed tomography or MRI scanning. Ultrasound, the cheapest option, has been reported to have a sensitivity of 89% and specificity of 93% for the identification of fatty liver[73]. Abdominal USG does not reflect changes in liver histology and it is not useful in distinguishing steatosis and NASH. Microvesicular steatosis is due to hereditary inborn errors of metabolism, urea cycle disorders and valproic acid toxicity, and it is more severe. USG with a good history taking and metabolic tests may be sufficient in diagnosis of microvesicular steatosis[15]. ALT and AST levels are not always in parallel with the histological state and therefore, in children with risk factors, USG should be performed even if ALT and AST are normal[74,75].

New non-invasive tests such as proton-magnetic resonance spectroscopy and transient elastography allow relatively accurate estimation of hepatic steatosis and fibrosis in the community[74-81].

Liver biopsy may be essential in the diagnosis of NAFLD and distinguishing NASH from other disorders. In obese patients, biopsy may be needed to differentiate NAFLD from hepatitis. Optimal timing for this is not certain. Some physicians delay biopsy for 3-6 mo, make the patient lose weight and perform biopsy if ALT is still high. In younger children and cases with acanthosis nigricans, biopsy may be performed but there is insufficient data for this[30,82].

TREATMENT

In childhood, fatty liver does not have a proven treatment[83]. In a meta-analysis evaluating studies on adults, losing weight is reported to improve histological activity in NASH but > 50% of the patients could not reach the estimated weight[84,85]. In the literature, results of the studies about antioxidants in NASH therapy are conflicting and heterogeneous. In studies with pentoxifylline, telmisartan, L-carnitine and polyunsaturated fatty acids, it is stated that these agents may improve different parameters (radiology, biochemistry, histology) of NASH[86-88]. Vitamin E or metformin is not efficient in fatty liver in children[89].

As apoptosis is the key pathogenic mechanism in NAFLD, antiapoptotic agents are considered to be efficient in treatment. Studies are proceeding on chemical chaperones (glycerol, 4-phenyl butyric acid, TUDCA), PUFA (decreases ER stress and cell death in liver caused by saturated FFA), protease inhibitors (pan-caspase inhibitor Z-VAD-fmk, VX-166) and kinase inhibitors[11,90-94].

Drugs increasing insulin sensitivity are also studied in NASH. Indeed, the best management of insulin resistance is losing weight but drugs are also used. In pediatric NASH, 1000 mg/d metformin decreased ALT, in 40% ALT became normal, and in 90% steatosis in liver detected by MR spectroscopy decreased 23%. Metformin is effective on SREBP-1c and it is used in adulthood NASH. If evidence of childhood obesity and insulin resistance is present, it is useful and advised to be used. It is used in childhood type 2 diabetes, PCOS and Prader-Willi syndrome[92]. Thiazolidinedione is reported to improve steatosis and inflammation but causes severe weight gain[85].

Exercise, diet and bariatric surgery improve liver histology. Standard obesity surgery is not studied in children and the effect on NAFLD is not known. None of the drug therapies in children is efficient in NAFLD[9,66,71,95,96].

Multi-disciplinary management is needed in obesity treatment. Decrease in weight normalizes transaminases and liver histology. The most acceptable strategy is lowering weight gain and regular medium level exercise. For losing weight, diets with a low glycemic index and realistic portions are helpful. Special diets bringing hyperinsulinism to a minimal level instead of standard low calorie diets are more effective in childhood obesity. Diets with low postglycemic index may be carried out longer than calorie restriction[96-98]. In the management of obesity, family based behavior therapies increase success. The other valuable factor is exercise because it decreases hyperinsulinemia[99-101].

CONCLUSION

Fatty liver is a growing health problem worldwide. It might evolve to nonalcoholic steatohepatitis, cirrhosis and cause hepatocellular carcinoma. There are two distinct subtypes of pediatric NAFLD associated with different clinical, demographic and possible pathophysiological features. In children with NAFLD aged 2-18 years, 51% is type 2 and 17% is type 1. The most important risk factors for NAFLD are obesity and insulin resistance. In general, NAFLD has no specific symptoms or signs but should be considered in obese children. The most common admission reason is slightly elevated transaminases or coincidentally noticed hepatomegaly. In NAFLD, serum aminotransferases are moderately high, ALT being higher than AST. Increase in AST and reversing of the AST/ALT ratio in NAFLD predicts a bad prognosis. Progression to cirrhosis in children is rare but possible. The treatment of this disease is not certain. It is demonstrated that decrease in weight normalizes transaminases and liver histology. Therefore, weight loss with regular medium level exercise and an applicable diet with low glycemic index and appropriate calorie intake are preferred. Drugs are promising but not sufficient in children for today.

In conclusion, since childhood obesity became epidemic in developed countries, NAFLD has become the most common cause of chronic liver disease in pediatrics. Therefore, it should be taken into consideration in obese children. After excluding other diseases, multidisciplinary management should be started for weight loss.

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REVIEW

Hepato-cardiac disorders

Yasser Mahrous Fouad, Reem Yehia

Yasser Mahrous Fouad, Reem Yehia, Gastroenterology and Hepatology Unit, Endemic Medicine Department, Minia University, Minia 19111, Egypt
Author contributions: Fouad YM and Yehia R contributed equally to this work; Both authors collected the data, every author wrote a part of the manuscript and both authors revised the manuscript.
Correspondence to: Yasser Mahrous Fouad, MD, Do, Professor, Gastroenterology and Hepatology Unit, Endemic Medicine Department, Minia University, Damaris, Minia 19111, Egypt. yasserfouad10@yahoo.com
Telephone: +20-11-14721500 Fax: +20-11-867827922
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Abstract

Understanding the mutual relationship between the liver and the heart is important for both hepatologists and cardiologists. Hepato-cardiac diseases can be classified into heart diseases affecting the liver, liver diseases affecting the heart, and conditions affecting the heart and the liver at the same time. Differential diagnoses of liver injury are extremely important in a cardiologist's clinical practice calling for collaboration between cardiologists and hepatologists due to the many other diseases that can affect the liver and mimic haemodynamic injury. Acute and chronic heart failure may lead to acute ischemic hepatitis or chronic congestive hepatopathy. Treatment in these cases should be directed to the primary heart disease. In patients with advanced liver disease, cirrhotic cardiomyopathy may develop including hemodynamic changes, diastolic and systolic dysfunctions, reduced cardiac performance and electrophysiological abnormalities. Cardiac evaluation is important for patients with liver diseases especially before and after liver transplantation. Liver transplantation may lead to the improvement of all cardiac changes and the reversal of cirrhotic cardiomyopathy. There are systemic diseases that may affect both the liver and the heart concomitantly including congenital, metabolic and inflammatory diseases as well as alcoholism. This review highlights these hepatocardiac diseases

Key words: Cardiac cirrhosis; Ischemic hepatitis; Fatty liver; Liver cirrhosis; Heart failure

Core tip: Acute and chronic heart failure may lead to acute ischemic hepatitis or chronic congestive hepatopathy. Treatment in these cases should be directed to the primary heart disease. In patients with advanced liver disease, cirrhotic cardiomyopathy may develop including hemodynamic changes, diastolic and systolic dysfunctions, reduced cardiac performance and electrophysiological abnormalities. Cardiac evaluation is important for patients with liver diseases especially before and after liver transplantation. Liver transplantation may lead to improvement of all cardiac changes and reversal of cirrhotic cardiomyopathy. There are systemic diseases that may affect both liver and heart concomitantly including congenital, metabolic, inflammatory diseases and alcoholism.

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INTRODUCTION

The heart and liver are organs that are closely related both in health and disease. According to traditional medicine, each body has its organ own specific temperament composed of four qualities (elements): "warmth", "coldness", "wetness" and "dryness". "Wetness" and "dryness" are considered on a spectrum of "tissue moistures" and "warmth" and "coldness" may be regarded as the basic metabolism of the organ. In his famous book ,"Canon" (The Law), Avicenna pointed to some of the interactive

effects occurring in the heart and the liver. Some of the most important include: (1) dominance of the "heart warmth" over "liver coldness" and (2) the dominance of "liver dryness" over "heart wetness". The impact and position of "heart temperament" as well as its effect on "liver intemperaments" may be definitive in diagnosis and assessment of the general prognosis of liver disease and in the treatment process[1,2].

Chronic liver diseases may affect cardiac functions in the absence of other heart disease. These effects are called cirrhotic cardiomyopathy and may aggravate the course during orthotropic liver transplantation (OLT). Most of these effects are reversed after OLT[3,4]. In case of ischemic hepatitis, patients with severe heart failure usually remain asymptomatic, while for patients with congestive hepatopathy, signs of right-sided heart failure could mask hepatic injury. However, changes in hepatic function, that are proven by laboratory tests are significant in predicting the survival of patients with severe heart failure. Therefore, the evaluation of cardiac and hepatic function is very important in patients with severe heart failure and hepatic injury. Their treatment options should be revised in order to ensure stable hemodynamics, as well as optimal liver function, and so in this way their survival and prognosis could be improved[5]. This review highlight the liver diseases affecting the heart, heart diseases affecting the liver and some systemic diseases affecting both heart and liver.

LIVER DISEASES AFFECTING THE HEART

Chronic hepatitis C virus

In hepatitis C virus (HCV) heart disease, most patients develop chronic inflammation of the myocardium and, later, dilated cardiomyopathy attributable to necrosis and loss of myocytes. However, because myocytes do not replicate, the proliferative stimuli induced by HCV infection may promote myocyte hypertrophy and hypertrophic cardiomyopathy[6]. A role of direct effect of HCV core proteins was suggested in the pathogenesis of cardiomyopathy[7]. Cardiac damage is a rare manifestation of HCV-related mixed cryoglobulinemia vasculitis. Despite favourable early outcomes, patients with cardiac damage had poorer survival than those without[8]. Chronic hepatitis C viral infection is independently associated with presence of metabolic conditions (insulin resistance, type 2 diabetes mellitus and hypertension) and congestive heart failure[9].

The connection between hyperlipidemia and atherosclerosis is not linear in people with hepatitis C. In a population-based study, although chronic HCV infection was associated with severe insulin resistance, the patients only had mild atherosclerosis, suggesting a unique characteristic of HCV-related metabolic abnormality. Chronic HCV-associated steatosis was suggested as a leading cause of coronary artery diseases through the modulation of atherogenic factors, such as inflammation and dysmetabolic milieu. Interestingly, interferon-based therapies in patients with chronic HCV were found to reduce the long-term risk of stroke. Thus, atherosclerosis in patients with hepatitis C is likely due to an inflammatory process rather than to a lipid related source[10-12]. Thus, even patients having healthy cholesterol and triglyceride levels in the presence of chronic hepatitis C infections should not engage in activities that could further increase the disease risk of their cardiovascular vessels.

Liver cirrhosis

Patients with liver cirrhosis (LC) frequently experience autonomic cardiovascular dysfunction, such as increased activity of the sympathetic nervous system and reduced vagal cardiac function, which has important implications for liver dysfunction and poor survival[13-15]. Baroreflex has been shown to be an important determinant of electrical stability in the heart and can predict increased mortality and end-organ damage[16-19]. Patients with liver cirrhosis have an enhanced activity of the sympathetic nervous system and hyperdynamic circulation showing increased cardiac output and reduced systemic vascular resistance. These changes may induce myocardial remodelling and LV hypertrophy (LVH), resulting in systolic and diastolic functional abnormalities and cardiomyopathy[20-22]. Cirrhotic cardiomyopathy was defined by a working group as a cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and or altered diastolic relaxation with electrophysiological abnormalities in the absence of known cardiac disease[23]. The criteria for the diagnosis of cirrhotic cardiomyopathy are shown in Table 1[24].

Systolic dysfunction is related to the inability of the heart to meet its demands with respect to the generation of an adequate arterial blood pressure and cardiac output. This dysfunction can be unveiled by physical exercise that increases left ventricular pressure, volume, and left ventricular ejection fraction and heart rate in some cirrhotic patients. Similarly, the administration of vasoconstrictors, such as angiotensin Ⅱ and terlipressin, increases the SVR and thereby the left ventricular afterload unmasking a latent left ventricular dysfunction in cirrhosis. In contrast, vasodilators, such as angiotensin-converting enzyme inhibitors and other afterload-reducing agents, should be used with caution due to the risk of further aggravation of the vasodilatory state[24]. Systolic dysfunction may have an impact on the development of complications, such as sodium and water-retention and ascites formation, as well as development and prognosis of renal dysfunction[25,26].

Diastolic dysfunction in cirrhosis is due to an increased stiffness of the myocardial wall owing to myocardial hypertrophy, fibrosis, and subendothelial edema. The prevalence of diastolic dysfunction has been reported to range from 45% to 56%. Diastolic dysfunction is most prominent in patients with severe decompensation, in whom, the combination of myocardial hypertrophy, contractile dysfunction, changes in heart volumes, and diastolic dysfunction may represent an essential element

Table 1 Proposal for diagnostic and supportive criteria for cirrhotic cardiomyopathy agreed upon at a working party held at the 2005 World Congress of Gastroenterology

A working definition of cirrhotic cardiomyopathy
A cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease
Diagnostic criteria
Systolic dysfunction
Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
Resting EF < 55%
Diastolic dysfunction
E/A ratio < 1.0 (age-corrected)
Prolonged deceleration time (> 200 ms)
Prolonged isovolumetric relaxation time (> 80 ms)
Supportive criteria
Electrophysiological abnormalities
Abnormal chronotropic response
Electromechanical uncoupling/dyssynchrony
Prolonged QTc interval
Enlarged left atrium
Increased myocardial mass
Increased BNP and pro-BNP
Increased troponin I

BNP: Brain natriuretic peptide; E/A: Early diastolic/atrial filling ratio; EF: Left-ventricular ejection fraction.

in cirrhotic cardiomyopathy[26-28]. The diastolic dysfunction may adversely affect the prognosis of patients with cirrhosis, by favouring the occurrence of complications and impairing the outcomes of manoeuvres that lead to rapid increases in preload, such as transjugular intrahepatic porto-systemic shunt (TIPS) insertion[24].

Patients with advanced cirrhosis usually exhibit tachycardia. The inability to increase the heart rate further contributes to an impaired ability to keep the cardiac output at a level adequate to meeting the needs of systemic circulation. At this point, the effective volemia suddenly worsens, similar to the events of post-paracentesis circulatory dysfunction and hepatorenal syndrome[29-31]. The prolongation of the electrocardiographic QT interval is common in cirrhosis, with a prevalence that exceeds 60% in patients with an advanced disease. In this case, drugs affecting QT should be avoided or used with caution and under close ECG monitoring[32]. Systemic and cardiac changes in patients with liver cirrhosis are shown in Figure 1.

Almost all cardiovascular abnormalities reverse a few months after liver transplantation[4,24,33].

Nonalcoholic fatty liver disease

It has been shown that the leading cause of death in patients with nonalcoholic fatty liver disease (NAFLD) is coronary events. In patients with diabetes mellitus, NAFLD is associated with cardiovascular disease (CVD) independent of the classical risk factors, glycaemic control, medications, and metabolic syndrome features. When diabetic patients with and without NAFLD were compared, those with NAFLD had a higher prevalence of coronary vascular disease, hypertension, central obesity, poor glycaemic control, and dyslipidaemia and greater carotid intimal thickness. Furthermore, with the development of steatohepatitis, the degree and severity of CVD became directly proportional to the severity of inflammation on liver biopsy. Cardiovascular mortality is also increased at least two-fold in non-alcoholic steatohepatitis (NASH). The presence of liver fat is associated with lower adiponectin levels and increased levels of fibrinogen, C-reactive protein (CRP), and plasminogen activator inhibitor 1 (PAI-1), which are markers of inflammation and risk factors of coronary vascular disease independent of BMI and intra-abdominal obesity. Patients with NAFLD also have significantly higher mean values of intima-media thickness and prevalence of plaques resulting in an increased risk of atherosclerosis in subjects with metabolic syndrome. It has also been shown that NASH predicts plasma inflammatory biomarkers independent of visceral adiposity and other potential confounders. These findings suggest that NASH is not simply a marker of CVD but may also be involved in its pathogenesis. Steatosis has been found to be the strongest independent risk predictor of vascular damage, followed by age and blood pressure. Patients with NAFLD and systolic BP $\geqslant$ 130 mmHg are 4.7 times more likely to have a positive treadmill test[34-36].

In a recent study, asymptomatic obese children with NAFLD exhibited features of early LV diastolic and systolic dysfunction. These abnormalities were more severe in those with NASH[37].

Primary biliary cirrhosis

Circulating cholesterol levels are elevated in most with primary biliary cirrhosis. Hypercholesterolemia in patients with primary biliary cirrhosis should be considered a cardiovascular risk factor only when other factors are present. Ursodeoxycholic acid, the standard treatment for primary biliary cirrhosis, improves cholestasis, thereby lowering the circulating levels of cholesterol. Thus, hypercholesterolemia in the absence of other cardiovascular risk factors does not require specific therapeutic interventions in patients with primary biliary cirrhosis.

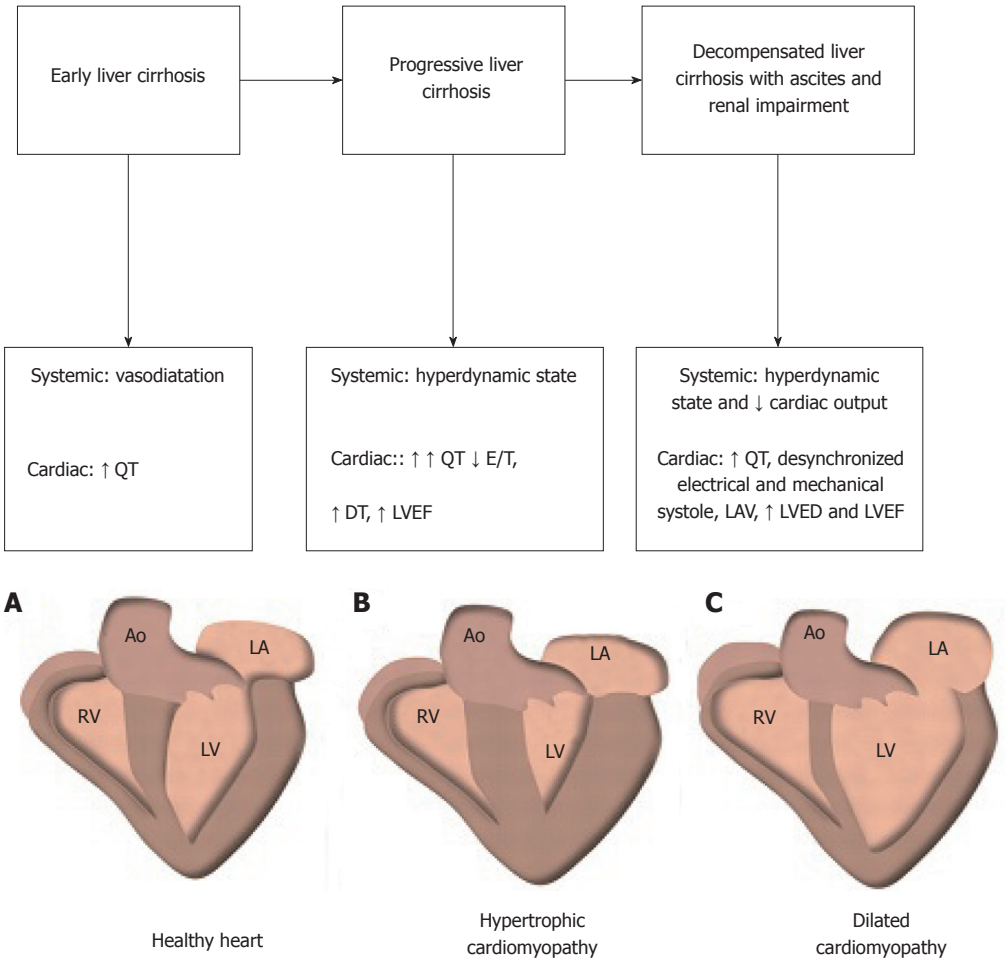

Figure 1 Proposal of changes in cardiac output during the course of the liver disease. DT: Deceleration time; LAV: Left atrial volume; LVEDV: Left end-diastolic volume; LVEF: Left ventricular ejection time.

Epidemiological studies have shown significantly increased all-cause mortality rates in comprehensive PBC patient groups, with a significant component of this increased mortality coming from non-liver-related causes[38,39]. These studies were not designed to address the cause of this increase in non-liver-related mortality. There is, however, convincing evidence from the same populations to suggest that malignant disease makes little or no contribution to this excess non liver mortality[38,40]. Given the importance of cardiovascular mortality in the general population, the possibility must be considered that cardiac mechanisms contribute to the excess non liver mortality rates seen in these populations. Autonomic dysfunction has been seen in PBC and was associated with an increased cardiac mortality risk in non-liver chronic disease states[41,42]. Furthermore, a significant peripheral muscle bioenergetics abnormality has also been reported in PBC[43]. Raising the possibility that similar bioenergetic abnormalities may also be present in the cardiac muscle. The effects of autonomic dysfunction may alter the perfusion patterns in tissues, potentially reducing muscle perfusion and contributing to peripheral mechanisms of fatigue. A generic tendency towards altered myocardial function was shown in PBC and did not typically appear to be symptomatic in terms of "classical" myocardial dysfunction symptoms[44].

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of affecting the large bile ducts and is characterized by periductal fibrosis and stricture formation. Arteriosclerosis involves the accumulation of altered lipids and lipoproteins in large arteries; this drives inflammation and fibrosis and ultimately leads to the narrowing of the arteries and hypoperfusion of dependent organs and tissues. Knowledge of the causative factors is crucial to the understanding of disease mechanisms and the development of specific treatment. Based on the pathogenic similarities and common molecular, cellular, and morphological features that provide the conceptual framework for a deeper understanding of their pathogenesis between PSC and arteriosclerosis, it has been hypothesized that PSC represents "arteriosclerosis of the bile duct" initiated by toxic biliary lipids[45]. This hypothesis should stimulate translational research to facilitate the search for novel treatment strategies for both diseases.

Hepatocellular carcinoma

Cardiac complications of hepatocellular carcinoma hepatocellular carcinoma are rare. Cases of right atrial invasion of HCC had been reported[46], which led in some

cases to right ventricular outflow obstruction and Budd Chiari syndrome[47,48]. Hepatocellular carcinoma patients with cardiac metastases are usually found in advanced stages. These patients have limited survival from the diagnosis of cardiac metastases. The most common causes of death are related to HCC itself or to the underlying liver disease. Only a few patients will die due to cardiac metastases[49]. The palliative treatments for tumor thrombi may include transcatheter chemotherapy, transarterial chemoembolization and radiation therapy with a partial improvement of patient symptoms[50].

Budd-chiari syndrome

Primary Budd-chiari syndrome (BCS) is a rare clinical entity characterized by hepatic venous outflow obstruction at various levels from the small hepatic veins to the inferior vena cava. There are three main types of BCS: Type Ⅰ, occlusion of the IVC; type Ⅱ, occlusion of the hepatic veins; and type Ⅲ, occlusion of the IVC and the hepatic veins. The incidence of HCC combined with BCS varies among the types of BCS[50,51]. Type I BCS is more prone to inducing HCC and the incidence ranges between 10.7% and 43.5%. The mechanisms of HCC induction unknown. The therapeutic treatments of BCS combined with HCC includes TACE, surgery and more recently angioplasty followed by percutaneous microwave ablation[52-55].

Portal hypertension

Three important complications are associated with portal hypertension hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax.

The hepatopulmonary syndrome: This entity is defined by an oxygenation defect caused by the development of intrapulmonary vascular dilation in patients with either advanced liver disease and/or portal hypertension[56]. Angiogenesis was shown to be induced by an increased level of nitric oxide and vascular endothelial growth factor in patients with advanced liver disease or portal hypertension[57,58]. Patients with the hepatopulmonary syndrome (HPS) may present with the insidious onset of dyspnea or remain completely asymptomatic during the early stages. Dyspnea upon standing (platypnea) and hypoxemia exacerbated in the upright position (orthodeoxia) are present in almost 25% of HPS patients[59]. Patients with severe HPS may display digital clubbing and cyanosis.

Chest radiographs may be normal or show bibasilar nodular or reticulonodular opacities, reflecting diffuse vascular pulmonary dilation[60,61]. Pulmonary function tests typically demonstrate a reduced diffusion capacity for carbon monoxide[61]. There is no established medical therapy currently available for HPS. In patients with PaO2 < 60 mmHg at rest or with exertion, the administration of supplemental oxygen is appropriate, because chronic hypoxemia itself may contribute to the mortality in HPS[62,63]. The administration of garlic resulted in improvements in the PaO2, in two uncontrolled trials and a small randomized study[64].

Portopulmonary hypertension: Portopulmonary hypertension (POPH) is characterized by pulmonary arterial hypertension (PAH) that occurs in the setting of portal hypertension, with or without advanced liver disease[65]. The severity of POPH does not correlate with the degree of liver dysfunction or the severity of portal hypertension[66,67]. The pathophysiology of POPH is not fully understood. The histopathology of POPH is similar to that of idiopathic PAH, and is triggered by vascular injury as reflected by the development of plexiform arteriopathy, concentric intimal fibrosis, and proliferation and muscularization of the pulmonary arterioles[68]. Dyspnea on exertion is the most common initial symptom of POPH and fatigue, orthopnea, chest pain, peripheral edema, syncope, and dyspnea at rest may develop as the disease progresses[69,70]. Medical treatment includes the following: prostacyclin analogs (prostanoids), Endothelin receptor antagonist and Phosphodiesterase-5 inhibitors[71-73]. A single short-term study in patients with moderate to severe POPH, found that the use of β-blockers was associated with worsening exercise capacity[72].

Hepatic hydrothorax: This entity is characterized by a transudative pleural effusion in the absence of underlying cardiac or pulmonary disease. Its prevalence has been estimated to be 5%-10% in cirrhotics, based on retrospective observational data[73]. The most important mechanism leading to the passage of ascitic fluid from the peritoneal into the pleural cavity is the presence of diaphragmatic defects. These defects were corroborated by showing passage of 99mTc-human albumin from the abdominal into the pleural cavity, even in the absence of underlying ascites[74]. Symptoms include cough, dyspnea, chest discomfort, hypoxia, and in the most severe cases respiratory failure with or without ascites[74,75]. Spontaneous bacterial pleuritis (SBPL) results when hepatic hydrothorax (HH) becomes infected in the absence of pneumonia. Symptoms in SBPL vary from fever and pleuritic chest pain to subtle worsening of encephalopathy or renal function, necessitating a high index of suspicion. A PMN > 500 cells/mm^3 is diagnostic for SBPL in a pleural effusion, although SBPL with PMN between 250-500 cells/mm^3 is documented by positive pleural fluid culture[76]. Chest tube placement is contraindicated in SBPL, in the absence of empyema, due to the risk of protein loss, prolonged drainage, secondary infection and hepatorenal syndrome[77]. Treatment of HH includes the restriction of sodium intake with the administration of diuretics. This approach is effective in controlling HH, although fluid mobilization from the pleural cavity may be slower than from the peritoneal cavity and approximately 20% of patients develop refractory HH[77]. Percutaneous drainage, and chest tube placement can be used in some cases[77,78]. The standard of care treatment for refractory HH is TIPS placement with response rates

of 70% to 80%[79,80]. Video assisted thoracoscopy (VATS) with pleurodesis is a potential treatment alternative for patients with refractory HH, who are not eligible for or who have failed TIPS[81-83].

Liver transplantation

Patients with cirrhosis requiring liver transplantation (LT) usually demonstrate increased cardiac output. Low systemic vascular resistance and bradycardia are also commonly seen in cirrhosis and can be aggravated by beta-blocker use. These physiologic changes increase the risk of cardiovascularn complications, in addition to altered hemodynamic stresses that LT patients face in the immediate post-operative period. Post-transplant reperfusion may result in cardiac death due to a multitude of causes, including arrhythmia, acute heart failure (HF), and myocardial infarction[84].

The unusually high perioperative mortality in transplant patients with CAD warrants a systematic evaluation in every patient that thought to have a greater risk of atherosclerotic coronary disease. No single test has a predictive value of 100%. Therefore, diagnostic protocols must account for the variation in prevalence that occurs in subsets of transplant candidates and the limitation of each type of test[85]. In contrast to ischemic heart disease, most patients with advanced liver disease have myocardial defects that cause systolic and diastolic impairments not always evident at rest. There are also underlying electrophysiological defects that cause an uncoupling of the mechanical and electrical activity. Diagnosis of "cirrhotic cardiomyopathy" is difficult because the findings can be subtle as some patients develop frank heart failure when exposed to pharmacological or physiological stressors such as during liver transplantation[85].

Almost all cardiovascular abnormalities can be reversed 6 to 12 mo after liver transplantation. Namely, indices of both systolic and diastolic function, cardiac workload, and exercise capacity can be substantially improved or normalized. QT interval prolongation can also revert after OLT, even though this occurs in about half of cases suggesting that liver disease may not be the only pathogenic factor[4,24,33].

CARDIAC CAUSES OF HEPATIC DISORDERS

Heart failure

The cardiac causes of hepatic dysfunction include constrictive pericarditis, severe pulmonary arterial hypertension (PAH), mitral stenosis, tricuspid regurgitation (TR), corpulmonale, ischemic cardiomyopathy, and postoperative consequences of the Fontan procedure for pulmonary atresia and hypoplastic left heart syndrome. All of these causes can lead to passive congestion due to the elevated right ventricular (RV) pressure and right sided heart failure. The outcomes of heart failure have dramatically improved, due to the increased efficiency of medical treatment, as a result, cardiac cirrhosis prevalence is declining[24,86].

Pathophysiology: In chronic heart failure (backward failure), the increase in venous pressure caused by RV dysfunction leads to the atrophy of hepatocytes and causes perisinusoidal edema which can impair the diffusion of oxygen and nutrients to the hepatocytes[87,88]. This backward failure is also responsible for the enhanced hepatic lymph formation, leading to ascites when its production rate exceeds the draining capacity of the lymphatic system. Moreover, increased pressure within the hepatic sinusoid favours bile duct damage by disrupting endothelial cells and the interhepatocyctic tight junctions that separate the extravascular space from the bile canaliculus. Finally, stagnant flow favors thrombosis within sinusoids, hepatic venules, and portal tracts; thereby contributing to liver fibrosis[24,89,90].

On gross examination, the congestive liver is enlarged, with a purple or reddish hue and prominent hepatic veins. The cut surface shows a classic nutmeg appearance, reflecting an alternating pattern of haemorrhage and necrosis of zone 3 with normal or slightly steatotic areas in zones 1 and 2. Microscopically, the hallmark features of hepatic venous hypertension are the prominence of the central veins, central vein haemorrhage, and sinusoidal engorgement[87,91,92]. Untreated, longstanding congestion can lead to cardiac fibrosis and,ultimately cardiac cirrhosis[93]. Acute HF (forward failure): most commonly arises in the context of profound systemic hypotension from acute cardiopulmonary collapse after myocardial infarction, exacerbation of HF, or pulmonary embolism. In the absence of established hypotension, ischemic hepatitis has been shown in instances of severe hypoxemia, such as obstructive sleep apnea, respiratory failure, and in conditions of increased metabolic demand, such as those seen in toxic/septic shock[94-96]. Ischemic liver injury is characterized by centrolobular necrosis of zone 3 hepatocytes in the absence of histological evidence of inflammation characteristic of viral hepatitis[97-101].

Oxygen consumption can be easily increased when the hepatic blood flow is decreased. The mechanism by which the liver protects itself from damage in hypoxia is increasing oxygen extraction by the hepatocytes up to 95% as the blood passes through the liver. When inadequate end-organ perfusion and tissue hypoxia is persistent or when acute shock develops this protecting mechanism against hypoxic liver damage is overwhelmed. Hepatocellular injury ensues, accompanied by a sharp elevation of the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), prolongation of the prothrombin time, and occasionally functional renal impairment. These abnormalities reach their peak 1 to 3 d after the onset of cardiogenic ischemic hepatitis and return to normal within 5 to 10 d from onset of the disorder[102].

These forward and backward factors often coexist and potentiate each other. Additionally, the presence of hepatic steatosis due to diabetes, obesity, or other causes may increase liver susceptibility to the ischaemic reperfu-

sion injury[24,103].

Clinical presentations: As for the acute ischemic hepatitis, no specific symptoms but patients may present with symptoms of nausea, vomiting, anorexia, malaise, right-upper quadrant pain, jaundice, oliguria, and flapping tremors representing cerebral hypoperfusion rather than hepatic encephalopathy. Ischemic hepatitis is usually benign and self-limited. The clinical diagnosis of liver injury is almost always incidental when liver enzymes are found to be massively elevated 1 to 3 d after an episode of systemic hypotension. This condition may be associated with increased serum creatinine level from acute tubular necrosis[102].

Congestive hepatopathy: The term congestive hepatopathy replaced cardiac cirrhosis. Patients experience mild, dull right upper quadrant pain caused by the stretching of the liver capsule. Hepatomegaly with a firm, tender liver edge and peripheral edema are typically the most prominent findings in patients with chronic right-sided HF, but these may also occur rapidly in acute HF. Ascites may be present in up to 25% of these patients and splenomegaly is characteristically absent[86]. Jaundice is not commonly reported. In patients with considerable TR, a prominent systolic pulsation of the liver, attributable to an enlarged right atrial V wave, is often noted. A presystolic pulsation of the liver, attributable to an enlarged right atrial A wave, can occur in tricuspid stenosis, constrictive pericarditis, restrictive cardiomyopathy involving the RV, and pulmonary hypertension[5].

Laboratory data: As for the acute ischemic hepatitis, severe jaundice is common, with a bilirubin level as high as 15 to 20 mg/dL, elevation of AST to more than 10 times the upper reference range limit, a marked increase in serum LDH, an elevated ALP level, and prolongation of the prothrombin time. Increases in LDH tend to be massive and an ALT/LDH ratio of less than 1.5 helps distinguishing ischemic injury from other forms of acute hepatitis[104,105].

As for the congestive hepatopathy, the usual findings are moderate elevations of the biochemical parameters of liver function 2 to 3 times the upper normal reference level. These parameters include AST, ALT, LDH, gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP). Hyperbilirubinemia, secondary to an increase in both the direct and indirect bilirubin, is also common. The total bilirubin level is rarely greater than 3 mg/dL. In patients with long-standing HR, albumin synthesis may be impaired, leading to hypoalbuminemia and intensifying the accumulation of fluid[102].

Treatment: Treatment of the cardiac problem is the key to improvement in hepatic dysfunction.

As for the AHF and ischemic hepatitis, correcting underlying circulatory or respiratory disturbances is the main treatment. It is recommended that doctors identify and remove any precipitating cause, such as medications with negative inotropic or hypotensive effects (certain antiarrhythmic drugs, calcium-channel blockers, and vasodilators), medications likely to cause impairment of renal function (high doses of angiotensin-converting enzyme (ACE) inhibitors, angiotensin Ⅱ receptor blockers), or medications likely to accumulate with evolving renal failure (like digoxin)[106]. Oxygen should be administered as early as possible in hypoxemic patients to achieve an arterial oxygen saturation > 95%. Administration of intravenous diuretics is recommended with caution in acute HF patients in the presence of symptoms secondary to congestion and volume overload. Inotropic agents should be considered in patients with low output states and low systolic blood pressure. When needed, inotropic agents should be administered as early as possible and withdrawn as soon as adequate organ perfusion is restored and/or the congestion is reduced. Vasopressors are only indicated in cases of cardiogenic shock when the combination of an inotropic agent and fluid challenge fails to restore systolic blood pressure > 90 mmHg, with inadequate organ perfusion, despite an improvement in cardiac output[5,106].

As for the chronic HF and congestive hepatopathy, the main lines of treatment are angiotensin-converting enzyme (ACE) inhibitors and beta blockers. The addition of a low-dose aldosterone antagonist should be considered in all patients with an LV systolic dysfunction. ACE Inhibitors increase cardiac output and decrease LV filling pressure due to their vasodilatory effect. Some ACE inhibitors are prodrugs, which require transformation by the liver into active metabolites. These drugs include enalapril, ramipril, fosinopril, trandolapril, quinapril, benazepril, and moexipril. With liver dysfunction, decreases in the prodrug transformation and inactivation of the active drug may occur[107]. For those patients who cannot tolerate ACE inhibitors due to cough, angiotensin receptor blockers (ARBs) are recommended instead. ARBs reduce morbidity and mortality in patients with systolic HF. Losartan is metabolized to the active metabolite *via* hepatic carboxylation. In patients with hepatic impairment, the bioavailability is doubled and the total plasma clearance is halved. Therefore, lower initial doses are recommended. Valsartan undergoes little metabolic conversion. Caution is recommended in patients with mild to moderate liver dysfunction but dosage adjustments are generally not needed. Similar to valsartan, irbesartan does not require biotransformation, thus dosage modification is not necessary[108-111].

The use of *b*-blockers is associated with a 30% reduction in total mortality in HF. Propranolol should be administered cautiously in patients with hepatic impairment. No dose adjustments are necessary for atenolol, nadolol, esmolol, sotalol, or acebutolol[112-116].

Diuretics: Loop diuretics, such as furosemide, bumetanide, and torsemide, are used for volume management in HF because of their superior natriuretic effects compared with other classes of diuretics. For unknown

Table 2 Comparison between acute and chronic hepatic complications of cardiac failure

	Chronic congestive hepatopathy	Acute ischemic hepatitis
Aetiology	Chronic heart failure	Acute heart failure
Pathophysiology	Perisinusoidal edema	Tissue hypoxia
	Increased lymph flow	Zone 3 necrosis
	Zone 3: alternating necrosis and hemorrhage	
	Sinusoidal thrombosis	
Manifestations	Right hypochondrial pain	Asymptomatic or nonspecific
	Edema, ascites, jaundice	(nausea, vomiting, jaundice, right hypochondrial pain)
Laboratory data		
Bilirubin	Mild increase	Marked elevation
ALT and AST	Normal mild elevation	Marked elevation
LDH	Normal or mild elevation	Marked elevation
Prothrombin time	Prolonged	Normal or prolonged
ALP	Normal or mild elevation	Increased
Albumin	Hypoalbuminemia	Normal
Traetment	ACE inhibitors	Oxygen therapy
	b-blockers	Avoid precipitating factors
	Diuretic	Inotropic agents with caution
	Amiodarone	Vasopressor with caution
	Statins with caution	Diuretics in hypervolemia
Prognosis	Slowly progressive course	Benign and usually self limited

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactic dehydrogenase; ALP: Alkaline phosphatase; ACE: Angiotensin-converting enzyme.

reasons, the pharmacologic response in patients with liver dysfunction and HF is diminished, and there is a net decreased in sodium excretion when compared with healthy individuals taking the same dose. No adjustments are necessary if renal function is normal[115].

In patients with severe HF, amiodarone has proven to be effective for suppressing ventricular arrhythmias, reducing sudden death and cardiac mortality, and improving exercise tolerance and ejection fraction. This drug undergoes an extensive hepatic metabolism to active metabolite, but no dosage reduction is indicated in hepatic impairment[116].

Statins undergo extensive hepatic metabolism. In patients with active liver disease or persistent unexplained elevations in serum transaminases to above 3 times the upper limit of normal, the use of statins is contraindicated as they may worsen liver function[117].

For patients, who are refractory to medical therapy and who may be candidates for cardiac surgery, CH due to chronic HF can improve and reverse after temporary LV assistive device support or for selected patients or cardiac transplantation[118,119]. The differences between acute and chronic hepatic impairment are summarized in Table 2.

Ventricular assist devices

Ventricular assist devices (LVADs) lead to volume shifts from the intrathoracic area to the systemic circulation, thus improving liver blood flow, as assessed by indocyanine green clearance. Studies have shown improvement in the liver function in patients with mild abnormalities in pre-implant liver tests, and no deterioration in those with normal baseline values, up to 6 mo[118,120]. However, pre-existing or post-LVAD severe liver dysfunction strikingly influences patients' prognosis and endangers their survival[121]. Liver dysfunction can also occur or worsen after LVAD implantation. Pre-, peri-, and post-operative factors, such as large doses of vasopressors, prolonged cardiopulmonary bypass time, arterial hypotension, systemic inflammatory responses and, mainly, right ventricular failure predispose a patient to liver damage, often presenting with intrahepatic cholestasis[121]. The model for end-stage liver disease (MELD), a scoring system assessing the severity of chronic liver disease based on serum bilirubin, creatinine and INR for prothrombin time that is widely used to determine prognosis and prioritize the receipt of a liver transplant, is able to predict mortality and morbidity following LVAD. The severity and course of post-ventricular assist devices liver damage can be monitored by sequential assessment of MELD-XI, a modified MELD score excluding INR to overcome the problem posed by concomitant anticoagulation[24,122].

Heart transplantation

Chronic cardiac hepatopathy is common in patients evaluated for heart transplantation-x (HTx), and liver dysfunction predicts an adverse outcome following transplantation. At the same time, altered pre-HTx liver tests can significantly improve after surgery, suggesting that chronic cardiac hepatopathy is a potentially reversible disease. In a large cohort study over 10 years among patients who had received LTx, all cholestatic parameters, transaminases and LDH improved after the procedure. Interestingly, a complete reversal of cardiac cirrhosis 10 years after HTx has even been reported[123,124].

A careful assessment of liver function and detection of liver cirrhosis is required in all candidates for HTx. An ultrasound of the abdomen with an echo-Doppler study of portal and tributary veins should be performed. Endoscopy may be necessary to assess the presence of

Table 3 Diseases affecting both the liver and the heart concomitantly

	Hepatic manifestations	Cardiac manifestations
Congenital		
Allagile syndrome	Cholestasis	Congenital heart defects
Situs Inversus totalis	Concerns with liver or heart transplantation	
Infections		
Sepsis	Acute liver failure	Acute heart failure
Hepatitis C	Hepatitis	Myocarditis, cardiomyopathy
Cytomegalovirus	Hepatiitis	Myopericarditis
HIV	Hepatitis, granuloma	Myocarditis , cardiomyopathy
Malaria	Hepatic necrosis	Cariac failure
Dengue fever	Hepatic necrosis	Myocarditis
Amebiasis	Hepatitis, hepatic abscess	Pericarditis, effusion
Metabolic		
Wilson disease	Cirrhosis, hepatitis	Left ventricular remodeling
Hemochromatosis	Cirrhosis, hepatitis	Cardiomyopathy
Systemic		
SLE	Steatosis, hepatomegaly	Endocarditis, pericarditis
Amyloidosis	Hepatomegaly, cholestasis	Cardiomyopathy
Sarcoidosis	Granuloma, cholestasis	Conduction defects, HF
Chronic alcoholism	Cirrhosis	Cariomyopathy
Autoimmune		
Grave's disease	Hepatitis, cholestasis	HF
Autoimmune hepatitis	Hepatitis, cirrhosis	Carditis

HF: Heart failure.

gastro-esophageal varices and congestive gastropathy in patients with portal hypertension. Liver biopsy may be needed in some cases. MELD or modified MELD scores should be calculated. Higher MELD scores predict higher postoperative complication rates, including reoperation for bleeding, bacterial infections, and in-hospital death[124].

Patients with chronic hepatitis C or chronic hepatitis B should be treated before HTx to avoid antiviral drug intake after HTx which may be associated with graft rejection[125]. Finally, patients with heart failure and irreversible cirrhosis could be offered combined heart and liver transplantation[126].

DISEASES AFFECTING BOTH THE HEART AND THE LIVER

There are many systemic diseases in addition to chronic alcoholism, that affect both the liver and the heart. This fact may have important implications, because the heart and the liver also interact particularly during surgical procedures, OLT, and TIPS insertion, thereby influencing the outcomes. The spectrum of these diseases include congenital , autoimmune, metabolic and infectious causes (shown in Table 3). We highlight some examples of these diseases.

Congenital causes

The famous example is Alagile syndrome (AS), which is a multisystemic disease that is autosomal dominant, with variable expression. The major clinical manifestations are as follows: chronic cholestasis, congenital heart disease, posterior embryotoxon in the eye, characteristic facial phenotype, and butterfly vertebrae. AS is caused by mutations in JAGGED1 (more than 90%) and in NOTCH2. Cholestasis, pruritus and xanthomas have been successfully treated with choleretic agents (ursodeoxycholic acid) and other medications (cholestyramine, rifampin, naltrexone). In certain cases, partial external biliary diversion has also proven successful. Liver transplantation is indicated in children with cirrhosis and liver failure[127].

Infections

Cytomegalovirus (CMV) infection in inmunocompetent hosts generally is asymptomatic; whoever, it rarely can lead to severe organ complications. A rare, but serious complication of cytomegalovirus infection is the presence of myopericarditis concomitant with hepatitis with a possible role of oral valganciclovir in these patients[128].

Metabolic causes

Wilson disease: Wilson disease is an inherited autosomal recessive disorder of the copper metabolism resulting in the pathological accumulation of copper in the liver, brain and other tissues. One of the reported manifestations is cardiac involvement. Cardiac involvement in Wilson disease patients is characterized by LV parietal thickening with an increased prevalence of concentric LV remodelling. Children with Wilson diseases were asymptomatic upon cardiological examination, but had significantly lower mitral E velocities, mitral E/A ratios as estimated by pulsed wave Doppler echocardiography[129,130].

Hemochromatosis: Hemochromatosis is an autosomal recessive disorder affecting the white population. In this disorder, the inappropriate absorption and deposi-

tion of dietary iron may result in the development of hepatic and non-hepatic end-organ injury, leading to liver cirrhosis, hepatocellular carcinoma, diabetes, arthritis, skin pigmentation and cardiac diseases[131]. Cardiac involvement in hemochromatosis affects mainly the myocardium: iron overload of the myocytes reduces left ventricular distensibility. Heart failure is the most frequent manifestation of cardiac involvement. Diagnosis of cardiac involvement depends essentially on Doppler echocardiography showing abnormal left ventricular filling and, later, ventricular dilatation with left ventricular systolic dysfunction. Magnetic resonance imaging can quantify intrahepatic and intramyocardial iron levels. The two principal means of treatment by iron depletion are phlebotomy in primary hemochromatosis and excretion of iron by chemical chelation in secondary hemochromatosis. Early diagnosis and iron depletion improve survival by reducing the organ iron overload, especially in the liver and myocardium. The recent guidelines issued by Anaes (national agency for health evaluation) make it possible to identify risk factors for complications early, to determine the disease stage, and to provide appropriate management as a function of disease severity. Combined liver transplantation and cardiac surgery may be needed in cases of hemochromatosis with end stage liver disease and heart failure[132].

Autoimmune diseases: The atypical clinical presentations of Graves' disease (GD) include anemia, vomiting, jaundice, and right heart failure. Hyperthyroidism may present with jaundice, and on the other hand, deep jaundice may develop with the onset of overt hyperthyroidism in previously compensated chronic liver disease patients. Jaundice may be caused by hepatitis or intrahepatic cholestasis. Pulmonary hypertension is reported to be associated with GD and to respond to its treatment. GD-related pulmonary hypertension may be so severe that it produce isolated right-sided heart failure, which is occasionally identified as the presenting manifestation of GD[133].

Chronic alcoholism: Patients with chronic alcoholism can be presented with both hepatic and cardiac complications. Actively drinking alcoholics with cirrhosis have significantly lower mean ejection fraction and shortening fraction, as well as a greater mean end-diastolic diameter and left ventricular mass than abstaining alcoholics with cirrhosis. Alcoholics admitted solely for cardiomyopathy have a higher prevalence of cirrhosis than unselected alcoholics without heart disease. Actively drinking alcoholics admitted only for cirrhosis show impaired cardiac performance, whereas abstaining alcoholics with liver disease tend to manifest normal cardiac function[134]. Patients with alcoholic cirrhosis should be screened for cardiomyopathy for at least three reasons: (1) asymptomatic systolic and diastolic dysfunctions can precede the overt manifestation of cardiomyopathy; (2) hyperdynamic circulatory syndrome may disguise the clinical expression of initial heart failure; and (3) prevention or treatment of some complications of cirrhosis, such as hepatorenal syndrome, is based on plasma expansion with albumin and the administration of vasoconstrictors. This would lead to deleterious effects if latent heart failure goes unrecognized[135].

CONCLUSION

Chronic liver diseases may induce systolic and diastolic dysfunctions in addition to electrophysiological changes, and the prolongation of QT interval in conditions of cirrhotic cardiomyopathy; all of these may improve completely after liver transplantations. Recent studies have found cardiac changes in patients with NAFLD, hepatitis C and primary biliary cirrhosis. On the contrary, acute and chronic heart failure have been shown to lead to acute hepatic injury and chronic congestive hepatopathy with manifestations of liver failure and laboratory data specific to ischemic hepatitis or congestive hepatopathy. There are systemic diseases that affect both the heart and the liver, thus necessitating good cardiac and hepatic evaluation. Collaboration between hepatologists and cardiologists is needed in these categories of patients for better diagnosis, treatment and prognosis. Liver and cardiac transplantation may solve this problem in some patients with heart and liver failure.

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SYSTEMATIC REVIEW

Human immunodeficiency virus and nodular regenerative hyperplasia of liver: A systematic review

Archita Sood, Mariana Castrejón, Sammy Saab

Archita Sood, Department of Medicine, Olive View Medical Center, Sylmar, CA 91342, United States
Mariana Castrejón, Department of Surgery, University of California at Los Angeles Medical Center, Los Angeles, CA 90095, United States
Sammy Saab, Departments of Medicine and Surgery, University of California at Los Angeles Medical Center, Los Angeles, CA 90095, United States
Author contributions: Saab S designed research; Saab S and Sood A performed research; Saab S, Castrejón M and Sood A analyzed data; Saab S and Sood A wrote the paper.
Correspondence to: Sammy Saab, MD, MPH, AGAF, Departments of Medicine and Surgery, University of California at Los Angeles Medical Center, 200 Medical Plaza, Suite 214, Los Angeles, CA 90095, United States. ssaab@mednet.ucla.edu
Telephone: +1-310-2066705 Fax: +1-310-2064197
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Abstract

AIM: To investigate the diagnosis, pathogenesis, natural history, and management of nodular regenerative hyperplasia (NRH) in patients with human immunodeficiency virus (HIV).

METHODS: We performed a systematic review of the medical literature regarding NRH in patients with HIV. Inclusion criteria include reports with biopsy proven NRH. We studied the clinical features of NRH, in particular, related to its presenting manifestation and laboratory values. Combinations of the following keywords were implemented: "nodular regenerative hyperplasia", "human immunodeficiency virus", "noncirrhotic portal hypertension", "idiopathic portal hypertension", "cryptogenic liver disease", "highly active antiretroviral therapy" and "didanosine". The bibliographies of these studies were subsequently searched for any additional relevant publications.

RESULTS: The clinical presentation of patients with NRH varies from patients being completely asymptomatic to the development of portal hypertension – namely esophageal variceal bleeding and ascites. Liver associated enzymes are generally normal and synthetic function well preserved. There is a strong association between the occurrence of NRH and the use of antiviral therapies such as didanosine. The management of NRH revolves around treating the manifestations of portal hypertension. The prognosis of NRH is generally good since liver function is preserved. A high index of suspicion is required to make a identify NRH.

CONCLUSION: The appropriate management of HIV-infected persons with suspected NRH is yet to be outlined. However, NRH is a clinically subtle condition that is difficult to diagnose, and it is important to be able to manage it according to the best available evidence.

Key words: Human immunodeficiency virus; Nodular regenerative hyperplasia; Ascites; Systematic review; Liver complications

Core tip: Liver complications in patients with human immunodeficiency virus (HIV) is emerging as a public health concern. The appropriate management of HIV-infected persons with suspected nodular regenerative hyperplasia (NRH) is yet to be outlined. However, NRH is a clinically subtle condition that is difficult to diagnose, and it is important to be able to manage it according to the best available evidence. We believe the implications of our manuscript will have immediate clinical implications.

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INTRODUCTION

Nodular regenerative hyperplasia (NRH) is the diffuse transformation of the liver parenchyma into micronodules without intervening fibrosis[1]. NRH is associated with a number systemic diseases, including human immunodeficiency virus (HIV) infection, and over the past several years, it has become an increasingly recognized entity that causes noncirrhotic portal hypertension (NCPH)[2].

The pathogenesis of NRH is thought to be vascular in origin, initiated by endothelial damage and causing an uneven distribution of obliteration of the small portal venules throughout the liver parenchyma[3]. In addition to endothelial damage, recurrent micro-thrombosis of the portal vasculature is also thought to contribute to the obliterative phenomenon. These micronodules tend to form in areas of preserved blood flow and are thought to represent a compensatory hypertrophic response to the neighboring acini with impaired blood flow[2,4]. The diagnosis of NRH is definitively made with the histological presence of micronodules not greater than 3 mm thick and without intervening fibrosis[1].

The pathogenesis of NRH in HIV infection remains unclear. Several theories have been proposed, including a "two-hit" model in which recurrent gut bacterial translocation to the portal tract in combination with vascular endothelial damage ultimately results in portal hypertension[5]. Other theories suggest that direct viral or immune-mediated damage contribute to the obliterative venopathy[6]. However drug-induced hepatotoxicity has become the prevailing theory. The prolonged exposure to highly active antiretroviral therapy (HAART), namely didanosine (DDI) has been strongly correlated, and in all cases of proposed HAART-associated NRH, DDI has been present in each[5-15].

The significance of the association between NRH and HIV is underscored by the evolving patterns of disease in HIV-infected persons. Approximately 34 million people are currently infected with the virus worldwide. In developed nations, where individuals have ready access to HAART the mortality of HIV is decreasing[5]. The causes of death are shifting and studies have shown that liver disease accounts for as high as 18% of deaths in the post-HAART era[6]. These findings place liver disease in the top three causes of mortality in HIV-infected persons, out ranking opportunistic infections and acquired immune deficiency syndrome (AIDS)-defining illnesses. While hepatic viral co-infection accounts for a majority of the liver disease in HIV patients, both alcoholic and non-alcoholic liver diseases are also important. Of emerging relevance, is the burden of NCPH, namely NRH.

The purpose of this paper is to perform a systematic review of the clinical syndrome and outcomes in patients with NRH specifically related to HIV. The manifestations of NRH in HIV patients are similar to those that have previously been well defined in patients with NRH of other etiologies. We will focus on the clinical manifestations reported and suggest a methodical approach to the HIV patient with known or suspected NRH.

MATERIALS AND METHODS

We performed a search of the MEDLINE database for all published studies in all available languages on NRH in HIV-infected patients. Combinations of the following keywords were implemented: "nodular regenerative hyperplasia", "human immunodeficiency virus", "noncirrhotic portal hypertension", "idiopathic portal hypertension", "cryptogenic liver disease", "highly active antiretroviral therapy" and "didanosine". The bibliographies of these studies were subsequently searched for any additional relevant publications.

Our search yielded 68 unique hits (Figure 1). These publications were reviewed for relevance to the topic of interest. A total of 49 publications pertaining to the phenomenon of NCPH in the context of HIV-infection and its treatment were found. The papers were then reviewed in further detail to identify cases where the specific diagnosis of NRH was made, and cases were only included if diagnosis was based on histologic identification. A total of 95 cases that met our inclusion criteria were found. We excluded any cases where the diagnosis of NCPH was attributed to conditions other than NRH, therefore cases of hepatoportal sclerosis (HPS) and other obilterative portal venopathies not meeting diagnostic criteria for NRH were excluded. Of note, we did include cases where both HPS and NRH were found in the same liver. We excluded any cases where liver biopsy was not done and therefore no definitive diagnosis of NRH could be made.

RESULTS

Epidemiology

NRH is a rare condition, and although it has become increasingly recognized, its epidemiology remains poorly understood. The incidence in the general population is approximately 2.6%, an estimate that comes from a large autopsy study done in 1990[1]. The majority of the existing data is based from case reports and case series, and the incidence appears to be increasing as NRH is becoming more widely recognized[7]. The diagnosis is frequently missed as liver biopsy is usually only undertaken in symptomatic patients and NRH often exists subclinically. Moreover, diagnosis requires adequate specimen, appropriate use of reticulin staining and evaluation by a skilled pathologist, making histologic confirmation difficult[8].

The first published case of a patient with HIV found

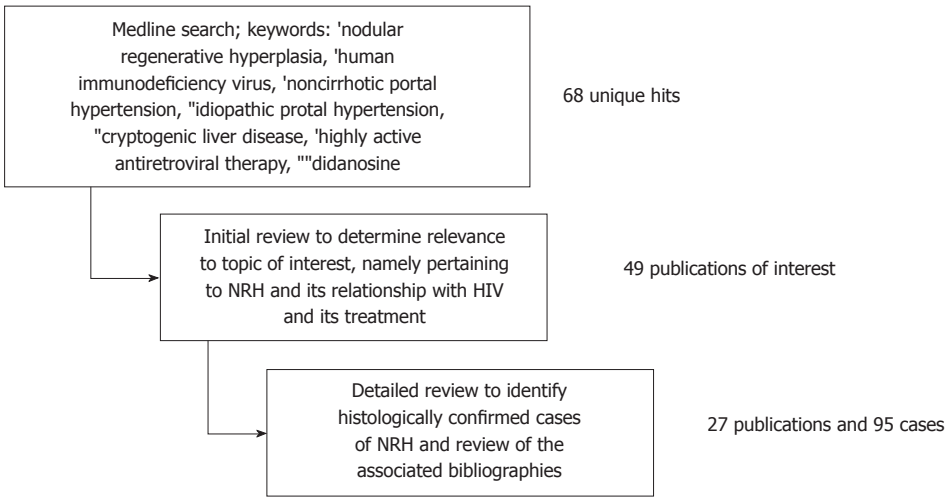

Figure 1 Flow diagram outlining methods of search. NRH: Nodular regenerative hyperplasia; HIV: Human immunodeficiency virus.

Table 1 Literature review of nodular regenerative hyperplasia in human immunodeficiency virus positive patients (biopsy confirmed)

Ref.	Study type	Number of patients	Clinical presentation
Arey *et al*[21]	Case report	1	Abdominal distention, abdominal, pain, EV
Bihl *et al*[31]	Case report	1	Abdominal pain, ALP, ascites, EV, GIB, splenomegaly
Bissonnette *et al*[11]	Case report	2	Ascites, EV, GIB
Cachay *et al*[15]	Case series	1	ALP
Saifee *et al*[52]	Case series	11	Ascites, EV, GIB
Cesari *et al*[53]	Case control	5	Ascites, EV, GIB, splenomegaly
Cotte *et al*[12]	Case control	13	Abdominal pain, ALP, ascites, EV, GIB, splenomegaly
Alvarez Díaz *et al*[33]	Case report	2	ALP, ascites, EV, GIB
Ding *et al*[54]	Case report	1	ALP, EV, GIB, ascites
Dinh *et al*[55]	Case control	3	Ascites, encephalopathy, EV
Fernandez-Miranda *et al*[9]	Case report	1	Unknown
Garvey *et al*[19]	Case report	2	EV, splenomegaly
Hofmaenner *et al*[27]	Case report	1	Epigastric pain, ALP
Kochin *et al*[56]	Case report	1	EV, GIB
Kovari *et al*[23]	Case control	1	EV
Maida *et al*[8]	Case series	2	Splenomegaly
Mallet *et al*[4]	Case control	13	ALP, EV, GIB
Mallet *et al*[57]	Case report	1	Portal hypertension
Mallet *et al*[30]	Case series	8	ALP, ascites, EV, splenomegaly
Mendizabal *et al*[58]	Case control	5	EV, GIB
Podevin *et al*[59]	Case report	1	Ascites, EV, splenomegaly
Sandrine *et al*[20]	Case report	1	ALP, ascites, EV, splenomegaly
Santiago *et al*[28]	Case report	1	Abdominal distention, splenomegaly
Schiano *et al*[22]	Case report	1	ALP, EV, splenomegaly
Scourfield *et al*[60]	Retrospective cohort	4	Unknown
Schouten *et al*[61]	Case report	3	EV, GIB
Stebbing *et al*[62]	Retrospective cohort	2	ALP
Tateo *et al*[13]	Case report	3	ALP, ascites, EV, GIB
Vispo *et al*[29]	Case report	3	ALP, ascites, EV, GIB

ALP: Abnormal liver panel; EV: Esophageal varices; GIB: Gastrointestinal bleed.

to have NRH was reported from Spain in 1993 in a patient with HIV infection and visceral leishmaniasis[9]. We identified a total of 94 additional cases of biopsy-confirmed NRH in HIV-positive patients, most of which were reported within the last decade (Table 1). Given that the same limitations in diagnosis apply to HIV-infected persons, the incidence is likely grossly underestimated in this patient population as well. Epidemiological studies geared toward select patient populations are needed and may shed more light on the actual incidence of NRH in HIV patients as well as in the general population.

Clinical presentation

The clinical presentation of the cases found was highly variable. The diagnosis was prompted by incidental lab abnormalities in asymptomatic patients, and in other cases, patients presented with manifestations of portal hypertension such as esophageal varices, ascites, and

Table 2 Manifestations of portal hypertension in patients with nodular regenerative hyperplasia and human immunodeficiency virus *n* (%)

Manifestation	Patients identified	References
Ascites	30 (32)	[4,12,19,20,28,33,52,53,58,60]
Esophageal varices	61 (66)	[4,12,19,20,28,33,52,53,58,60]
Hepatic encephalopathy	1 (1.1)	[54]
Splenomegaly	25 (27)	[4,12,19,20,31,52,53,54,58,60]
Portal thrombosis	11 (12)	[4,12,19,20,31,52,53,54,58]

hypersplenism (Table 1). Jaundice was universally not reported. According to our findings, the most common manifestation of NRH in HIV-positive patients was esophageal varices, which were identified in at least 66 of 95 cases. Only 28 patients developed gastrointestinal bleeding in the setting of esophageal varices (Table 2). In many cases, once the clinical syndrome of portal hypertension was identified, patients underwent screening esophagogastroduodenoscopy and were placed on prophylactic non-selective beta-blockers (NSBB) if varices were found. Patients were reported to be on NSBB in almost all cases.

Liver synthetic function as indicated by INR and albumin is well preserved across all cases in which it was reported. Liver associated enzymes may be only mildly elevated (Table 3). Patients were also not uncommonly found to have thrombophilias including protein C and protein S deficiencies, which may be associated with the pathogenesis of NRH and the development of portal vein thrombosis in these patients (Table 3).

When compared to the clinical presentation of patients with NRH without HIV, similar findings have been reported. In one recent series including 42 patients, the most common presenting abnormality was an abnormal liver profile, existing in 76% of cases. Varices were detected in 26% of patients. None of these patients had synthetic liver dysfunction as implicated by normal INR[10]. In another series of 24 patients, similar rates of various clinical features of NRH were reported[11]. These findings mimic those of other similar case reports and are also similar to the findings presented in patient's specifically with NRH and HIV.

Diagnosis

Tthe diagnosis of NRH is a histologic one, requiring liver biopsy. Histologic features are shown in Figure 2. The use of a reticulin stain is usually necessary to make the diagnosis. Important features on the reticulin stain include: nodular apperance, characterized by alternating hypertrophic and atrophic hepatocytes. Highlighting the frequent delay in diagnosis, in one report of 13 patients on HAART who developed NRH, the mean time from presentation to diagnosis of NRH was approximately 38 mo[12]. This point highlights the sub-optimal diagnosis of NRH, leading to its under-appreciation as an important clinical entity in the HIV population. Diagnosis is further limited by the presence of a clear workup bias in that it is usually either the symptomatic patient, or the patient with long-term DDI exposure who undergoes diagnostic testing for NRH. Furthermore, consideration of NRH is certainly more common in the academic setting[13].

Radiologically, the diagnosis of NRH is also difficult. Findings are variable and range from none to diffuse hypoechoic nodules. On ultrasound, findings may include widespread nodularity of the liver can mimic cirrhosis[14]. On computed tomography, the nodules are usually hypodense and typically do not enhance with contrast. Finally on magnetic resonance imaging, suface nodularity and nodules of similar signal intensity to the liver may be noted[14]. Because the findings on imaging are non-specific and non-diagnostic, clinical correlation is key in determining the next best step in diagnosis.

Natural history

The natural history of NRH is poorly understood. There is likely an inherent bias to diagnose and report symptomatic cases, and NRH is likely more indolent than appreciated. This notion is supported by the large autopsy study by Wanless in which only one of 64 patients had been diagnosed with NRH prior to death. Few of these patients had developed manifestations of portal hypertension prior to death[1]. These findings are likely explained by the preservation of hepatic synthetic function observed in patients with NRH. From the available data, the presentation of NRH is variable and ranges from subtle findings on serum liver tests, to vague abdominal symptoms, to overt gastrointestinal hemorrhage and other severe manifestations of portal hypertension. To date, the overall prognosis has not been well defined, as there have not been substantial outcomes data reported in the literature. In one long-term follow up study of a cohort of eight HIV-infected patients with NCPH, there was only one death, which was attributed to non-NCPH related causes. The remainder of the patients underwent regular screening EGD and was placed on NSBB therapy. If the patients were found to have NCPH prior to the development of variceal bleeding, they tended to remain minimally symptomatic with supportive and preventative care. On the other hand patients who were not treated in a timely manner tended to develop refractory bleeding. One patient with severe NRH required repeated TIPS and was placed on the liver transplant waiting list while another underwent surgical hepatorenal shunt[15].

Associated conditions and medications

Nodular regenerative hyperplasia has long been associated with rheumatologic, autoimmune, hematologic and myeloproliferative disorders[7]. Of particular clinical consequence is the link between NRH and thrombophilias. The association is theoretically attributed to the increased chronic micro-thrombosis of the small portal venules, leading to their constriction, obliteration and eventually to intrahepatic portal hypertension[16]. Many of these patients are also predisposed to the development of portal vein thrombosis, which can lead to end-

Table 3 Select laboratory tests associated with nodular regenerative hyperplasia

Laboratory test	Range	References
Albumin (g/dL)	1.9-4.5	[22,28,52,54,55]
Aspartate transaminase (IU/L)	15-139	[4,8,20-22,30,31,38,54,55,59,60]
Alanine transaminase (IU/L)	13-196	[3,7,19-21,30,31,52,54,55,59,60]
Alkaline Phosphatase (IU/L)	92-541	[4,20-23,28,31,52,53,55,59,60]
Total bilrubin (mg/dL)	0.6-3.6	[21,22,31,52,54,55,59,60]
Gamma glutamyl transpeptidase (IU/L)	12-771	[4,20,22,28,31,53,55,59,60]
White blood cell count (cells/mm^3)	1090-4800	[4,21,22,28,30,31,33,53-55,60]
Hemoglobin (g/dL)	6.6-13	[22,55,60]
Platelet (1000/mm3)	61-273	[4,22,23,52,54,55,59,60]

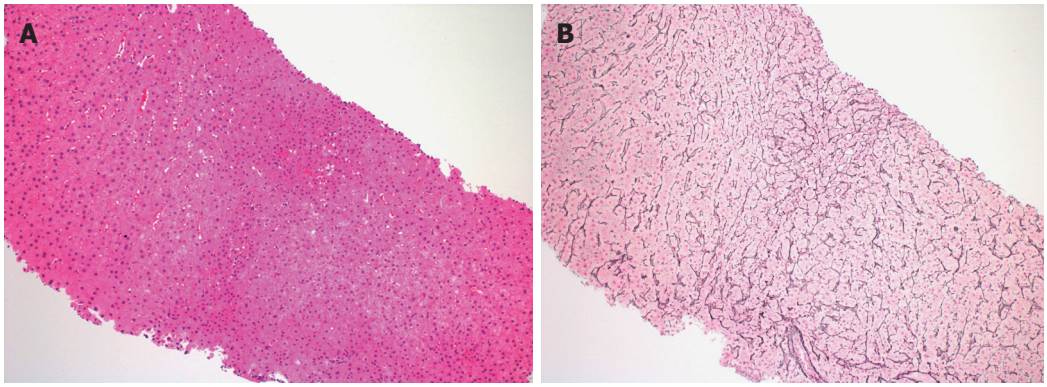

Figure 2 Needle liver biopsy of male infected with human immunodeficiency virus. A: His risk factor for the development of Nodular Regenerative Hyperplasia was long term use of didanosine. Hepatocytes size varies zonally, occasional areas of small hepatocytes with increased nuclear cytoplasmic ratio alternate with areas of a more normal appearing morphology in the hematoxylin-eosin stain (original magnification × 100); B: The reticulin stain highlights and confirms nodular regeneration throughout the specimen with nodular areas of regenerative hepatocytes as characterized by widened hepatocellular plates alternating with areas of normal appearing lobular architecture and then areas of narrowed, attenuated hepatocytes (original magnification × 100).

stage disease. In one study, 12 out of 2600 persons with HIV infection were found to have NCPH, and NRH was a common histologic diagnosis. Of the 12 patients with NCPH, half were found to have portal thrombosis[17]. Among all cases, the percentage of patients with portal thrombosis was close to 15% (Table 2).

The association between NRH and antiretroviral therapy has been identified mostly through case reports and small case-control studies. In particular, specific associations have been made with DDI. One of the earliest associations with DDI and NCPH and NRH was from a case-control analysis[18]. Their findings were supported in a number of succeeding publications[14,15,17,19-23]. More recently, the results of another analysis suggested that patients with NRH had a longer exposure not only to DDI, but stavudine, tenofovir, and a combination of DDI and stavudine and DDI and tenofovir as well[12].

Aside from HAART, other medications have also been linked to NRH. Its association with azathioprine (AZA), 6-mercaptopurine, 6-thioguanine, busulphan, cyclophosphamide and most recently, oxaliplatin-based therapies have also been reported[24,25]. A presumed mechanism is damage of the endothelium in the small hepatic veins leading to the phenomenon of obliterative portal venopathy. Interestingly, in one report of AZA-induced NRH, some patients demonstrated normalization of liver enzyme markers and histological regression of NRH after withdrawal of AZA[26]. Such histological regression has never been reported in the case of HAART and HIV-associated NRH.

Treatment

There is no definitive treatment for NRH. The mainstay of management is removal of the offending agent and prevention and supportive care of disease manifestations. It is important to note that in many of the cases in which NRH was linked to DDI, the exposure had been long-since stopped prior to the time of NRH diagnosis. Cessation of DDI or other implicated HAART agents may improve outcomes, however it has not been shown to result in reversal of the disease process[27]. In part because of its associated hepatotoxicity, the use of DDI has declined substantially and it is now regarded as a lower-tier anti-retroviral medication[12]. Although it is clear that DDI-induced NRH does persist for years after cessation of the medication; interruption has still been associated with an overall better prognosis[27-29].

Treatment of the clinical manifestations of NRH revolves around the primary prophylaxis of esophageal variceal bleeding in asymptomatic patients. For cases in which details were provided, we observed that in almost all asymptomatic cases of esophageal varices, primary prophylaxis with NSBB was started, and propranolol was the usual drug of choice. Many patients also under-

went endoscopic band ligation (EBL), either as primary prophylaxis or after manifestation with bleeding. There were several cases of failure of NSBB or EBL, for which patients underwent transjugular intrahepatic portosystemic shunt (TIPS). At least one of these cases was documented as refractory and TIPS was done as bridge to transplant[15]. In contrast to non-HIV related NRH, ascites was not uncommonly reported in our review of HIV patients with NRH. At least 12 cases of ascites were reported, however the need for paracentesis was not reported. Ascites is infrequently reported in NRH with patients without HIV[10].

The utility of anticoagulation in patients with NRH is a burgeoning concept. Mallet *et al*[30] described a series of 21 patients with clinical evidence of prothrombotic state in the setting of NCPH. The median protein S level in this group was nearly half of normal. The coagulation abnormalities in patients with NRH have particular significance as suggested by Bihl *et al*[31], who reported a case in which the patient's clinical course improved dramatically after initiation of anticoagulation. It appears that the benefit of anticoagulation in these patients may be multifactorial. One theory is that it slows disease progression by preventing the micro-thrombosis thought to play a pathogenic role in NRH. In addition, given the noted thrombophilias in these patients, anticoagulation prevents portal vein thrombosis, which can lead to refractory manifestations of portal hypertension and end-stage liver disease[30-32]. These findings suggest potential benefit of anticoagulation therapy and warrant further studies specifically in the context of NRH.

Patients with severe liver disease and intractable symptoms of portal hypertension should be considered for liver transplant, which has been successfully described in 7 cases of patients with HIV and NRH[13,30]. In most of these cases, the indication for liver transplant was severe and intractable symptoms portal hypertension, with or without complete portal vein thrombosis. In one case, the indication to consider transplant was hepatic encephalopathy secondary to TIPS placement[33]. All 7 patients who underwent liver transplant reportedly had excellent survival. However, it is important to note that there have been cases in which NRH reappears in the transplanted liver[34], although this has yet to be described in a patient with NRH in the setting of HIV. Regardless, for this reason, continued anticoagulant therapy even after transplant may be warranted and necessitates further investigation.

DISCUSSION

The burden of liver disease in HIV-infected persons is substantial and a comprehensive and interdisciplinary approach to management is crucial. All HIV-positive individuals should undergo regular liver function testing at least biannually as they are routinely exposed to hepatotoxic medications and are generally at increased risk for both viral and non-viral hepatitides[35]. NRH should be considered in all HIV-positive patients with unexplained signs and symptoms of portal hypertension. A thorough history of past and current antiretroviral drug regimens should be obtained as it has been shown that the effects of NRH persist long after cessation of the offending agent.

Diagnosis of NRH requires a high index of suspicion given its uncommon incidence and varied presentation of portal hypertension. Imaging techniques, such as abdominal ultrasound or computed tomography (CT) are frequently used to further evaluate patients with liver disease. Hepatic nodularity may be appreciated on liver ultrasound, and when combined with a clinical context of relatively preserved hepatic function, NRH should remain high on the differential. The hepatic nodularity on ultrasound is often followed up with CT imaging, however findings of diffuse micronodularity can also mimic cirrhosis[14,36].

NRH is one of the potential causes of non-cirrhotic portal hypertension in patients with HIV. Other potential causes of non-cirrhotic intrahepatic portal hypertension include schistosomiasis, sinusoidal obstruction syndrome, and idiopathic portal hypertension (hepatoportal sclerosis)[7,22,37]. In particular, antiretroviral therapy has been associated with both NRH and idiopathic portal hypertension. It has been hypothesized that idiopathic portal hypertension can lead to both NRH and portal vein thrombosis[2].

Accurate diagnosis of NRH requires the histological assessment[7]. Since the nodularity is often heterogeneously distributed, liver biopsy requires an ample sized tissue. The transjugular route is often used to minimize bleeding complications[38]. However, there have been cases where diagnosis was initially missed and later found only *via* wedge biopsy[39]. Classification of non-neoplastic, diffuse parenchymal liver disease necessitates a sample of at least 2-3 cm in length and at least a 16-gauge caliber needle[40]. The hepatocyte atrophy, a key histologic feature is best identified with reticulin staining which must be employed to make the diagnosis[41].

The pathogenesis of NRH is believe to be related to the differential of blood supply to the liver that leaves some areas ischemic, and other with compensatory hypertrophy which leads to the formation of hepatic nodules. There are multiple diseases, conditions, and medications associated with its development[7]. In contrast to non-HIV patients, patients with HIV and NRH tend to have a higher incidence of asictes. It is unclear why the incidence differs but the variance may be potentially related to the underlying cause of NRH in HIV patients being largely pharmacologic from antiretroviral drugs.

DDI which has been most strongly linked to the development of NRH, belongs to a class of medications known as nucleoside reverse transcriptase inhibitors (NRTI). It functions as a purine analogue and interferes with the transcription of DNA and RNA[27]. Azathioprine, 6-mercaptopurine 6-thioguanine and other chemotherapeutic agents that have been previously linked to NRH have a similar mechanism of action[42]. Although

current knowledge suggests that NRH is not a reversible condition, several studies have shown improved outcomes with cessation of causative medications.

Treatment of NRH generally revolves around manifestations of portal hypertension. Once the diagnosis is confirmed, patients should undergo screening for esophageal varices with esophagogastroduodenoscopy (EGD)[43]. Patients with NRH should be considered for screening for HCC. Although this remains a relatively controversial topic, a possible pathogenetic relationship between NRH and HCC has been described[1,25,44-50]. The inability to conclusively establish a propensity of NRH to develop into HCC may be a result of its underestimated incidence, rather than a lack of association between the two conditions. Liver transplantation is an uncommon treatment for NRH since liver function is usually preserved. In a recently published systematic review, the authors found severe portal hypertension as the most common indication for liver transplantation[51].

The importance of NRH in HIV-infected individuals is growing, especially as patients are experiencing increased longevity and longer exposure to medications. High index of suspicion is required to make a diagnosis since there are patients with HIV who develop manifestations of portal hypertension such as ascites and variceal bleeding from cirrhotic and non-cirrhotic causes. Treatment generally revolves around treating the manifestation of portal hypertension.

COMMENTS

Background

Nodular regenerative hyperplasia (NRH) causes portal hypertension in patients with human immunodeficiency virus (HIV). Unlike cirrhosis, NRH is not associated with liver synthetic function. On imaging, NRH and cirrhosis appear similar with nodular liver contours. Patients with NRH can present with ascites and variceal bleeding.

Research frontiers

Further research in needed in the utility of non-invasive methods of making the diagnosis of NRH. Studies are essential to determine the long term consequences of NRH. More research is needed to understand the pathogenesis of NRH.

Innovations and breakthroughs

There is increasing appreciation of the epidemiology and association of NRH with HIV. There is also enhanced awareness of the association of certain antiretroviral medications such as didanosine and NRH.

Applications

The article adds to the literature the current understanding of the diagnosis, risk factors, natural history and, management of NRH.

Terminology

The diagnosis of NRH requires a liver biopsy. Liver parenchymal cells are clustered in nodules. Unlike cirrhosis, there are fibrotic bands encompassing the nodule.

Peer review

One of the most important issues raised during peer review was that there may be differences in the presentation in patients affected by NRH with and without HIV. Patients with NRH and HIV are more likely to have ascites than those patients with NRH without HIV.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

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Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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