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World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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REVIEW

Systemic hemodynamics in advanced cirrhosis: Concerns during perioperative period of liver transplantation

Tomohide Hori, Yasuhiro Ogura, Yasuharu Onishi, Hideya Kamei, Nobuhiko Kurata, Motoshi Kainuma, Hideo Takahashi, Shogo Suzuki, Takashi Ichikawa, Shoko Mizuno, Tadashi Aoyama, Yuki Ishida, Takahiro Hirai, Tomoko Hayashi, Kazuko Hasegawa, Hiromu Takeichi, Atsunobu Ota, Yasuhiro Kodera, Hiroyuki Sugimoto, Taku Iida, Shintaro Yagi, Kentaro Taniguchi, Shinji Uemoto

Tomohide Hori, Yasuhiro Ogura, Yasuharu Onishi, Hideya Kamei, Nobuhiko Kurata, Department of Transplant Surgery, Nagoya University Hospital, Nagoya 466-8550, Japan

Motoshi Kainuma, Hideo Takahashi, Shogo Suzuki, Takashi Ichikawa, Shoko Mizuno, Tadashi Aoyama, Yuki Ishida, Takahiro Hirai, Tomoko Hayashi, Kazuko Hasegawa, Hiromu Takeichi, Atsunobu Ota, Department of Intensive Care Unit, Nagoya University Hospital, Nagoya 466-8550, Japan

Yasuhiro Kodera, Hiroyuki Sugimoto, Second Department of Surgery, Nagoya University Hospital, Nagoya 466-8550, Japan

Taku Iida, Shintaro Yagi, Shinji Uemoto, Department of Transplant Surgery, Kyoto University Hospital, Kyoto 624-0802, Japan

Kentaro Taniguchi, First Department of Surgery, Mie University Hospital, Tsu 437-6001, Japan

Author contributions: Hori T wrote this review; Ogura Y, Onishi Y, Kamei H, Kurata N, Kainuma M, Takahashi H, Suzuki S, Ichikawa T, Mizuno S, Aoyama T, Ishida Y, Hirai T, Hayashi T, Hasegawa K, Takeichi H, Ota A and Sugimoto H gave academic opinions for peri-operative period and helped to review the papers; Kodera Y and Uemoto S supervised this review; Iida T, Yagi S and Taniguchi K helped to collect clinical data and to review important papers.

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Correspondence to: Tomohide Hori, MD, PhD, Department of Transplant Surgery, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. horit@kuhp.kyoto-u.ac.jp
Telephone: +81-52-7442248
Fax: +81-52-7441911

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Abstract

Advanced liver cirrhosis is usually accompanied by portal hypertension. Long-term portal hypertension results in various vascular alterations. The systemic hemodynamic state in patients with cirrhosis is termed a hyperdynamic state. This peculiar hemodynamic state is characterized by an expanded blood volume, high cardiac output, and low total peripheral resistance. Vascular alterations do not disappear even long after liver transplantation (LT), and recipients with cirrhosis exhibit a persistent systemic hyperdynamic state even after LT. Stability of optimal systemic hemodynamics is indispensable for adequate portal venous flow (PVF) and successful LT, and reliable parameters for optimal systemic hemodynamics and adequate PVF are required. Even a subtle disorder in systemic hemodynamics is precisely indicated by the balance between cardiac output and blood volume. The indocyanine green (ICG) kinetics reflect the patient's functional hepatocytes and effective PVF, and PVF is a major determinant of the ICG elimination

constant (*k*ICG) in the well-preserved allograft. The *k*ICG value is useful to set the optimal PVF during living-donor LT and to evaluate adequate PVF after LT. Perioperative management has a large influence on the postoperative course and outcome; therefore, key points and unexpected pitfalls for intensive management are herein summarized. Transplant physicians should fully understand the peculiar systemic hemodynamic behavior in LT recipients with cirrhosis and recognize the critical importance of PVF after LT.

Key words: Liver cirrhosis; Portal hypertension; Liver transplantation; Indocyanine green; Hyperdynamic

Core tip: In patients with advanced cirrhosis who undergo liver transplantation (LT), perioperative management greatly influences the postoperative course and outcome. This review covers key points and unexpected pitfalls of intensive management in these patients. A peculiar systemic hemodynamic state (hyperdynamic state) persists in recipients with cirrhosis even after LT, and stability of optimal systemic hemodynamics is important for adequate portal venous flow (PVF) and successful LT. Reliable parameters for optimal systemic hemodynamics (a balance between cardiac output and blood volume) and adequate PVF (indocyanine clearance) during and after LT are herein described. Transplant physicians should fully understand these peculiar hemodynamic phenomena.

Hori T, Ogura Y, Onishi Y, Kamei H, Kurata N, Kainuma M, Takahashi H, Suzuki S, Ichikawa T, Mizuno S, Aoyama T, Ishida Y, Hirai T, Hayashi T, Hasegawa K, Takeichi H, Ota A, Kodera Y, Sugimoto H, Iida T, Yagi S, Taniguchi K, Uemoto S. Systemic hemodynamics in advanced cirrhosis: Concerns during perioperative period of liver transplantation. *World J Hepatol* 2016; 8(25): 1047-1060 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i25/1047.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i25.1047

INTRODUCTION

Advanced liver cirrhosis (LC) is usually accompanied by portal hypertension (PH). Long-term PH results in various vascular alterations, such as venous dilatation, endothelial damage, collateral pathway formation, and shunt development[1-3]. Some pathognomonic findings (*e.g.,* varices, splanchnic congestion, intractable ascites, hepatic encephalopathy, and hepatorenal syndrome) are directly related to PH[3,4], and the pathophysiology of PH involves a complex of humoral and neural mechanisms[3]. These mechanisms determine hemodynamic changes and lead to a peculiar systemic circulation pattern[3]. The clinical implications of these peculiar systemic hemodynamics in patients with LC have been described as a hyperdynamic state (so-called "hyperdynamic syndrome")[3]. Specific manifestations that have been described include high cardiac output (CO), a large blood volume (BV), low total peripheral resistance (TPR), hyponatremic electrolyte abnormalities, and a lower potassium level due to secondary aldosteronism[5].

Here, we reviewed the peculiar systemic hemodynamics in patients with advanced LC. We focused particularly on the systemic hemodynamic phenomena in liver transplantation (LT) recipients with LC because such LT recipients usually have long-term PH due to advanced LC. Adequate portal venous flow (PVF) to acquire satisfactory graft function is attributed to continuous optimal systemic hemodynamic stability beginning immediately after LT[1,2]. Therefore, we herein review the optimal state of the systemic hemodynamics after LT for excellent outcomes and discuss key points and unexpected pitfalls in the perioperative intensive managements of recipients with LC. We also demonstrate the usefulness of indocyanine green (ICG) during and after LT to estimate optimal systemic hemodynamics and adequate PVF.

SYSTEMIC HEMODYNAMICS IN PATIENTS WITH ADVANCED LC

The systemic hemodynamic state in patients with LC has been characterized as hyperdynamic[3,6,7]. Cirrhotic hemodynamics are characterized as hyperdynamic by a high CO, large BV, low TPR, mildly tachycardic heart rate (HR), and low or normal mean arterial pressure (MAP)[1-4,6,8-10]. Parameters of peripheral resistance, such as TPR, clearly reflect various vascular alterations[1-3,9,11,12].

NONINVASIVE METHODOLOGY FOR REAL-TIME ASSESSMENT OF SYSTEMIC HEMODYNAMIC STATE

The ICG dye dilution curve can be used to measure hemodynamic parameters[13,14]. The currently available noninvasive method for measuring systemic hemodynamic parameters is pulse dye densitometry (PDD). Its basic principles have been described in detail elsewhere[13-16]. This noninvasive method is more reliable than invasive methods[13-15] and is suitable for clinical use because of its simplicity for bedside use, real-time presentation of results, and cost-effectiveness[15-17].

The principles of BV measurement using radioactive isotopes have already been established[18-20]. However, these techniques are associated with potential biohazards due to the use of radioactive indicators and require complex management. Indeed, these invasive methods using radioactive isotopes are completely unsuitable for BV monitoring during the perioperative period[14,15]. BV measurement by noninvasive PDD is considerably correlated with BV measurement by radioactive isotope

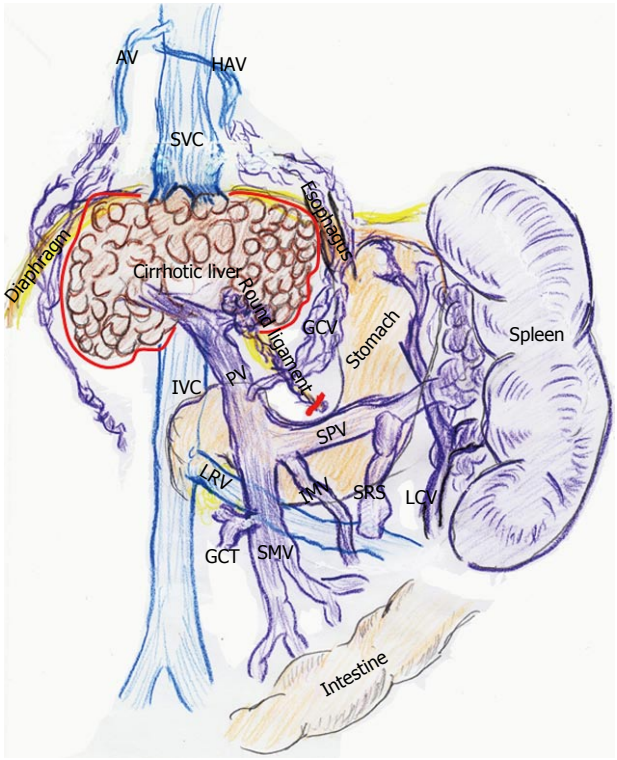

Figure 1 Vascular alterations in advanced liver cirrhosis. Collaterals along the round ligament are removed with native liver (red line). Collaterals developed around the native liver are also ligated (red line). AV: Azygos vein; GCT: Gastro-colic trunk; GCV: Gastric coronary vein; HAV: Hemi-azygos vein; IMV: Inferior mesenteric vein; IVC: Inferior vena cava; LCV: Left colic vein; LRV: Left renal vein; PV: Portal vein; SMV: Superior mesenteric vein; SPV: Splenic vein; SRS: Splenorenal shunt; SVC: Superior vena cava.

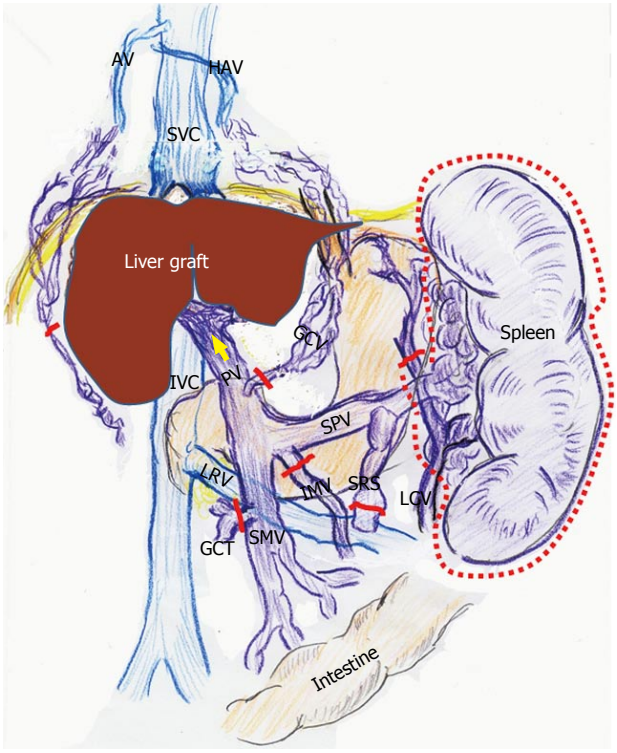

Figure 2 Intentional modulation of portal venous pressure during living-donor liver transplantation. Splenectomy is chosen to reduce PVP (red dotted line). Ligations (red lines) of vessels (GCV, IMV, and GCT), collaterals (along LCV and around the native liver) and shunt (SRS) prevent a steal of PVF, and thereafter, PVF will increase (yellow arrow). AV: Azygos vein; GCT: Gastro-colic trunk; GCV: Gastric coronary vein; HAV: Hemi-azygos vein; IMV: Inferior mesenteric vein; IVC: Inferior vena cava; LCV: Left colic vein; LRV: Left renal vein; PV: Portal vein; SMV: Superior mesenteric vein; SPV: Splenic vein; SRS: Splenorenal shunt; SVC: Superior vena cava.

methods[21-23]; it is thus advantageous for real-time evaluation of BV[1,15].

SYSTEMIC HEMODYNAMIC BEHAVIOR AFTER LT

Adult LT recipients often develop peculiar hemodynamics due to advanced LC[1,2] (Figure 1). Mainly in the 1990s, various researchers focused on systemic hemodynamics after LT[8,9,11,12,24-28]. Controversial opinions exist regarding these systemic hemodynamic behaviors after LT. While several investigators found persistence of hyperdynamic state[8,11,24-26], others insisted on a decrease toward normal ranges[12,27,28]. This discrepancy is believed to be due to the peculiarity of cirrhotic hemodynamics[9,11].

According to studies of TPR in recipients with LC, vascular alterations including venous dilatation and the development of collateral vessels and shunts do not disappear within the first month after LT[1,2]. These vascular alterations remain on imaging studies even several years after LT[29,30]. Various alterations in systemic hemodynamics in recipients with LC should be maintained despite restoration of the liver function and portal venous pressure (PVP) after LT[8,11,24-26], and most systemic parameters are very slowly restored to the normal range after LT[9,11] (Figure 2).

ACTUAL CHANGES IN SYSTEMIC AND SPLANCHNIC HEMODYNAMIC PARAMETERS AFTER LT

Hemodynamic and splanchnic systemic parameters were analyzed in 35 adult recipients who underwent living-donor LT (LDLT). All patients had advanced LC based on imaging studies and histopathological assessments. ABO blood groups were identical or compatible. Combinations of lymphoid cross-matches were all negative. The CO, CI, BV, central blood volume (CBV), and HR were measured with a PDD apparatus. The TPR was measured simultaneously with the PDD examination; calculation of the TPR has been described in detail elsewhere[2,9]. Splanchnic circulatory parameters were simultaneously assessed using Doppler ultrasound. Measurements of splanchnic parameters including PVF has been described in detail elsewhere[2]. Measurements were performed before LDLT and from 1 to 14 d after LDLT. Measurements were repeated every 12 h until 72 h after LDLT. To establish the normal ranges of each parameter, the variables were investigated in 16 healthy individuals (live donors before LDLT). Our 35 recipients were retrospectively classified into 2 groups based on graft functions that corresponded to outcomes[31,32].

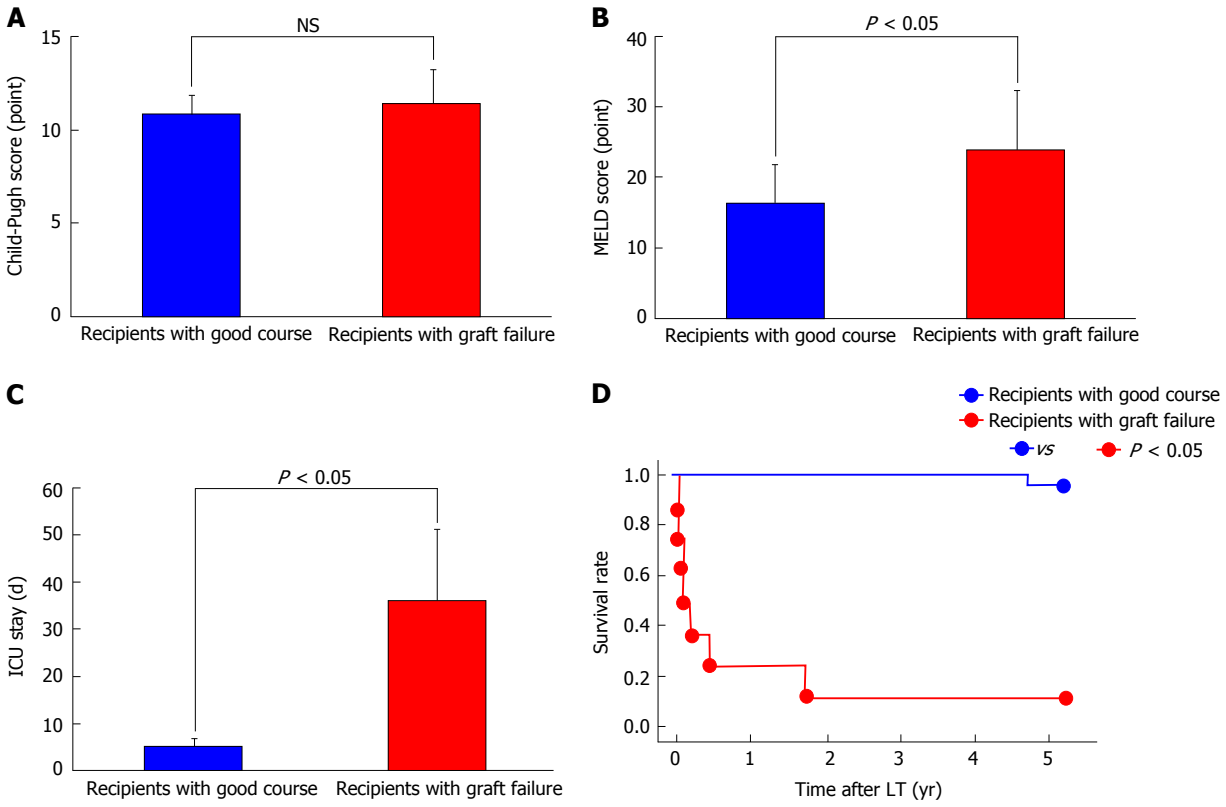

Figure 3 Pre-transplant factors and post-transplant course. A: Child-Pugh score; B: MELD score; C: Duration of ICU stay; D: Survival rate. ICU: Intensive care unit; LT: Liver transplantation; MELD: Model for end-stage liver disease; NS: Not significant.

Twenty-seven recipients had good clinical courses after LDLT, although eight recipients developed graft failure. No significant differences were found in the Child-Pugh score (Figure 3A), graft-to-recipient weight ratio (GRWR), operative time, or intraoperative blood loss between the two groups; however, significant differences were found in the Model for End-Stage Liver Disease score (Figure 3B), duration of intensive care unit al) stay (Figure 3C), and survival rate (Figure 3D). In addition, in the patients who survived, the above-mentioned parameters were measured 3 mo after LDLT. All protocols used in the present study were approved by our institutional review board (approved No. C-297) and were based on the ethical guidelines of the Helsinki Declaration. Informed consent was obtained from all patients before enrollment. For individually, temporally, and repeatedly measured data, differences in the changes over time after LDLT between the two groups were analyzed by repeated-measures analysis of variance. Differences in unpaired discontinuous data between the two groups were analyzed by the Mann-Whitney *U* test. Survival rates were calculated by the Kaplan-Meier method, and the log-rank test was used for between-group comparisons of recipient survival. Values of $P < 0.05$ were considered statistically significant.

There were no significant differences in the absolute CO (Figure 4A), CI, BV (Figure 4B), CBV (Figure 4C), or MAP between the two groups, although the absolute HR showed differences (Figure 4D). There were also no significant differences in the absolute TPR, which closely reflected vascular alterations (Figure 5A). The balance between CO and BV (*i.e.,* CO/BV) clearly showed significant differences between the groups (Figure 5B). There were significant differences in the PVF velocity (Figure 6A) and PVF volume (Figure 6B) between the groups, although the variables for hepatic arterial flow showed no differences. There were also significant differences in the ICG elimination constant (*k*ICG), which mainly reflects PVF in the early postoperative period[1,2,32].

The CBV reflects the greater circulatory system, and some researchers have suggested that this greater circulation in patients with LC may be slightly lower than that in healthy individuals[33], although the total BV is significantly higher in patients with LC. Our data also demonstrated no remarkable differences in the greater circulation itself between patients with LC and healthy individuals.

The absolute CO, BV, CBV, HR, TPR, and *k*ICG in LT recipients who were still alive 3 mo after LDLT are summarized in Figure 7. Our data support the previous opinion that cirrhotic vascular alterations still remain long after LT[29,30].

OPTIMAL HEMODYNAMIC STATE IN RECIPIENTS WITH LC AFTER LT

As described above, recipients with LC exhibit a persistent systemic hyperdynamic state even after LT[1,2,8,11,24-26].

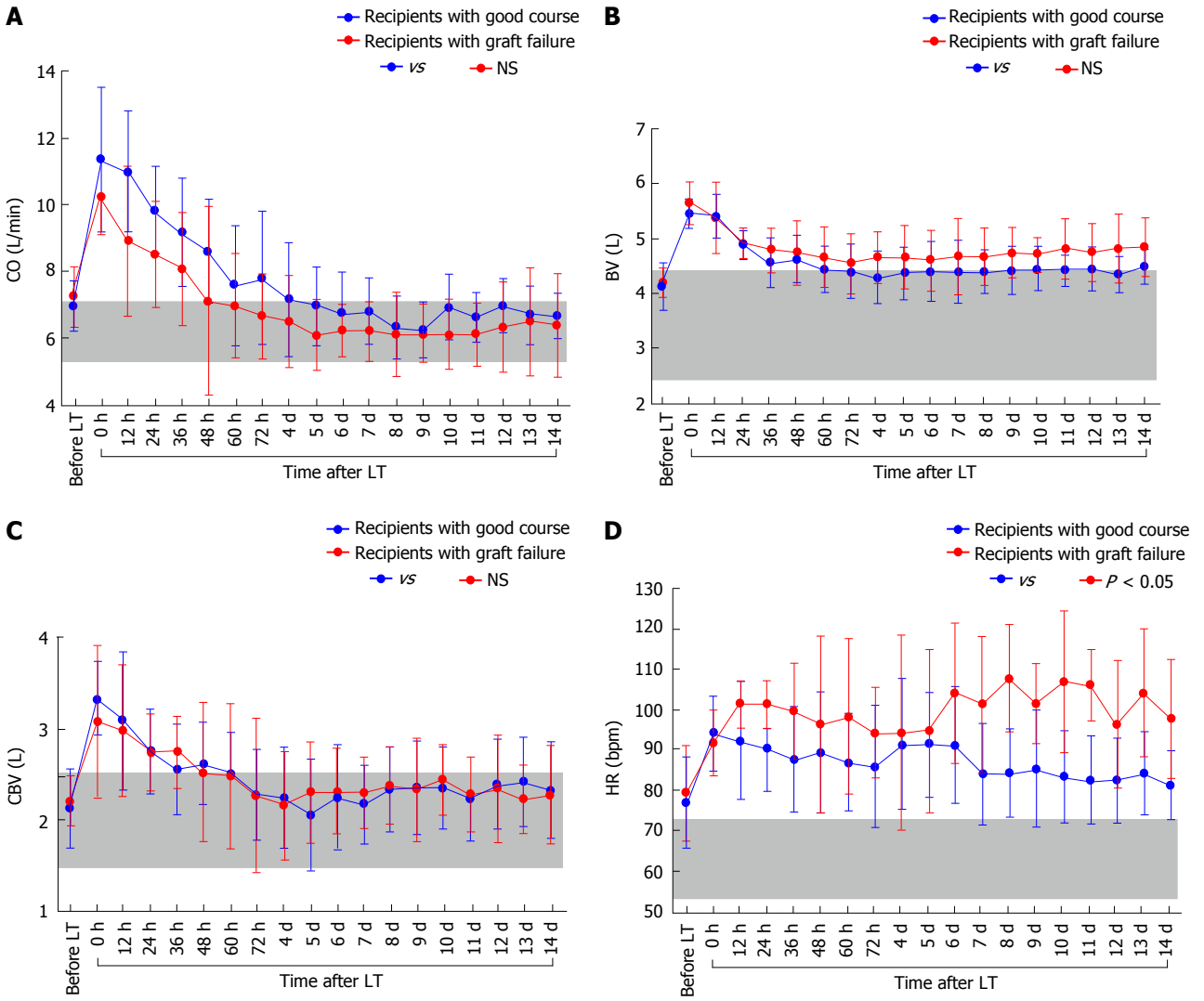

Figure 4 Actual changes in systemic hemodynamic parameters. A: CO; B: BV; C: CBV; D: HR. Gray zones represent normal ranges. BV: Blood volume; CBV: Central blood volume; CO: Cardiac output; HR: Heart rate; LT: Liver transplantation; NS: Not significant.

Stability of characteristic systemic hyperdynamic parameters after LT is necessary for successful LT in recipients with LC[1,2]. Because recipients with LC exhibit these peculiar systemic hyperdynamics even after LT[8,9,11,24-26], an accurate real-time evaluation is necessary to ensure appropriate intensive management after LT[1,2,15,32]. The optimal systemic hemodynamics needed for excellent outcomes and the precise parameters for the most appropriate clinical strategy remain unclear[1,32] because the absolute values themselves, such as CO, CI, BV, CBV, and MAP, are not necessarily satisfactory for the detection of the subtle instabilities of these patients' peculiar hyperdynamic state[1,2].

CONCEPT OF CO STANDARDIZATION AGAINST BV

Several investigators have used CO and/or CI to assess hemodynamics after LT[8,11,12,25]. Use of the CI, an index that concisely standardizes CO against the body surface area, has been popularized as a standardized CO value for better assessment. Similar to CO, BV is also one of the most important factors affecting cardiac preload[14,34]. Intrinsically, preload is a concept that represents the blood load in the left ventricle and considers the left ventricle as the center of blood ejection[1,15]. Therefore, the left ventricular end-diastolic volume becomes a quantitative parameter[1,15]. The preload usually replaces actual clinical assessment with parameters representing pressures such as the pulmonary capillary wedge pressure and central venous pressure[14,35]. The central venous pressure can be a useful indicator of the filling status of the right ventricle; it is especially useful when followed over time and combined with a measurement of cardiac output[36]. Pressure-expressing parameters including the pulmonary capillary wedge pressure and central venous pressure are mainly provided by the CO and BV[35]. Therefore, although pressure-expressing parameters do not necessarily reflect the left ventricular end-diastolic volume[14,15], pressure-expressing parameters that reduce the precision of assessment of the systemic hemodynamics have been paradoxically used to judge

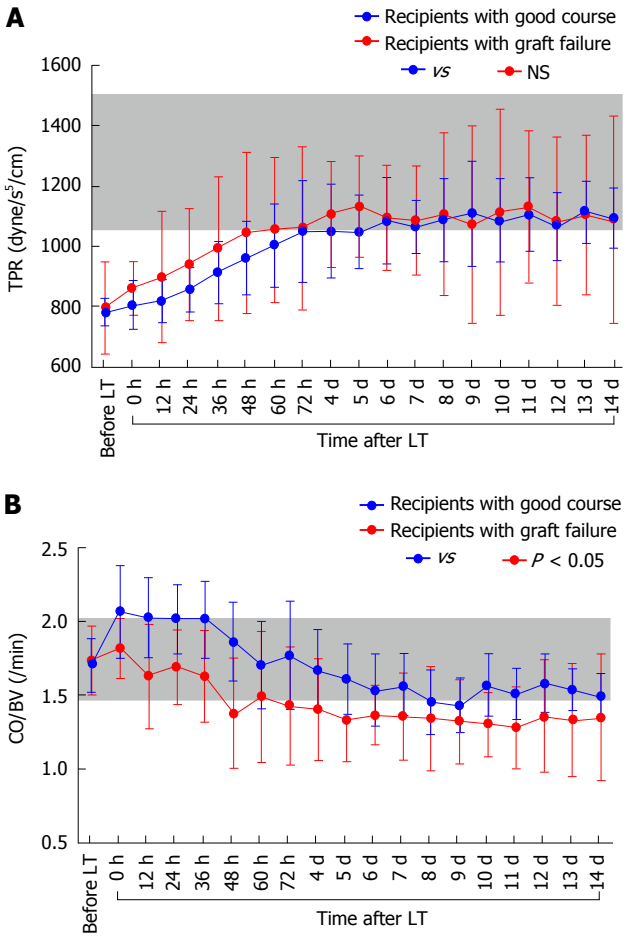

Figure 5 Actual changes in systemic hemodynamic parameters. A: TPR; B: CO/BV. Gray zones represent normal ranges. BV: Blood volume; CO: Cardiac output; LT: Liver transplantation; NS: Not significant; TPR: Total peripheral resistance.

distinct factors that represent the amount of BV and strength of CO clinically because BV monitoring has been impossible in the past[14,15]. It is necessary to standardize CO against BV, but not against the body surface area, for precise evaluation of preload[1]. Currently, the PDD guarantees noninvasive vigilance of the balance between CO and BV as an index for precise assessment of the systemic hemodynamic state[1,15]. The CO/BV ratio is a reliable indicator of the optimal systemic hemodynamic state after LT[1,2]. Preload focuses on the balance between CO and BV, and cirrhotic systemic hemodynamics are characterized by a high CO and large BV[6-9,12,24-26,35]. Real-time assessment of CO and BV by making the best use of noninvasive PDD may become an effective strategy for evaluating the systemic hemodynamic state in LT recipients with LC.

IMPACT OF SYSTEMIC HEMODYNAMIC STATE ON PVF AFTER LT

Postoperatively, LT recipients with LC show a clear tendency toward PVF overflow compared with healthy individuals[2]. The systemic hemodynamics impact the local graft circulation after LT[1,2], and even a subtle systemic

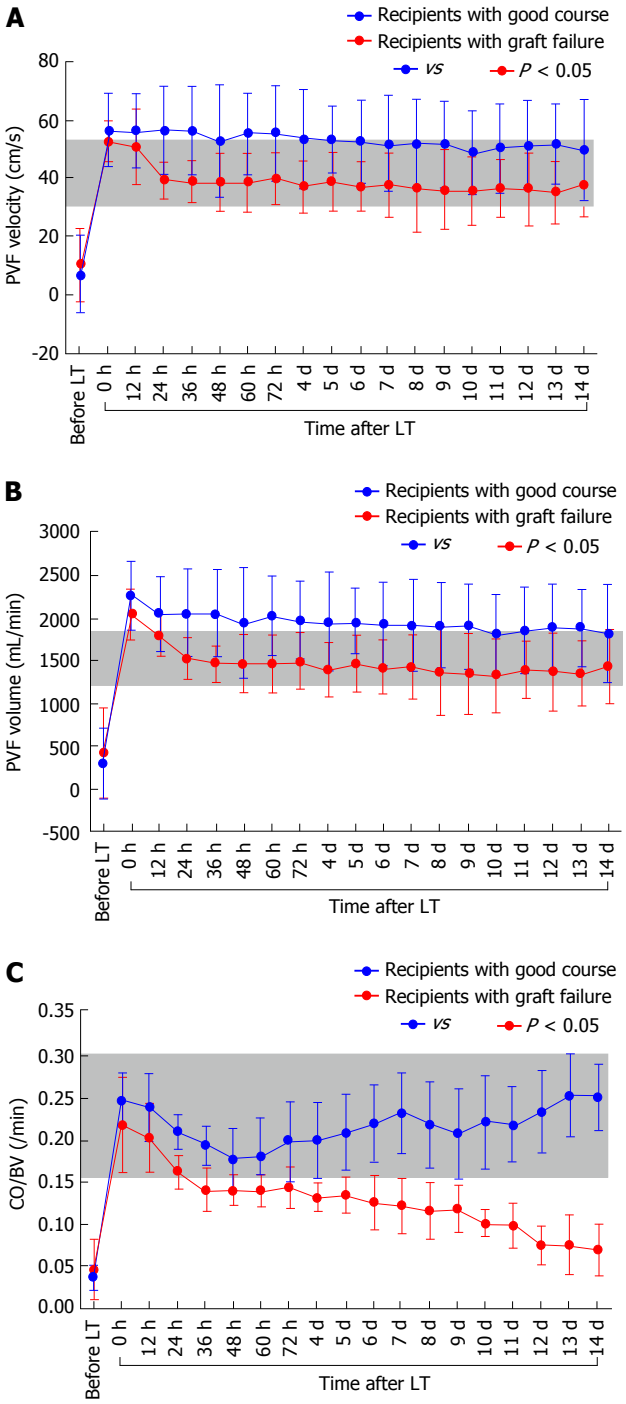

Figure 6 Actual changes in portal venous flow and indocyanine green elimination constant. A: PVF velocity; B: PVF volume; C: *k*ICG. Gray zones represent normal ranges. ICG: Indocyanine green; *k*ICG: Indocyanine green elimination constant; LT: Liver transplantation; PVF: Portal venous flow.

hyperdynamic disorder strongly affects the splanchnic circulation. An imbalance between CO and BV decreases the PVF, which results in critical outcomes[1,2]. In brief, an optimal balance between CO and BV guarantees adequate PVF after LT[1,2]. Interestingly, subtle disorders in the optimal systemic hyperdynamic state more easily influence the PVF than the hepatic arterial flow[2]. Vascular alterations secondary to PH develop in the vessels that originally flow into the portal vein under normal PVP. Such alterations are one cause of a large BV[2]. The

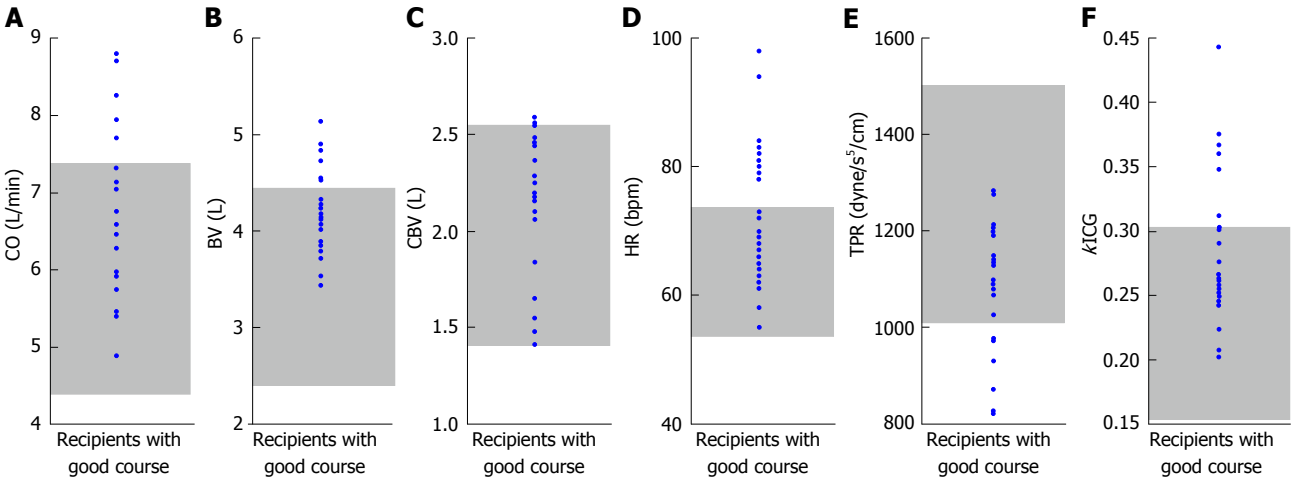

Figure 7 Systemic hemodynamic parameters 3 mo after liver transplantation. A-F: CO, BV, CBV, HR, TPR, and *k*ICG in patients who survived are shown. Gray zones represent normal ranges. BV: Blood volume; CBV: Central blood volume; CO: Cardiac output; HR: Heart rate; ICG: Indocyanine green; *k*ICG: Indocyanine green elimination constant; LT: Liver transplantation; TPR: Total peripheral resistance.

intestine and spleen become a pool for the large BV[37]. Postoperative imbalance between the greater CO and larger BV cause stagnation of the tributary blood flow in the dilated veins and collateral pathways, resulting in a decrease in PVF[2]. Transplant physicians should never forget that the systemic hyperdynamic state persists in recipients with LC even after LT[1,2,8,11,24-26] and that this peculiar systemic hemodynamic stability is indispensable for adequate PVF after LT[1,2].

Actual images of Doppler ultrasound in cases without stability of systemic hemodynamic state (*i.e.,* an imbalance of CO and BV in the lower TPR) are shown in Figure 8. The PVF should be detected as a stationary wave. However, in a case of unstable systemic hyperdynamic state, the waveform of PVF may seem to be undulant. Moreover, HA waveform may blend into the background of a decreased PVF.

INTENTIONAL MODULATION OF PVP DURING LDLT

Partial liver grafting is inevitable in the LDLT setting, and the allograft size from the live donor is therefore insufficient. Intentional modulation of the PVP to ⩽ 15 mmHg is a simple and sure strategy during LDLT[38-42]. Detailed surgical procedures for intentional modulation of PVP have been described elsewhere[40,41]. Paradoxically, the acceptable minimum GRWR of < 0.7 is possible at graft selection[40] because intentional PVP modulation during LDLT will prevent small-for-size syndrome after LDLT[38-42]. Although intentional PVP control seems to overcome an GRWR of < 0.7, these grafts still cause critical problems when evaluated retrospectively[40]. Selection of a graft with an GRWR of ⩾ 0.8 and establishment of a target PVP of ⩽ 15 mmHg during LDLT are considered keys for successful LDLT[40]. Optimal PVF is required for successful LDLT[2,43]. Ligation of collaterals and shunts often require an advanced surgical technique because these vessels are always abnormal[41,42]. However, intentional setting of the PVF during LDLT is effective not only to trigger liver regeneration after LT, but also to prevent steal of PVF after LDLT.

STRATEGIC VALUE OF ICG KINETICS DURING LT

ICG is widely used for analysis of liver functions because it is exclusively eliminated by the liver without involvement of the enterohepatic circulation and does not accumulate in the body[44]. Asialoglycoprotein receptors on hepatocytes are characteristic of functional liver cells[45], and liver scintigraphy using ^{99m}Tc-galactosyl human serum albumin has been used as a reliable method of assessment of the hepatic functional reserve in hepatectomy and graft parenchymal function after LT[46-48]. There is a correlation between ICG clearance and the hepatic uptake ratio assayed by liver scintigraphy[45,46].

ICG kinetics reflect the functional hepatocytes (cell volume) and effective PVF (clearance)[31,49-52], and PVF is a major determinant of *k*ICG in the normal liver[32,34,49,51,53]. The PVF has a large influence on liver regeneration after LT[32,43], and reversible damage to hepatocytes begins immediately after graft recirculation[32,38,39,43]. Some researchers have focused on ICG kinetics as a liver function test after LT[31,32], and *k*ICG values can predict clinical outcomes in the early postoperative period after LDLT by closely reflecting the influence of systemic dynamics on the splanchnic circulation[32].

Hepatocytes are well preserved in LDLT because the cold storage time (CIT) is shorter. The *k*ICG reflects the optimum PVF value during LT and in the early postoperative period[41,42]. Hence, a division by graft weight is a simple resolution to ensure that the *k*ICG reflects only the PVF based on the advantage of well-preserved hepatocytes during LDLT[41,42]. Intentional PVP modulation based on real-time PVP monitoring and the confirmation of an optimal *k*ICG/graft weight value reflecting the PVF are useful procedures used by transplant surgeons

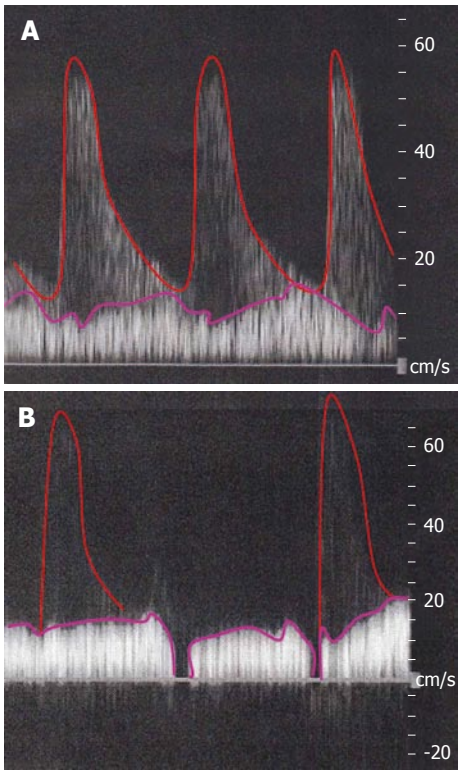

Figure 8 Decreased portal venous flow due to unstable systemic hyperdynamic state (A and B). Even a subtle instability of systemic hyperdynamic state (*i.e.*, an imbalance of CO and BV in the lower TPR) results in a decreased PVF. During the PVF measurement by Doppler ultrasound, HA waveform (Red line) blends into the background of a decreased PVF (purple lines). BV: Blood volume; CO: Cardiac output; HA: Hepatic artery; PVF: Portal venous flow; TPR: Total peripheral resistance.

during LDLT[41,42]. Actually, in some cases, the *k*ICG value did not change even with intentional controls to decrease or increase the PVP[41]. In other cases, the *k*ICG values improved with an increased PVP by ligation of portosystemic collaterals or a decrease in the PVP by splenectomy[41]. Thus, these factors seemed to show some discrepancies in some cases[41,42]. The relationship between PVP and PVF remains unclear[42]. The usefulness of ICG kinetics during LT was first described in 2012[41]. Simultaneous fulfillment of a final PVP of $\leqslant$ 15 mmHg and a final *k*ICG of $> 4 \times 10^{-4}$/g × the graft weight (g) is a sure strategy for achieving the optimal PVF during LDLT[41]. Thereafter, the cut-off level of the final *k*ICG/graft weight was demonstrated as 3.1175×10^{-4}/g[42]. The final *k*ICG/graft weight during LT has potential as an accurate parameter for the optimal PVF and as a reliable predictor of the postoperative course and outcome after LT[41,42].

KEY POINTS AND UNEXPECTED PITFALLS IN PERIOPERATIVE MANAGEMENT OF LT RECIPIENTS WITH ADVANCED LC

Liver allografts are at risk of problems such as cold ischemia/warm reperfusion injury, acute rejection, disease recurrence and hepatic blood flow disorders[32]. Transplant physicians should consider many factors simultaneously.

Eventration of the diaphragm because of intractable ascites, or easily broken ribs, often disrupts ventilation[54]. Vascular alteration due to long-term PH causes endothelial injury and permeant breakdown and subsequently results in large amounts of ascites, pleural effusion, and gastric fluid[55]. The electrolyte composition of these third-space fluids may not be similar to that of the extracellular fluid, and the electrolyte composition of third-space fluids should be checked once if the quantity is large[56]. Replenishment for third-space loss should be performed using not Ringer's solution but bicarbonated Ringer's solution[57-59] if the electrolyte composition is similar to that of the extracellular fluid and if the third-space loss is quantitatively large.

Careless management techniques, such as rapid increases or decreases of transfusions and medications, are detrimental[60,61]. Effects of increases or decreases of transfusions are usually reflected on a day-to-day basis because of the peculiar cirrhotic hemodynamics[55,60,61], and a roller-coaster management technique that repeatedly changes within a single day will trigger poor clinical courses with unexpected complications[60,61]. All transfusion management plans should be handled with great caution, and transplant physicians should very carefully evaluate the effects of increases or decreases of transfusions[60-62]. A response time lag due to endothelial injury and permeant breakdown should be considered in LC recipients with long-term PH[63-65]. Adequate hydration is also required; dehydration should be avoided because of these patients' peculiar hemodynamics. Even temporal dehydration causes unexpected thrombosis, renal failure, and impaired drug metabolism[60-62]. Plans to stay within stable systemic hemodynamics (*e.g.,* noradrenaline to maintain CO and well-hydration with human atrial natriuretic peptide) should be considered. Tachycardia may lower the CO. A lower CO that is insufficient to circulate the larger BV decreases the PVF, and a lower PVF results in a poor outcome. As described above, vascular alterations cause the large BV in these patients[2], and the intestine and spleen become pools for the large BV[37]. Even a subtle imbalance between the greater CO and larger BV induced by roller-coaster management triggers a decrease in the PVF[2,60,61].

Long-term PH causes splanchnic congestion and intractable ascites. Splanchnic congestion results in breakdown of the enteric barrier[66], and portal venous gas and/or abdominal compartment syndrome may be temporally observed[66-68]. Induction of drugs with fibrolytic activity (not heparin, but urokinase and warfarin) should be initiated without hesitation based on the endothelial damage in patients with LC, although heparin induction may be effective from the viewpoint of thromboprophylaxis[69]. Notably, long-term biliary drainage may cause coagulopathy due to impaired absorption of vitamins[70]. Massive ascites is usually intractable due to endothelial injury and

permeant breakdown, and systemic arterial pressure may be effected even by body motion[63-65]. Diuretics (*e.g.,* furosemide and potassium-conserving diuretics) and a water-clearance mediator (*e.g.,* tolvaptan) are available[71]. Hemodynamic disorders such as hepatic venous obstruction and portal thrombosis may develop if no response is observed after diuretic induction[72].

The most frequent cause of morbidity and mortality after LT is not immunological rejection but infection-related complications[73-75]. Some infections are usually intractable in patients with LC, including bacterial cholangitis[76], spontaneous bacterial peritonitis[77], spontaneous bacterial empyema[78], viral infection[79], aspergillosis[80], and *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia)[81]. Because the postoperative risk of complications is associated with the pretransplant conditions[82,83], these infections should be ruled-out and/or treated beforehand. Even a subtle infection will trigger severe complications after LT[73-75,83,84]. Evaluation of LT candidates should be carefully performed[83,85,86]; pretransplant infections may greatly impair the clinical course and outcomes after LT[83,87,88]. Transplant physicians should never forget that intentional pretransplant control of infections, including bacterial, viral, and fungal infections, has a large influence on allograft function and survival[89,90]. Uncontrolled infections will have catastrophic effects[83,87,88], and any infections should therefore be treated before LT.

Glycemic control also has an influence on the clinical course after LT[91]. Good glycolytic activity and glycemic control in the perioperative period will help to ensure adequate liver regeneration[92,93].

DISTINCTION BETWEEN HEPATOPULMONARY SYNDROME AND PORTOPULMONARY HYPERTENSION

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are cardiopulmonary complications[3,94-97] that are frequently seen in patients with LC[54,94-98]. Both conditions result from a lack of hepatic clearance of vasoactive substances produced in the splanchnic territory[95]. These substances mainly cause subsequent pulmonary vascular remodeling. In previous studies, some degree of vasoconstriction in patients with PPHTN resulted in pulmonary arterial hypertension (PAH) and right ventricular dysfunction[54,98]. The current definition of PPHTN includes secondary PAH due to portosystemic shunts[98]. In patients with HPS, these vasoactive mediators cause intrapulmonary shunts with hypoxemia[97]. The HPS is accompanied by abnormal pulmonary gas exchange and evidence of intrapulmonary vascular dilatation that results in a right-to-left intrapulmonary shunt[98]. These entities are both clinically and pathophysiologically distinct[3,94,95], and PPHTN and HPS should be considered as different pathological states[98]. HPS is characterized by abnormal pulmonary vasodilation and right-to-left shunting that result in gas exchange abnormalities[3,54,94,95,97,98], whereas PPHTN is caused by pulmonary artery vasoconstriction that leads to hemodynamic failure[3,94-96]. Both HPS and PPHTN are associated with significantly increased morbidity and mortality[3,94,95,97], although these patients are commonly asymptomatic. All candidates for LT should be actively screened for the presence of these two complications[54,94,95,97,98].

Although LT results in the disappearance of HPS within 1 year[95,99], the effect of LT on PPHTN is highly unpredictable[54,95,98-101]. PPHTN with PAH has historically been a contraindication for LT[54,98-100]. However, the diagnosis and treatment of PPHTN have advanced during the past two decades[54]. Assessment of patients' preoperative reactivity and response to pharmacological therapies for moderate-to-severe PPHTN is important to ensure excellent survival rates after LT[102]. Prostaglandin I_2 has drastically improved outcomes[103] and is currently considered a key drug in the control of PPHTN[103]. Modern strategies in managing HPS and PPHTN rely on a thorough screening and grading of the disease severity to tailor the appropriate therapy and select only the patients who will benefit from LT[54,95,97-101]. Hemodynamic and respiratory modifications in the perioperative period must be avoided through continuation of the preoperatively initiated drugs, appropriate intraoperative monitoring, and proper hemodynamic and respiratory therapies[54,95,98,99]. The most reliable monitoring factor for PPHTN with PAH during the perioperative period is the mean pulmonary arterial pressure[54,98], though supplemental oxygen and monitoring of oxygen saturation during the perioperative period are adequate for monitoring of HPS[97,104,105].

COAGULOPATHY AND ENDOTHELIAL INJURY

The systemic hyperdynamic state causes vessel dilation and collateral development, and the venous endothelium becomes damaged[4,65]. An intact endothelial barrier is important, especially in critical situations such as sepsis and thrombotic microangiopathy[106,107]. High mobility group box 1 (HMGB1) is an evolutionarily conversed nuclear protein that is passively released by almost all cells during cellular necrosis and is actively secreted from activated macrophages, monocytes, and endothelial cells[108]. Once secreted into the extracellular space, HMGB1 serves as a dangerous signal that stimulates inflammatory reactions[108]. Thrombomodulin (TM) is an endothelial anticoagulant cofactor that promotes thrombin-mediated formation of activated protein C[109]. TM plays an anti-inflammatory role through inactivation of HMGB1[109,110]. Recombinant human soluble TM (rTM) has recently become available[111], and this novel drug is effective for sepsis[110]. Thrombotic microangiopathy and a positive lymphoid cross-match combination will result in poor outcomes after LT, especially in adult recipients[112,113]. Intrahepatic and vascular conditions pathophysiologically overlap. Pathophysiologically, rTM

is effective for sepsis and thrombotic microangiopathy in LT recipients[107,111], although there are no reports of its usefulness for ABO incompatibility in patients undergoing LT. Vascular alterations including endothelial injury still remain even after LT. Based on our experience, the dose of rTM should be reduced to two-thirds of the regular dose in LT recipients with LC, although one-half of the regular dose loses any effects.

MEDICAL ECONOMY

Insurance systems are different in each country[114,115], and every country has its own limitations of medical resources[116]. Hence, transplant physicians should always consider a cost-benefit analysis if they want to continue an effective LT program[116,117]. Dialysis treatment, plasma exchange, blood derivatives, and direct-acting antivirals are very expensive[62,118,119]. Notably, attempts to perform blood transfusion and infusion of fraction products are ill-advised because they are very detrimental to the medical economy[62,116,117,119]. A shorter intensive care unit (ICU) stay has benefits for patients[120], although expensive and intensive care during the ICU stay is needed for post-transplant management. Longer hospital stay impairs quality of life and spoil social status after hospital discharge[121,122].

DISCUSSION

It is necessary to standardize CO against BV for precise evaluation of preload[1]. Considering that cirrhotic hyperdynamics are consolidated in patients with a large BV and high CO under a low TPR[3,6,8-10] and that the concept of preload is focused on the balance between CO and BV[35], we can now use the new concept of the CO/BV ratio by making the best use of available devices that can noninvasively measure BV[1,2,15]. The PDD guarantees noninvasive vigilance of the balance between CO and BV as an index for precise assessment of the systemic hemodynamic state in LT recipients with LC[1]. The CO/BV ratio expresses the CO per min corresponding to a fraction of the BV, which represents how the heart efficiently ejects the BV that should be circulated[1,2]. Interestingly, previous studies revealed no differences in the CO/BV among recipients with LC, recipients without LC, and healthy individuals[1,2]. This variable has potential as a reliable clinical marker after LT. Subtle instabilities that do not appear when comparing absolute values themselves are simply indicated by the balance between CO and BV[1,2]. It seems reasonable that tachycardia resulted in a lower CO in recipients with poor outcomes (Figure 4D) and that the decreased CO could not circulate the large BV in these recipients (Figure 5B).

In LDLT, the CIT is short and the hepatocytes are well preserved[41]. Therefore, division by the graft weight is a simple method that allows the *k*ICG to reflect only the PVF, by taking advantage of the shorter CIT in LDLT[41]. Strategic values in ICG kinetics are used to set the optimal PVF during LDLT and to evaluate the optimal systemic hemodynamics after LT[1,2,32,41,42]. ICG kinetics reflects the functional hepatocyte volume and effective PVF[31,49-52]. Advanced selection criteria of a graft with an GRWR of $\geqslant$ 0.6 and establishment of a target PVP of $\leqslant$ 15 mmHg during LDLT are currently documented for successful LDLT[123-126]. This defiant set-up with lower GRWR has advantages for donor pool and safety, although these grafts may cause critical problems[40]. ICG kinetics is useful to set-up of adequate PVF during LDLT with lower GRWR. Conversely, in deceased-donor LT, although PVF is a major determinant of *k*ICG in the normal liver[32,34,49,51,53], the *k*ICG value may be affected by damaged hepatocytes due to the longer CIT. The decreased *k*ICG may not indicate only an inadequate PVF in deceased-donor LT because ICG kinetics is dually factorial.

CONCLUSION

LT recipients with LC exhibit peculiar hemodynamics (*i.e.*, systemic hyperdynamic syndrome and PH). Vascular alterations do not easily disappear despite restorations of PH and liver function in recipients with LC, and PVF impacts liver regeneration after LT[43]. Stability of characteristic systemic hyperdynamics is indispensable for adequate PVF and successful LT[1,2]. Even a subtle disorder of the systemic hyperdynamics dictates PVF[1,2]. ICG kinetics is useful to set an adequate PVF during LDLT and evaluate the optimal systemic hemodynamics after LT[1,2,32,41,42]. Perioperative management has a large influence on the postoperative course and outcome. Transplant physicians should fully understand the peculiarities of cirrhotic hemodynamics. We hope that this review will be informative for transplant physicians.

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MINIREVIEWS

Inhibition of apoptosis by oncogenic hepatitis B virus X protein: Implications for the treatment of hepatocellular carcinoma

Chuck C K Chao

Chuck C K Chao, Department of Biochemistry and Molecular Biology, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan

Chuck C K Chao, Graduate Institute of Biomedical Sciences, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan

Chuck C K Chao, Chang Gung Memorial Hospital at Linkuo, Liver Research Center, Taoyuan 33305, Taiwan

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Correspondence to: Chuck C K Chao, PhD, Department of Biochemistry and Molecular Biology, College of Medicine, Chang Gung University, No.259, Wenhua 1st Rd., Guishan Dist, Taoyuan 33302, Taiwan. cckchao@mail.cgu.edu.tw
Telephone: +886-32-118800-5151
Fax: +886-32-118700

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Abstract

Hepatitis B virus X protein (HBx) plays an important role in the development of hepatocellular carcinoma (HCC). In addition, hepatoma upregulated protein (HURP) is a cellular oncogene that is upregulated in a majority of HCC cases. We highlight here recent findings demonstrating a link between HBx, HURP and anti-apoptosis effects observed in cisplatin-treated HCC cells. We observed that Hep3B cells overexpressing HBx display increased HURP mRNA and protein levels, and show resistance to cisplatin-induced apoptosis. Knockdown of HURP in HBx-expressing cells reverses this effect, and sensitizes cells to cisplatin. The anti-apoptotic effect of HBx requires activation of the p38/MAPK pathway as well as expression of SATB1, survivin and HURP. Furthermore, silencing of HURP using short-hairpin RNA promotes accumulation of p53 and reduces cell proliferation in SK-Hep-1 cells ($p53^{+/-}$), whereas these effects are not observed in p53-mutant Mahlavu cells. Similarly, HURP silencing does not affect the proliferation of H1299 lung carcinoma cells or Hep3B HCC cells which lack p53. Silencing of HURP sensitizes SK-Hep-1 cells to cisplatin. While HURP overexpression promotes p53 ubiquitination and degradation by the proteasome, HURP silencing reverses these effects. Inoculation of SK-Hep-1 cancer cells in which HURP has been silenced produces smaller tumors than control in nude mice. Besides, gankyrin, a positive regulator of the E3 ubiquitin ligase MDM2, is upregulated following HURP expression, and silencing of gankyrin reduces HURP-mediated downregulation of p53. In addition, we observed a positive correlation between HURP and gankyrin protein levels in HCC patients (r^2 = 0.778; n = 9). These findings suggest a role for the viral protein HBx and the host protein HURP in preventing p53-mediated apoptosis during cancer progression and establishment of chemoresistance.

Key words: Hepatitis B virus X protein; Hepatocellular

carcinoma; Hepatitis B virus; Hepatoma upregulated protein; p53; Gankyrin; SATB1

Core tip: Hepatitis B virus X protein (HBx) plays a critical role in the development of hepatocellular carcinoma (HCC). Hepatoma upregulated protein (HURP) is an oncogene that is upregulated in a majority of HCC cases. However, the role of these proteins in the response of HCC cells to chemotherapeutic drugs remains unclear. We show here that the HBx/SATB1/HURP axis plays a critical role in down-regulating p53 and upregulating anti-apoptotic proteins *in vitro* and *in vivo*. We discuss the regulation of this novel pathway and its implications in resistance of HCC cells to chemotherapy.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection represents an important risk factor for the development of hepatocellular carcinoma (HCC)[1-3]. The hepatitis B virus X protein (HBx) is produced by HBV and is required for viral replication in host cells[4,5]. HBx interferes with a variety of cellular functions in host cells. It forms a heterodimeric complex with the host protein HBX interacting protein, and this interaction dysregulates centrosome dynamics and chromosomal stability[6]. HBx also interacts with the tumor suppressor p53 and modulates cellular apoptosis in the presence of various stimuli[7-9]. A recent study indicates that HBx binds to the DNA-repair protein damaged DNA binding protein 1 (DDB1), and redirects the CUL4-DDB1 E3 complex, a protein complex with ubiquitin ligase activity that is involved in regulating DNA replication and repair, transcription and signal transduction in host cells[10].

Recent studies suggest that HBx plays a role in HCC pathogenesis[11-14]. However, the effect of HBx on apoptosis remains incompletely understood as some authors have reported pro-apoptotic[15-19] as well as anti-apoptotic effects[8,20-23]. Importantly, experiments performed in laboratory animals indicate that the HBx protein may induce resistance to the anti-cancer drug cisplatin in hepatoma cells[16]. Here, I present recent experimental evidence highlighting a prominent pathway used by HBx to upregulate hepatoma upregulated protein (HURP) and avoid apoptosis in HCC cells.

HURP AS A MARKER IN HCC

HURP was initially shown to be overexpressed in HCC based on a bioinformatics analysis of sequence tags expressed in the human liver[24]. Also known as discs large homolog 7 or disks large-associated protein 5[25,26], HURP was previously thought to represent a stem cell marker as this protein is not detected in fully differentiated cells[27]. Previous reports indicate that HURP overexpression in differentiated cells blocks apoptosis and increases cell growth in response to serum starvation[24,28]. HURP also appears to regulate the cell cycle and act specifically during mitosis. More specifically, HURP represents a kinetochore protein that stabilizes microtubules in the vicinity of chromosomes[29-31]. That is, HURP is associated with the mitotic spindle where it helps to determine spindle bipolarity and participates in the growth of microtubules toward chromosomes during mitosis. Furthermore, HURP forms a Ran-dependent complex[29], and is a target of the serine/threonine kinase aurora-A, which possesses oncogenic properties[28]. Aurora-A thus phosphorylates HURP and this process may represent a cellular mechanism that controls mitotic spindle assembly and functions[32]. Therefore, HURP is implicated in stem cell functions[25-27] and carcinogenesis in cancer cells of human origins[24,28]. Analysis of gene expression showed that HURP represents a marker of cancer prognosis that can be used to distinguish between benign and malignant adrenocortical tumors[33,34]. In addition, HURP undergoes proteolysis following phosphorylation by Cdk1-cyclin B and recognition by the Fbx7-associated SCF complex that functions as an E3 ubiquitin ligase[35]. These results indicate that HURP is involved in control of the cell cycle, specifically during mitosis, suggesting that this protein may regulate apoptosis and be involved in tumor development. However, the role of HURP in HCC and apoptosis, and how this protein is regulated is incompletely understood.

HBx UPREGULATES HURP EXPRESSION IN HCC CELLS

Given that the viral protein HBx plays a critical role in the development of HCC and HURP is upregulated in a majority of HCC cases, we examined the possible link between HBx, HURP, and cisplatin resistance in HCC cells. Hep3B cells expressing HBx showed not only elevated HURP mRNA and protein levels but also resistance to apoptosis induced by cisplatin. HURP silencing in cells expressing HBx reversed this process and enhanced sensitization of Hep3B cells to apoptosis. Notably, HBx overexpression induced SATB1, a global gene regulator that is upregulated in breast cancer. However, the role of SATB1 in the regulation of cell survival is unclear. We found that the anti-apoptotic effect of HBx requires p38/MAPK pathway activation in Hep3B cells. HBx also induced the expression of the anti-apoptotic protein survivin in an HURP-dependent manner[36]. We observed that the HBx produces anti-apoptotic effects in HCC cells, a process that may lead to chemoresistance. Enhanced chemoresistance of HCC cells that express

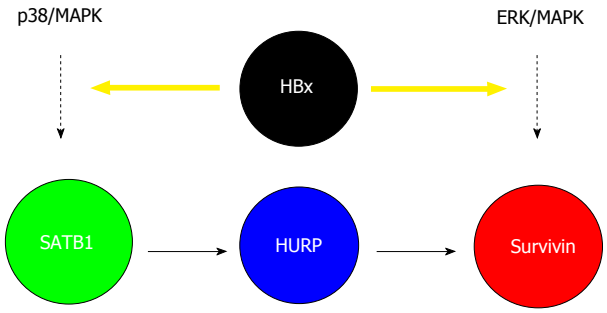

Figure 1 Proposed model to explain the link between hepatitis B virus X protein, p38/MAPK, SATB1, hepatoma upregulated protein, and survivin in mediating anti-apoptotic effects during cisplatin treatment. HBx upregulates the anti-apoptotic protein survivin through induction of p38/MAPK and ERK/MAPK pathways. Another less defined ERK/MAPK pathway which may regulate survivin independently of HURP is also shown. HBx: Hepatitis B virus X protein; HURP: Hepatoma upregulated protein.

HBx was associated with increased activity of several proteins, including STAB1, HURP, and survivin. Previous reports indicate that PKC negatively regulates SATB1 transactivation activity[37]. Our group showed that SATB1 and the p38/MAPK pathway mediates the anti-apoptotic activity of HBx. Therefore, it appears that HBx upregulates SATB1 and MAPK or HURP transcription. HURP induced survivin expression in HBx-expressing cells. ERK inhibition also inhibited surviving activity[36,38]; however, HURP protein levels remained constant in the presence of ERKi, an observation which suggested that HBx may induce survivin *via* another pathway that requiresthe ERK kinase (Figure 1). Our results may explain, at least in part, the cellular mechanism underlying the anti-apoptotic effect of HBx during the development of HBV-associated HCC. In agreement with our results, previous studies have shown that stable expression of HBx can stimulate PI3-kinase activity and suppress TGF-beta-induced apoptosis in Hep3B cells[8,22].

SATB1, a chromatin organizer, is involved in gene regulation and the formation of chromosome loops, in addition to its role in the organization of transcriptionally poised chromatin[39]. SATB1 was initially described as a protein mediator of apoptosis[40]. We have shown the role of SATB1 in upregulating surviving and preventing apoptosis during cancer progression and establishment of chemoresistance[36]. SATB1 phosphorylation also appears to control interleukin-2 transcription as shown based on results obtained in a T-cell activation model; a similar mechanism may potentially be associated with SATB1 and its gene regulation activity[37]. In addition, SATB1 cleavage *via* sumoylation-directed caspase activity appears to regulate gene expression or may lead to clearance of immune cells[41]. Furthermore, SATB1 promotes cancer cell metastasis and overexpression of this protein increases resistance to chemotherapeutic drugs in breast cancer cells[42,43]. These observations suggest that HBx induces HURP expression by activating the p38/MAPK pathway and SATB1, leading to accumulation of survivin. We conclude that activation of the HBx/SATB1/HURP axis may increase chemoresistance in hepatic cancer cells.

HURP/GANKYRIN/p53 AXIS IN REGULATING HCC APOPTOSIS

The tumor suppressor p53 inhibits cancer development by inducing cell cycle arrest and apoptosis[44,45]. Some human tumors (10%) are characterized by overexpression of MDM2, an E3 ubiquitin ligase known for its role in the ubiquitination of p53 and its subsequent degradation by the proteasome[46]; this phenomenon may account for the development of many cancers, even those in which the *p53* gene is no longer functional[47]. We found that overexpressing HURP in HEK293 cells induces p53 ubiquitination and degradation of the protein by the proteasome[48]. Conversely, HURP silencing with short-hairpin RNA reverses these processes. Knockdown of HURP promotes p53 accumulation and reduces cell proliferation in SK-Hep-1 cells ($p53^{+/-}$), while Mahlavu cells (p53-mutant) are not affected. HURP silencing showed no effect on cellular proliferation in Hep3B and H1299 cells (lung carcinoma) (both lack p53 activity). In comparison, HURP silencing sensitized SK-Hep-1 cells to cisplatin. HURP overexpression not only reduced exogenous p53 expression in H1299 and Hep3B cells but also reduced sensitivity of these cells to cisplatin. Notably, HURP expression induced HEK293 cell proliferation in an anchorage-independent manner; moreover, injection of SK-Hep-1 cancer cells in which HURP had been silenced produced tumors of smaller size in immunocompromised mice compared to control[48].

The ankyrin-repeat oncoprotein gankyrin[49] has also been shown to be upregulated in HCC. Previous work indicated that this protein interacts with the product of retinoblastoma (*Rb*) gene as well as a subunit of the 26S proteasome subunit (S6 ATPase), a process that increases degradation of *Rb*[50,51]. Gankyrin is part of the 19S cap of the proteasome. This protein has an ankyrin repeat that forms alpha helices[51]. Gankyrin can increase the E3 ubiquitin ligase activity of MDM2, which regulates the degradation of the tumor suppressors *p53* and *Rb*, which are both often mutated in human tumors[52,53]. Gankyrin regulates the cell cycle by mediating protein-protein interactions involving CDK4 (a cyclin-dependent kinase). Rb may inhibit the activity of gankyrin and lead to inhibition of MDM2-mediated p53 ubiquitination in HCC cells[54]. In our study[48], we observed that HURP represents an oncogene that reduces the level of p53 in normal cells and cancerous cells. Gankyrin was upregulated following HURP overexpression, and silencing of gankyrin reduced downregulation of p53 mediated by HURP. Importantly, high HURP levels positively correlated with gankyrin protein levels in HCC patients ($n = 9$; $r^2 = 0.778$).

We propose a mechanism to explain the activity of HURP and its action on gankyrin accumulation in cancer cells (Figure 2). In this model, HURP prevents the ubiqui-

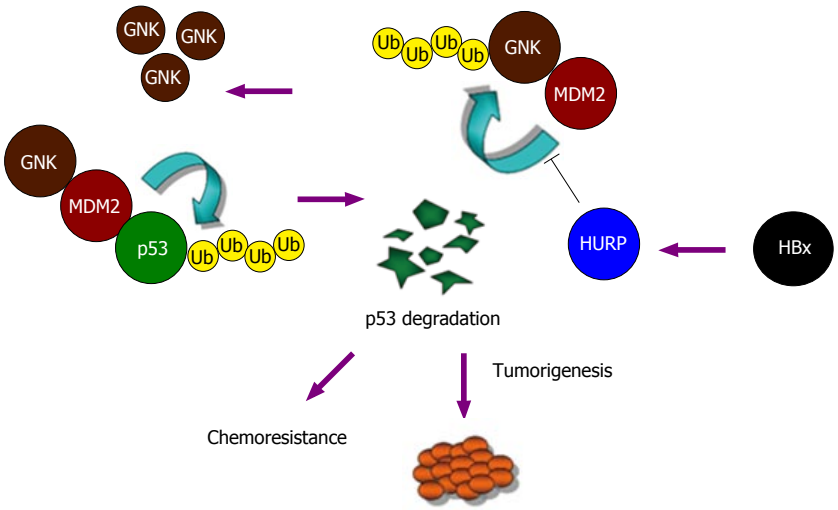

Figure 2 Simplified model illustrating the oncogenic properties of hepatitis B virus X protein and hepatoma upregulated protein in human liver cancer. In this cycle of gankyrin/MDM2-enhanced p53 degradation, HURP reduces MDM2-mediated ubiquitination of gankyrin, leading to accumulation of gankyrin in both normal and tumorigenic cells. Downstream effects of HURP appear to include malignant cell transformation and prevention of apoptosis induced by chemotherapeutic drug, processes which may in turn lead to the development of a chemoresistant cellular phenotype. HBx: Hepatitis B virus X protein; HURP: Hepatoma upregulated protein.

tination and degradation of gankyrin but in a process that does not involve the disruption of the interaction between MDM2 and gankyrin. Alternatively, HURP may regulate the activity of other deubiquitination enzymes by inducing binding to the gankyrin/MDM2 protein complex (not illustrated in the model shown in Figure 2), which may subsequently inhibit MDM2's effects on gankyrin degradation. More experimental data are needed to determine if HURP affects deubiquitination enzymes which interact with the MDM2/gankyrin protein complex. The degradation of p53 mediated by HURP may therefore be relevant to the development of HCC. Our findings identify a novel pathway for the malignant transformation induced by HURP and involving degradation of p53 and accumulation of gankyrin.

CONCLUSION

Our observations suggest that HBx induces HURP expression *via* the p38/MAPK pathway and SATB1 activity. This process leads to accumulation survivin, which possesses anti-apoptotic properties. Our results also identify a novel cellular pathway in which the oncogenic protein HURP induces cancer transformation by inducing p53 degradation and gankyrin accumulation. The processes of cell survival and apoptosis have been shown to be regulated by differential activation of p53 target genes[55]. For instance, CAS may bind to p53 on chromatin and this process may induce expression of a set of genes that facilitate apoptosis[56]. In contrast, interaction between the zinc-finger protein Hzf and p53 activates expression of growth-arrest genes and promotes cell survival[56,57]. HURP-mediated p53 degradation thus appears to be relevant for the development of HCC. In conclusion, recent advances regarding the oncogenic proteins HBx and HURP as described here offer new strategies to defeat human liver cancer.

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ORIGINAL ARTICLE

Retrospective Study

CD36 genetic variation, fat intake and liver fibrosis in chronic hepatitis C virus infection

Omar Ramos-Lopez, Sonia Roman, Erika Martinez-Lopez, Nora A Fierro, Karina Gonzalez-Aldaco, Alexis Jose-Abrego, Arturo Panduro

Omar Ramos-Lopez, Sonia Roman, Erika Martinez-Lopez, Nora A Fierro, Karina Gonzalez-Aldaco, Alexis Jose-Abrego, Arturo Panduro, Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara "Fray Antonio Alcalde", Guadalajara, Jalisco 44280, Mexico

Omar Ramos-Lopez, Sonia Roman, Erika Martinez-Lopez, Nora A Fierro, Karina Gonzalez-Aldaco, Alexis Jose-Abrego, Arturo Panduro, Health Sciences University Center, University of Guadalajara, Guadalajara, Jalisco 44340, Mexico

Author contributions: Ramos-Lopez O performed the genotyping experiments, statistical analysis and prepared the first draft of the manuscript; Roman S wrote, integrated the final version and critically revised the content of this article; Martinez-Lopez E provided the biochemical tests and critically revised the manuscript; Fierro NA wrote and critically revised the article; Gonzalez-Aldaco K and Jose-Abrego A wrote, revised statistical analysis and critically reviewed the manuscript; Panduro A conceived the study, performed clinical studies and transient elastography, wrote and critically revised the content of this article; all authors critically reviewed all drafts and approved the final manuscript.

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Correspondence to: Arturo Panduro, MD, PhD, FAASLD, Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara "Fray Antonio Alcalde", Hospital # 278, Col. El Retiro, Guadalajara, Jalisco 44280, Mexico. apanduro@prodigy.net.mx
Telephone: +52-33-36147743
Fax: +52-33-36147743

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Abstract

AIM

To analyze the association of the *CD36* polymorphism (rs1761667) with dietary intake and liver fibrosis (LF) in chronic hepatitis C (CHC) patients.

METHODS

In this study, 73 patients with CHC were recruited. The *CD36* genotype (G > A) was determined by a TaqMan real-time PCR system. Dietary assessment was carried out using a three-day food record to register the daily intake of macronutrients. Serum lipids and liver enzymes were measured by a dry chemistry assay. LF evaluated by transient elastography (Fibroscan®)

and APRI score was classified as mild LF (F1-F2) and advanced LF (F3-F4).

RESULTS

Overall, the *CD36* genotypic frequencies were AA (30.1%), AG (54.8%), and GG (15.1%), whereas the allelic A and G frequencies were 57.5% and 42.5%, respectively. CHC patients who were carriers of the *CD36* AA genotype had a higher intake of calories attributable to total fat and saturated fatty acids than those with the non-AA genotypes. Additionally, aspartate aminotransferase (AST) serum values were higher in AA genotype carriers compared to non-AA carriers (91.7 IU/L *vs* 69.8 IU/L, $P = 0.02$). Moreover, the AA genotype was associated with an increase of 30.23 IU/L of AST ($\beta = 30.23$, 95%CI: 9.0-51.46, $P = 0.006$). Likewise, the AA genotype was associated with advanced LF compared to the AG (OR = 3.60, 95%CI: 1.16-11.15, $P = 0.02$) or AG + GG genotypes (OR = 3.52, 95%CI: 1.18-10.45, $P = 0.02$).

CONCLUSION

This study suggests that the *CD36* (rs1761667) AA genotype is associated with higher fat intake and more instances of advanced LF in CHC patients.

Key words: Hepatitis C virus infection; *CD36* receptor; Lipids; Liver fibrosis; Mexico

Core tip: In this study, chronically infected hepatitis C patients who were carriers of the AA genotype of the *CD36* receptor polymorphism (rs1761667) showed a higher risk of advanced liver fibrosis compared to patients with an AG/GG genotype. This liver damage was associated with the consumption of a hepatopatogenic diet, high-calories and excessive intake of total and saturated fat, typical of the population of West Mexico. Thus, preventive nutritional intervention strategies based on the *CD36* genotype may be a useful tool to avoid further liver damage due to alterations in liver lipid metabolism and inflammation in patients with chronic hepatitis C infection.

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INTRODUCTION

The hepatitis C virus (HCV) is a hepatotropic human RNA virus, member of the *Flaviviridae* family[1]. Globally, it is estimated that nearly 170 million individuals are infected with HCV, causing yearly 350000 deaths[2]. Liver cirrhosis causes a high burden of liver disease in Mexico, and HCV infection represents one of its primary etiologies[3,4]. Approximately two million Mexican individuals are infected with HCV[5,6] and up to 64% of patients with acute HCV infection fail to undergo spontaneous viral clearance[7]. Thus, chronically infected patients may be at risk of liver fibrosis (LF), cirrhosis, and hepatocellular carcinoma during a period of 20 to 30 years[4,8].

Regardless of etiology, the pathogenesis of LF is influenced both by genetic and environmental factors[9,10]. High-fat diets, which have a significant content of saturated fatty acids (SFA), have been associated with the pathological processes known to be involved in liver fibrogenesis, including steatosis, inflammation, and insulin resistance[11-13]. Recently, we reported that in West Mexico, the general population and patients with liver disease consume an excessive amount of red meat, fried foods, sausages, and pastry products[14]. Consequently, these dietary trends have increased the proportional intake of calories, total fat, and SFA, which could eventually lead to liver damage in individuals that consume this type of hepatopathogenic diet.

In addition to the textural, olfactory, neural and hormonal mechanisms involved in food intake, taste perception is considered a critical determinant of dietary preferences[15,16]. There is growing evidence of the existence of a new taste modality related to fat preference[17]. Experimental studies suggest that the lingual cluster of differentiation 36 (CD36) receptor regulates the motivation for fatty food consumption in rodents[18,19]. This effect is carried out through the cellular capture of long-chain fatty acids by the CD36 receptors on the taste buds[20]; subsequently, lipid signals are transduced into the gustatory nervous pathway[21]. Therefore, genetic variations that lead to changes in the expression of CD36 could explain the interindividual differences in fat linking[15]. CD36 protein levels are modulated by several single nucleotide polymorphisms (SNPs) in the *CD36* gene on chromosome 7[22,23]. One SNP consists of a nucleotide substitution of guanine for adenine in the *CD36* gene promoter sequence (-31118G > A, rs1761667)[24]. This SNP has been associated with a significant reduction in the *CD36* expression in several tissues[25,26].

Recently, we reported an association between *CD36* with a higher intake of fat portions and high serum cholesterol among the general population of West Mexico[27]. However, its role in dietary intake and HCV-related liver damage is currently unknown. Therefore, this study aimed to analyze the association of the rs1761667 *CD36* polymorphism with dietary intake and LF in patients chronically infected with hepatitis C.

MATERIALS AND METHODS

Study design

In this retrospective study, 73 chronic hepatitis C (CHC) patients were recruited at the Department of Molecular Biology in Medicine from January 2012 to December 2014. Chronic HCV infection was defined as a positive

anti-HCV test result (ELISA Third-Generation, AxSYM, Abbott Laboratories, Illinois, United States) and the presence of serum HCV RNA for more than six months (COBAS® AmpliPrep/COBAS® Taqman® HCV Test; Roche Diagnostics, Pleasanton, CA, United States)[28,29]. Duration of infection (years) was estimated by the self-reported date of exposure to any known risk factor for HCV infection including the history of surgeries, blood transfusions, hemodialysis, acupuncture, injection drug use and tattooing[30]. Patients co-infected with the hepatitis B virus or human immunodeficiency virus, as well as alcohol abusers were excluded. Based on the pattern of alcohol intake in West Mexico, alcohol abusers were defined as those individuals that consumed more than two drinks per occasion, as previously described[31]. None of the CHC patients in the study group had received antiviral treatment for HCV infection.

Viral genotyping

A VERSANT HCV Genotype 2.0 line probe assay was used to determine the HCV genotypes (Innogenetics, Ghent, Belgium).

Body mass index measurement

An electrical bioimpedance apparatus was used to assess body mass index (BMI, kg/m^2) (INBODY 3.0, Analyzer Body Composition, Biospace, South Korea).

Dietary assessment

A three-day food record (two weekdays and one weekend day) was used as a tool to assess the patient's dietary intake, which has been previously used for our population[27,32-34]. This methodology provides accurate data concerning intake of food and nutrients[35]. Briefly, each subject was instructed on how to register the type, amount, and mode of preparation of all foods using food models[32]. The food records were coded by a qualified dietitian using a specialized software (Nutrikcal VO®, Mexico). This program calculated the total amount of calories, fat, protein, and carbohydrates as well as the daily intake of food group servings such as sugars, meat, fruits, vegetables, fats, milk, legumes, and cereals. Dietary data were averaged over the three-day food records and were compared with the recommended dietary intakes based on the Mexican System of Food and Equivalents[36,37].

Biochemical tests

Serum was obtained from 10 mL blood samples after a 12-h overnight fast. Biochemical tests included glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-c). The Friedewald formula was selected to estimate low-density lipoprotein cholesterol (LDL-c)[38]. The concentration of very low-density lipoprotein cholesterol (VLDL-c) was calculated as Total Cholesterol - (LDL-c + HDL-c). All biochemical tests were performed using a dry chemistry assay on a Vitros 250 Analyzer (Ortho-Clinical Diagnostics, Johnson and Johnson Co, Rochester, NY).

Liver fibrosis evaluation

Liver stiffness (fibrosis) was evaluated by transient elastography (TE) (FibroScan® Echosens, Paris, France). The average value of ten successful readings expressed in kilopascals (kPa) was used as an indicator of LF according to the following classification: F1 (< 7 kPa), F1-F2 (7 kPa-8.49 kPa), F2 (8.5 kPa-9.49 kPa), F3 (9.5 kPa-12.49 kPa) and F3-F4 (12.5 kPa-14.49 kPa) and F4 (> 14.5 kPa)[39]. For this study, patients in either the F1 or F2 stages were classified as having mild LF and those in the F3 or F4 stages were classified as having advanced LF[40]. This classification was corroborated by calculating the aspartate aminotransferase-to-platelet ratio index (APRI score), as previously described[41].

CD36 genotyping

Leukocyte genomic DNA was extracted by a modified salting-out method[42]. The rs1761667 *CD36* polymorphism was detected by an allelic discrimination assay (TaqMan, Applied Biosystems, ID C_8314999_10; Foster City, CA, United States) in a 96-well format (StepOnePlus thermocycler (Applied Biosystems, Foster City, CA, United States) as previously described[27,34].

Statistical analysis

The sample size was estimated by a formula for the comparison of proportions[43] resulting in a statistical power of 80% (β = 0.20) with a reliability of 95% (α = 0.05) based on the rs1761667 *CD36* allelic frequency in our population[24,27]. Quantitative variables were expressed as mean ± SD and analyzed by one-way ANOVA adjusted for age, gender, and BMI. Subsequently, post hoc tests were run (Bonferroni's test and Dunnett's T3 test). Finally, to quantify the effect of the *CD36* genotypes on quantitative variables, linear regression was performed. The Hardy-Weinberg equilibrium (HWE) and qualitative variables were evaluated by the χ^2 test. The association of the *CD36* genotypes with LF was assessed by odds ratio (OR) as well as logistic regression tests considering a confidence interval (CI) of 95%. A *P*-value of < 0.05 was considered significant. Statistical analyses were performed using Arlequin (version 3.1), Epi Info™ 7 (CDC, Atlanta, GA) and SPSS Statistics, Version 20.0 (IBM Corp, Armonk, NY). All statistical analyses were reviewed and approved by an expert biomedical statistician.

Ethical guidelines

This study was in compliance with the ethical guidelines defined by the Declaration of Helsinki 2013 and was approved by the Institutional Board Review (CI-01913). All patients who agreed to enter this study signed a written informed consent.

RESULTS

In this study, the genotypic frequencies were AA (30.1%),

Table 1 Demographical and clinical characteristics of the chronic hepatitis C patients classified by cluster of differentiation 36 genotype

Variable	*CD36* genotype			*P*-value
	AA	AG	GG	
No. of patients, *n* (%)	22 (30.1)	40 (54.8)	11 (15.1)	---
Age (yr)	48.1 ± 11.7	51.4 ± 11.1	53.7 ± 15.3	0.38
Gender (F/M)	(12/10)	(21/19)	(7/4)	0.68
BMI (kg/m^2)	26.6 ± 4.1	24.9 ± 4.2	24.4 ± 3.1	0.52
Duration of infection (yr)	26.9 ± 10.1	25.2 ± 8.1	25.4 ± 7.4	0.62
HCV genotype 1, *n* (%)	15 (68.2)	27 (67.5)	8 (72.7)	0.40
HCV genotype 2, *n* (%)	5 (22.7)	9 (22.5)	3 (27.3)	
HCV genotype 3, *n* (%)	2 (9.1)	4 (10)	0 (0)	

Quantitative values are expressed as mean ± SD. Frequencies are expressed as percentage. CHC: Chronic hepatitis C; F/M: Female/male; BMI: Body mass index; HCV: Hepatitis C virus; *CD36*: Cluster of differentiation 36.

AG (54.8%), and GG (15.1%), whereas the allelic A and G frequencies were 57.5% and 42.5%, respectively. These genotypes were concordant with the HWE (P = 0.50). In Table 1, the demographical and clinical characteristics of the CHC patients by *CD36* genotype are shown. No significant differences for the variables of age, gender, BMI, years of infection, and HCV genotypes between *CD36* genotypes were found. Only the CHC patients who were carriers of the AA genotype were overweight according to the WHO classification (BMI = 26.6 kg/m^2). HCV genotype 1 was the most frequent with 68.4% of the total cases, followed by HCV genotype 2 (23.3%) and HCV genotype 3 (8.2%).

The daily dietary intake of the CHC patients classified by *CD36* genotype is shown in Table 2. CHC patients who were carriers of the *CD36* AA genotype had a higher caloric intake relative to total fat, and SFA than those with the AG and GG genotypes. No differences in protein and CH intakes between *CD36* genotypes were observed. Subsequently, the daily intake of several food groups classified by *CD36* genotype is shown in Table 3. Fats were the only food group associated with the *CD36* genotype. The lipid and liver profiles of the CHC patients by *CD36* genotype are shown in Table 4. CHC patients with the *CD36* AA genotype had more elevated serum levels of AST than the AG genotype carriers (91.7 IU/L *vs* 69.8 IU/L, P = 0.02). Furthermore, an increase of 30.23 IU/L of AST was attributed to the AA genotype when compared with the AG genotype (β = 30.23, 95%CI: 9.0-51.46, P = 0.006). No differences for ALT and GGT were observed (Table 4).

According to the categories of LF established in this study, 47.9% of the CHC patients had mild fibrosis, whereas 52.1% presented advanced fibrosis (Table 5). Among the CHC patients, the kPa values and APRI score were higher in those with advanced fibrosis compared to those with mild fibrosis (22.7 kPa *vs* 6.5 kPa, P < 0.001 and 1.78 *vs* 0.81, P < 0.001, respectively). CHC patients with advanced fibrosis had a higher frequency of the *CD36* AA genotype than those with mild fibrosis (42.1% *vs* 17.1%, P = 0.002), respectively (Table 6). Additionally, patients who were AA genotype carriers had a higher risk for advanced fibrosis than those with the AG genotype (OR = 3.60, 95%CI: 1.16-11.15, P = 0.02) and AG + GG genotypes (OR = 3.51 95%CI: 1.18-10.45, P = 0.02). A logistic regression test was used to corroborate this association (OR = 2.23 95%CI: 1.03-4.81, P = 0.041).

DISCUSSION

Genetic polymorphisms in fat taste perception may partially explain the interindividual variability in fat intake[15] and their association with the risk of developing chronic diseases[15,44]. Over recent years, it has been proposed that the CD36 receptor is an oral fat sensor that may influence an individual's preference for high-fat foods[15-18]. Specifically, it has been shown that the *CD36* AA genotype decreases fat taste perception[45-48]. In this study, the frequency of *CD36* AA genotype was 30.1%. In regards to food consumption, despite that the three-day food record may not be representative of the long-term food variety, the amount of fat intake represented over 30% of the total daily calories. It has been documented that the prolonged ingestion of high-fat diets increases the risk for metabolic disorders[49]. These data were consistent with previous results found in overweight patients from the general population of West Mexico[27].

The association of high-fat diets with LF has been well documented in animal models[11-13] as well as in humans in different populations[50,51]. In this study, among the *CD36* AA genotype carriers, more cases of advanced LF were detected. This disease stage is characterized by steatosis and persistent inflammation[4]. Also, they exhibited significantly higher levels of AST, which is a better predictor of progression of LF than ALT or GGT[52]. Furthermore, two validated non-invasive methods (TE and APRI score) were used to evaluate LF[41,53]. Since no differences in demographic and viral characteristics between *CD36* genotypes were found, the likelihood of HCV-related LF seems to be enhanced because of the higher consumption of fat portions observed among the *CD36* AA genotype carriers.

The immunological mechanisms that regulate LF progression during HCV infection have been extensively studied[54-56]. However, alterations in lipid and lipoprotein metabolism have been reported to play a key role[9], considering that chronic HCV infection is characterized by hypocholesterolemia and reduced levels of LDL-c, TG and apolipoprotein B (apoB)[57]. Recently, a novel interaction of the CD36 receptor in liver VLDL-c metabolism has been proposed[58]. Findings in a further study, concurring with this hypothesis, have demonstrated that CD36 deletion can reduce VLDL output and liver fat in obese mice[59]. This finding was related to the enhanced production of the series-2 liver prostaglandins, which have been shown to suppress VLDL output and increase the hepatocyte triglyceride content in an inflammatory condition-dependent manner[60]. Thus, it is plausible that the AA genotype carriers may have a lower expression of the CD36 receptor that could contribute to liver steatosis and consequently to fibrosis similar to the effects of

Table 2 Daily dietary intake of the chronic hepatitis C patients classified by cluster of differentiation 36 genotype

Variable	Reference values	*CD36* genotype			*P*-value
		AA	AG	GG	
Total calories	-	2531.3 ± 301.3	1902.5 ± 396.1	1873.5 ± 345.7	0.021[a]
CH (%)	50-60	55.4 ± 10.5	54.3 ± 8.9	53.2 ± 6.4	0.76
Protein (%)	15	17.2 ± 4.6	16.3 ± 3.9	16.4 ± 2.9	0.81
Fat (%)	< 30	34.9 ± 7.5	27.5 ± 7.2	24.9 ± 1.1	0.001299[a]
SFA (%)	< 7	16.1 ± 6.1	8.1 ± 3.2	8.4 ± 2.7	0.2×10^{-6a}
MUFA (%)	20	13.1 ± 3.4	12.8 ± 7.6	12.1 ± 5.4	0.94
PUFA (%)	10	8.8 ± 6.5	5.6 ± 4.2	5.2 ± 1.3	0.11

[a]By post hoc tests: Total calories: AA genotype *vs* AG and GG genotypes, $P = 0.027$. Fat: AA *vs* AG, $P = 0.006$; AA *vs* GG, $P = 0.002$; SFA: AA *vs* AG, $P = 0.2 \times 10^{-6}$, AA *vs* GG, $P = 0.185 \times 10^{-4}$. Quantitative values are expressed as mean ± SD. CH: Carbohydrates; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; *CD36*: Cluster of differentiation 36.

Table 3 Daily intake of food group servings in chronic hepatitis C patients classified by cluster of differentiation 36 genotype

Variable	Reference values	*CD36* genotype			*P*-value
		AA	AG	GG	
Sugars	0-3	5.7 ± 4.3	5.5 ± 4.8	5.2 ± 4.1	0.85
Meat	2-3	5.7 ± 1.6	5.1 ± 2.8	4.4 ± 2.2	0.15
Fruits	2-4	2.0 ± 1.8	1.7 ± 0.9	1.4 ± 1.1	0.43
Vegetables	3-5	2.1 ± 1.6	1.9 ± 1.1	1.6 ± 0.8	0.42
Fats	0-3	6.5 ± 1.7	4.3 ± 3.1	3.9 ± 2.2	0.003207[1]
Milk	1-3	1.0 ± 0.7	0.8 ± 0.7	0.8 ± 0.9	0.86
Legumes	1-2	1.0 ± 0.7	0.9 ± 0.7	0.8 ± 0.7	0.88
Cereals	6-11	10.3 ± 5.4	9.6 ± 5.8	9.0 ± 5.1	0.77

Quantitative values are expressed as mean ± SD. [1]By Post hoc tests: Fats: AA *vs* GG, $P = 0.011608$. *CD36*: Cluster of differentiation 36.

Table 4 Biochemical profile of the chronic hepatitis C patients classified by cluster of differentiation 36 genotype

Variable	*CD36* genotype			*P*-value
	AA	AG	GG	
Glucose (mg/dL)	109.5 ± 59.3	106.7 ± 42.9	97.4 ± 19.8	0.78
TC (mg/dL)	146.8 ± 35.1	162.2 ± 44.2	157.8 ± 51.1	0.40
TG (mg/dL)	112.8 ± 43.3	140.8 ± 60.8	142.3 ± 51.1	0.30
HDL-c (mg/dL)	42.7 ± 15.1	40.4 ± 13.1	33.8 ± 9.8	0.21
LDL-c (mg/dL)	83.1 ± 28.8	95.4 ± 42.6	101.1 ± 42.6	0.44
VLDL-c (mg/dL)	22.6 ± 8.7	28.2 ± 12.1	28.9 ± 10.1	0.27
ALT (IU/L)	93.8 ± 42.6	73.4 ± 73.1	71.5 ± 46.4	0.38
AST (IU/L)	91.7 ± 41.3	61.5 ± 40.3	69.8 ± 53.9	0.028[1]
GGT (IU/L)	85.9 ± 56.2	66.4 ± 40.8	43.1 ± 33.2	0.18

[1]By post hoc tests: AA genotype *vs* AG genotype, $P = 0.024$. Quantitative values are expressed as mean ± SD. TC: Total cholesterol; TG: Triglycerides; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; VLDL-c: Very low-density lipoprotein cholesterol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl-transferase; *CD36*: Cluster of differentiation 36.

a CD36 deletion. Nonetheless, further investigation is required to elucidate the correlation between the *CD36* genotype and liver steatosis and clarify its interaction with other key molecules involved in this metabolic alteration, such as the microsomal triglyceride transfer protein (MTTP), apolipoprotein E and apoB[61,62].

Concerning the nutritional management of liver disease,

Table 5 Kilopascals and aspartate aminotransferase to platelet ratio index score values by the severity of liver fibrosis among chronic hepatitis C patients

Variable	Mild fibrosis	Advanced fibrosis	*P*-value
No. of patients, *n* (%)	35 (47.9)	38 (52.1)	-
kPa	6.5 ± 1.7	22.7 ± 13.4	< 0.001
APRI score	0.81 ± 0.33	1.78 ± 0.53	< 0.001

Quantitative values are expressed as mean ± SD. kPa: Kilopascals; APRI: Aspartate aminotransferase to platelet ratio index.

including HCV infection, the majority of international guidelines focus on the reduction of total fat and SFA intake[51,63] without taking into account the nutrigenetics and food cultures of individual populations. We advocate shifting towards a genome-based nutrition approach as a preventive and intervention strategy for chronic diseases given the fact that, worldwide, human populations differ[64]. Specifically, in the case of Mexico and most of Latin America, the people in these regions are genetically an admixture of Amerindian, Caucasian, and African ancestries with a heterogeneous inter-regional distribution[65,66]. Furthermore, 70% of the Mexican general population is overweight or obese due to the consumption of an obesogenic and hepatopatogenic diet that was previously described[4,14,64]. Thus, based on the gene-environmental interactions that currently prevail in the Mexican population, specific preventive strategies are crucial to diminish the progression of liver damage caused by alterations in lipid metabolism and inflammation.

In this study, the frequency of the *CD36* AA genotype (30.1%) was comparable to the pattern of distribution (28.4%) observed in non-diabetic individuals of Caucasian origin[24]. These findings are consistent with the high Caucasian ancestry that prevails among Mexican-Mestizos and HCV patients that have been previously reported[7], whereas different frequencies have been reported elsewhere[67-69]. Thus, we consider that the detection of the *CD36* genotype, as well as other nutrient-interacting genes[31-34] could be used as auxiliary tools to predict the adherence to dietary regimens and for the implementation of genome-based intervention

Table 6 Association of the cluster of differentiation 36 genotype with the severity of liver fibrosis among chronic hepatitis C patients

CD36 genotype	Mild fibrosis *n* (%)	Advanced fibrosis *n* (%)	Genotype comparison	Odds ratio (95%CI)	*P*-value
AA	6 (17.1)	16 (42.1)	AA *vs* GG	3.20 (0.70-14.52)	0.12
AG	23 (65.7)	17 (44.7)	AA *vs* AG	3.60 (1.16-11.15)	0.02
GG	6 (17.1)	5 (13.2)	AA *vs* AG/GG	3.51 (1.18-10.45)	0.02

CD36: Cluster of differentiation 36.

strategies[64] aimed at reducing fat intake and dyslipidemia in our population[27].

In conclusion, the AA genotype of the rs1761667 *CD36* polymorphism was associated with higher fat intake and more instances of advanced LF in CHC patients. However, further genomic studies are needed to analyze the role of the *CD36* polymorphism on liver disease in other populations within Mexico and worldwide.

COMMENTS

Background

Regardless of etiology, liver fibrosis (LF) pathogenesis is influenced by genetic and environmental factors, such as dietary intake. Diets that are high in saturated fatty acids have been associated with the pathological processes involved in liver fibrogenesis, including steatosis, inflammation, and insulin resistance. There is growing evidence that suggest that the lingual cluster of differentiation 36 (*CD36*) receptor regulates the motivation for fatty food consumption. Therefore, genetic variations in *CD36* expression could explain the global heterogeneity of fat linking and its association with chronic diseases. This study aimed to analyze the association of the *CD36* polymorphism (rs1761667) with dietary fat intake and LF in chronically infected hepatitis C patients.

Research frontiers

The results of this study contribute to the understanding of the specific gene-environmental interactions that occur among a population with an admixture genome. The role of *CD36* genetic variation on hepatitis C virus (HCV)-related liver disease or other chronic diseases in distinct populations worldwide requires further studies.

Innovations and breakthroughs

In this study, the authors provide evidence regarding the effect of the *CD36* (AA) risk genotype on the consumption of a high-fat diet and its association with LF in HCV patients.

Applications

The detection of the *CD36* genotype together with other nutrient-sensing genes could be useful for the implementation of genome-based intervention strategies aimed at reducing fat intake and dyslipidemia in chronic hepatitis C patients.

Peer-review

The authors of this paper evaluated the dietary fat intake and the degree of LF in patients chronically infected with hepatitis C based on the *CD36* genotypes. The results suggest that the risk AA genotype of the *CD36* polymorphism was associated with higher dietary fat intake and more instances of advanced LF in chronic hepatitis C patients.

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EVIDENCE-BASED MEDICINE

Therapeutic alternatives for the treatment of type 1 hepatorenal syndrome: A Delphi technique-based consensus

Juan P Arab, Juan C Claro, Juan P Arancibia, Jorge Contreras, Fernando Gómez, Cristian Muñoz, Leyla Nazal, Eric Roessler, Rodrigo Wolff, Marco Arrese, Carlos Benítez

Juan P Arab, Rodrigo Wolff, Marco Arrese, Carlos Benítez, Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago 833-0024, Chile

Juan C Claro, Departamento de Medicina Interna and Programa de Salud Basada en la Evidencia Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago 833-0024, Chile

Juan P Arancibia, Sección de Gastroenterología, Departamento de Medicina, Hospital Clínico Universidad de Chile and Clínica Santa María, Santiago 838-0456, Chile

Jorge Contreras, Unidad de Gastroenterología, Universidad del Desarrollo, Clínica Alemana, Santiago 765-0568, Chile

Fernando Gómez, Cristian Muñoz, Servicio de Gastroenterología, Unidad de Trasplante Hepático, Hospital del Salvador, Facultad de Medicina, Universidad de Chile and Unidad de Gastroenterología, Clínica Alemana de Santiago, Clínica Indisa, Santiago 750-0922, Chile

Leyla Nazal, Clínica Las Condes y Servicio de Gastroenterología, Hospital Fuerza Aérea de Chile, Santiago 756-0171, Chile

Eric Roessler, Departamento de Nefrología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago 833-0024, Chile

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Correspondence to: Carlos Benítez, MD, Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Marcoleta #367, Santiago 833-0024, Chile. benitezc@gmail.com
Telephone: +56-2-23543820
Fax: +56-2-26397780

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Abstract

AIM

To propose several alternatives treatment of type 1 hepatorenal syndrome (HRS-1) what is the most severe expression of circulatory dysfunction on patients with portal hypertension.

METHODS

A group of eleven gastroenterologists and nephrologists performed a structured analysis of available literature. Each expert was designated to review and answer a question. They generated draft statements for evaluation by all the experts. Additional input was obtained from medical community. In order to reach consensus, a modified three-round Delphi technique method was used. According to United States

Preventive Services Task Force criteria, the quality of the evidence and level of recommendation supporting each statement was graded.

RESULTS

Nine questions were formulated. The available evidence was evaluated considering its quality, number of patients included in the studies and the consistency of its results. The generated questions were answered by the expert panel with a high level of agreement. Thus, a therapeutic algorithm was generated. The role of terlipressin and norepinephrine was confirmed as the pharmacologic treatment of choice. On the other hand the use of the combination of octreotide, midodrine and albumin without vasoconstrictors was discouraged. The role of several other options was also evaluated and the available evidence was explored and discussed. Liver transplantation is considered the definitive treatment for HRS-1. The present consensus is an important effort that intends to organize the available strategies based on the available evidence in the literature, the quality of the evidence and the benefits, adverse effects and availability of the therapeutic tools described.

CONCLUSION

Based on the available evidence the expert panel was able to discriminate the most appropriate therapeutic alternatives for the treatment of HRS-1.

Key words: Hepatorenal syndrome; Delphi; Consensus; Evidence-based medicine; Treatment

Core tip: The available evidence for the treatment of type 1 hepatorenal syndrome (HRS-1) was evaluated. The role of terlipressin and norepinephrine was confirmed as the pharmacologic treatment of choice. On the other hand the use of the combination of octreotide, midodrine and albumin without vasoconstrictors was discouraged. The role of several other options was also evaluated and the available evidence was explored and discussed. Liver transplantation is considered the definitive treatment for HRS-1 and the necessary conditions to optimize the recovery of renal function was also discussed.

Arab JP, Claro JC, Arancibia JP, Contreras J, Gómez F, Muñoz C, Nazal L, Roessler E, Wolff R, Arrese M, Benítez C. Therapeutic alternatives for the treatment of type 1 hepatorenal syndrome: A Delphi technique-based consensus. *World J Hepatol* 2016; 8(25): 1075-1086 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i25/1075.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i25.1075

INTRODUCTION

Hepatorenal syndrome (HRS) is a severe disease strictly related to the presence of portal hypertension (PHT). The cumulative probability of HRS in patients with cirrhosis and ascites was initially reported as 18% at one year and 39% at five years[1]. More recently and employing the Ascites Club criteria, the incidence of HRS was estimated as 7.1% in a cohort that was followed for 41 ± 3 mo[2]. Table 1 depicts the diagnostic criteria proposed by the Ascites Club for the diagnosis of HRS[3]. These criteria are the result of a consensus based on clinical knowledge of the condition, and at this time, there are no biochemical tests clinically available for the diagnosis of HRS. Two types of HRS have been defined by the Ascites Club. Type 2 (HRS-2) is a slowly progressive disease, clinically expressed as refractory ascites with an average median survival of approximately six months. In contrast, type 1 HRS (HRS-1) is a catastrophic disease characterized by a rapid decrease in glomerular filtration rate[3], and it is considered the most extreme expression of circulatory dysfunction secondary to PHT. Its diagnosis requires the exclusion of intrinsic renal disease, hypovolemia, shock and exposure to nephrotoxic drugs. It has a very poor prognosis with a mean survival of only two weeks without treatment[4]. Thus, HRS-1, is considered one of the most severe complications of cirrhosis and PHT, and it represents a therapeutic challenge for hepatologists.

Several alternatives have been proposed for the treatment of HRS-1. Although liver transplantation (LT) appears to be the logical definitive treatment for this condition, other interventions are needed while the patient is on the waitlist, sometimes for several weeks before LT. Moreover, for a myriad of reasons, some patients cannot be considered appropriate candidates for LT. Hence, LT it is not a proper alternative for every patient, and other therapeutic alternatives must be considered.

Recently, the Chilean Gastroenterology Society provided a consensus for the treatment of HRS-1. The aim of this article is to show the results of the consensus and to suggest a therapeutic approach based on the best available evidence.

MATERIALS AND METHODS

Participants and literature search

The consensus organizing committee [under the sponsorship of the Chilean Society of Gastroenterology (http://sociedadgastro.cl)] assembled a group of adult gastroenterologists and nephrologists with expertise in the management of advanced liver disease patients and evidence-based medicine. The panel generated a list of questions relevant for the treatment of HRS-1. To address these questions, two members of the panel (JCC and JPA) performed separate searches in PubMed®, retrieving reports published in English or Spanish through June 2014. The search results were distributed. Simultaneously, each individual panelist contributed additional data and abstracts presented at meetings. Each expert was designated to review and answer a question. They generated draft statements for evaluation by all the experts; the answers were to

Table 1 Criteria for the diagnosis of hepatorenal syndrome

HRS
Presence of cirrhosis and ascites
Serum creatinine > 1.5 mg/dL (or 133 micromoles/L)
No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 h of diuretic withdrawal and volume expansion with albumin (recommended dose: 1 g/kg per day up to a maximum of 100 g of albumin/day)
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/d, microhematuria (> 50 RBCs/high power field, and/or abnormal renal ultrasound scanning
HRS-1
Rapidly progressive renal failure defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL or 220 μmol/L in less than 2 wk
Although it may appear spontaneously, HRS-1 often develops with a precipitating event, particularly spontaneous bacterial peritonitis
HRS-1 occurs in the setting of an acute deterioration of circulatory function (arterial hypotension and activation of the endogenous vasoconstrictor systems) and is frequently associated to rapid impairment in liver function and encephalopathy
HRS-2
Characterized by a moderate renal failure (serum creatinine greater than 1.5 mg/dL) which follows a steady or slowly progressive course. It appears spontaneously in most cases
HRS-2 is frequently associated with refractory ascites. Survival of patients with HRS-2 is shorter than that of patients with ascites but without renal failure

HRS: Hepatorenal syndrome; HRS-2: Type-2 HRS; HRS-1: Type-1 HRS.

Table 2 Levels of evidence according to the study design

Level of evidence	Description
Type Ⅰ	Evidence obtained at least from one well-designed, randomized, controlled[1] trial or from a systematic review of randomized clinical studies
Type Ⅱ	Ⅱ-1 evidence obtained from non-randomized, prospective, controlled[1] studies
	Ⅱ-2 evidence obtained from cohort observational studies[2] or case-control studies, preferably multi-centric
	Ⅱ-3 evidence obtained from case series
Type Ⅲ	Opinion of authorities on the subject matter based on expertise, expert committees, case reports, pathophysiological studies or basic science studies

[1]A controlled study is a study where the intervention is managed by the researcher; [2]An observational study is a study where the intervention is not controlled by the researcher.

be supported through a review of the literature. The quality of the evidence (Table 2) and the level of recommendation (Table 3) were graded following the United States Preventive Services Task Force criteria[5,6].

Consensus methodology

Initially, each expert wrote a draft recommendation statement and sent to organizing committee for evaluation and distribution among the entire panel. A 1 to 5 Likert scale (where 1 means "totally disagree" and 5 "totally agree") was used to measure agreement. To reach a final consensus a modified three-round Delphi technique method was used as described by Arab *et al*[7].

The final statements and recommendations were exposed during the XLI Chilean Congress of Gastroenterology and the Ⅰ Chilean Symposium on HRS-1 treatment in Coquimbo, Chile, in November 2014. The audience of approximately 450 physicians voted in real-time. The approved final recommendations (those with average scores ⩾ 4 on the Likert scale) are presented below.

Statistical analysis

Statistical review of the study was performed by a biomedical statistician. Level of agreement from the Delphi panel was expressed in mean ± SD.

RESULTS

Are vasoconstrictors effective in the treatment of HRS-1?

Terlipressin: Terlipressin is the vasoconstrictor of choice for the treatment of HRS-1, due to the large number of studies (and enrolled subjects) showing its effectiveness and its positive effects on survival. Terlipressin is a synthetic analogue of vasopressin acting through V1 receptors, increasing effective circulating volume, and by means of an increase in resistance in the splanchnic territory (which reduces portal pressure), it allows for the redistribution of the bloodstream, increasing renal perfusion[8]. Two important controlled, randomized and multicenter trials showed that terlipressin associated with albumin resulted in an improvement in renal function and could also reverse HRS-1[9,10]. A recently published meta-analysis, which included 320 subjects, proved 50% effectiveness with an OR of 7.5[11].

An Italian trial reported on the impact of terlipressin on the survival rate of HRS-1 patients. This randomized

Table 3 Levels of recommendation according to the available evidence

Recommendation	Description
A	The consensus strongly recommends the mentioned intervention or service. This recommendation is based on high quality evidence, with a benefit that significantly exceeds the risks
B	The consensus recommends the regular clinical use of the mentioned intervention or service. This recommendation is based on moderate quality evidence, with a benefit that exceeds the risks
C	The consensus does not make any positive or negative recommendation regarding the mentioned intervention or service. A categorical recommendation is not provided, because the evidence (of at least moderate quality) does not show a satisfactory risk/benefit relationship. The decision has to be made on a case-by-case basis
D	The consensus makes a negative recommendation against the mentioned intervention or service. The recommendation is based on at least moderate quality evidence, not showing any benefit or where the risk or damage exceeds the benefits of the intervention
I	The consensus concludes that the evidence is insufficient, due to low-quality studies, heterogeneous results or because the risk/benefit balance cannot be determined

trial included 52 subjects and showed a higher and more significant probability of survival in the group treated with terlipressin[12]. These findings were confirmed in a recent meta-analysis published by Cochrane, including 6 trials and 309 subjects, in which a statistically significant reduction in the mortality rate was observed in HRS-1 patients treated with terlipressin (RR = 0.76, 95%CI: 0.61-0.95)[13].

For the treatment of HRS-1, it is recommended to start the administration of terlipressin at an initial dose of 0.5-1 mg every 4-6 h as an IV bolus, with the possibility of increasing the dose up to 2 mg every 4-6 h if there is no proper response after 3 d; a proper response is defined as a reduction > 25% from basal plasma creatinine. It is recommended to maintain the administration of terlipressin until creatinine levels decrease to less than 1.5 mg/dL or for a maximum of 14 d[14]. Recurrence can occur after discontinuation of the therapy (< 20%)[15], in which case, the recommendation is to repeat a new cycle. The most frequent side effects are abdominal pain, diarrhea, arrhythmia and ischemic complications. The incidence of serious effects requiring suspension of terlipressin is close to 7%[16]. The presence of coronary, vascular or peripheral arterial ischemic disease must be considered a contraindication for the use of terlipressin and other systemic vasoconstrictors.

Recommendation: Treatment with terlipressin associated with albumin represents the drug therapy of choice in HRS-1 patients, and it is capable of reversing this condition and reducing the associated mortality rate (Evidence Level Ⅰ, grade of recommendation A, Agreement 5 ± 0).

Norepinephrine: Norepinephrine, an adrenergic agonist widely available in critical care units, is regarded as an alternative therapy in association with albumin, and it is effective and safe for the treatment of HRS-1[17]. Two randomized trials compared norepinephrine to terlipressin, reporting similar efficacy levels for reversal of HRS-1, as well as a comparable safety profile[18,19]. A recent study conducted in India enrolled 46 HRS-1 patients and reported results that confirmed previously published results[20], in addition to a recently published meta-analysis[21]. The effects of both drugs on mortality rates after 30 d and the probability of HRS-1 recurrence were also similar. In this meta-analysis, adverse effects were less common with the use of norepinephrine; however, only four studies were considered[21].

Norepinephrine is used as a continuous intravenous infusion at a 0.5 mg/h initial dose, with the purpose of achieving a > 10 mmHg increase in basal mean blood pressure (MBP). Accordingly, the dose can be adjusted by 0.5 mg/h every 4 h until a maximum dose of 3 mg/h is attained[20].

The significantly reduced cost and broad availability of norepinephrine are attractive[18,20]. It must be considered, however, that the number of cases treated with norepinephrine remains low, compared to the number of cases treated with terlipressin.

Recommendation: The use of norepinephrine associated with albumin represents an alternative to the use of terlipressin for the treatment of HRS-1; however, the currently available information is not as abundant in comparison to terlipressin (Evidence Level Ⅰ, grade of recommendation B, Agreement 5 ± 0).

Octreotide plus midodrine: The most studied vasoconstrictor used for the treatment of HRS-1 is terlipressin, and it results in complete reversal of the disease and a reduction in the associated mortality rate. However, many studies have assessed the use of other vasoconstrictors, with or without volume expansion agents, with variable results[22]. The association of midodrine, a systemic vasoconstrictor acting on alpha-adrenergic receptors, and octeotride, a synthetic analogue of vasopressin that inhibits the release of endogenous vasodilators, has shown a benefit to mortality rates in some small studies[23,24]. Regarding reversal, some studies have shown complete response with reduction in creatinine to values less than 1.5 mg/dL; nevertheless, other studies have shown contradictory results[25]. These two points were assessed in a meta-analysis published in 2012[26] that included 256 subjects from 3 separate observational studies. This meta-analysis showed a reduction in mortality rates at 30 d (OR = 0.33; 95%CI: 0.18-0.60) and 90 d (OR = 0.17; 95%CI: 0.03-0.96) but no conclusive results in terms of HRS-1 reversal; however, a delay in progression was observed, based on

a reduction in creatinine levels that was not statistically significant. It is important to note that, in the cases of the control groups in these three studies, two studies used dopamine, and one study used albumin. This reduction in the progression of renal function would be the mechanism believed to reduce the mortality rate, even without achieving HRS-1 reversal.

A randomized, monocentric trial including 23 subjects compared the association of midodrine and octeotride with noradrenaline[27], with complete response in 73% and 75% of subjects, respectively, without significant differences between the two therapeutic options. However, the small number of subjects included in this study limited the interpretation of the results. In contrast, a recent prospective, randomized trial compared the use of terlipressin plus albumin (27 subjects) with the combination of midodrine/octreotide plus albumin (22 subjects). This study showed a 70.4% response rate in the terlipressin branch *vs* a 28.6% response rate in the midodrine/octreotide branch. Moreover, the complete response rate was significantly higher in the terlipressin branch [55.5% *vs* 4.8% in the midodrine/octreotide group ($P < 0.001$)], showing low efficacy in terms of complete response in the midodrine/octreotide group[28]. These results were consistent with the low reversal rate described in previous studies.

Some studies have suggested that an increase in MBP is necessary for reverting alterations in renal hemodynamics specific to HRS-1; this increase is greater in patients responding to vasoconstrictor treatment compared with non-responding patients, regardless of the vasoconstrictor used. In a joint analysis of 501 patients from 21 studies, Velez *et al*[29] proved a significant correlation between an increase of 10 to 15 mm in MBP and the HRS-1 patient's response to treatment, with improvement in renal function. Other studies have not been able to prove this association. The main limitation of the study by Velez *et al*[29] is that it gathered information from previous studies that were not designed to assess the measured result. Therefore, their study cannot be regarded as having sufficient evidence for issuing a recommendation.

With regard to the safety and efficacy of the use of midodrine and octreotide, these data were assessed in a retrospective study[30] including 60 HRS-1 patients, compared to 21 patients treated only with albumin. Midodrine treatment combined with octeotride was not associated with significant adverse effects.

Recommendation: Although the midodrine-octeotride combination is a safe treatment with easy administration, its beneficial effects on survival and improvement in renal function have not been consistent across trials. Therefore, we do not recommend its use for the treatment of HRS-1 (Evidence Level Ⅰ, grade of recommendation B, Agreement 4.6 ± 0.5).

Vasopressin: Vasopressin has been proposed as a vasoconstrictor for the treatment of HRS-1 in some countries where no other therapies are available.

A retrospective study[31] compared the use of vasopressin alone and in combination with octeotride in HRS-1 patients *vs* the use of octeotride. This study showed a reduction in creatinine to values < 1.5 mg/dL with the use of vasopressin with or without octeotride *vs* octeotride alone (42% *vs* 38% *vs* 0%, respectively, $P = 0.001$), with an OR of 6.4 as well as an improvement in the survival rate and the possibility of being candidate for LT.

The dose required for achieving this objective has not yet been established. The aforementioned study required a dose of 0.23 + 0.19 U/min for a period of 5 to 9 d. In contrast, the use of low doses of vasopressin (1 U/h)[32] was effective for the restoration of urine volume in HRS-1 patients and patients with congestive heart failure, without improving the overall prognosis of the patients or their creatinine levels.

The use of vasopressin requires strict monitoring to avoid adverse effects associated with ischemic phenomena.

Recommendation: We do not recommend the use of vasopressin for the treatment of HRS-1, due to several adverse effects and the lack of randomized, clinical trials supporting its use (Evidence Level Ⅱ-2, grade of recommendation Ⅰ, Agreement 4.8 ± 0.3).

Efficacy of the use of albumin

The use of human albumin in cirrhosis is based mainly on its hemodynamic properties, improving oncotic pressure in patients with circulatory disorders, and it is characterized by dilatation of the splanchnic territory, effective hypovolemia and activation of the renin-angiotensin-aldosterone system. In addition, albumin has antioxidant and immunomodulatory functions; albumin also has the capacity to transport and metabolize other substances and has hemostatic and endothelial stabilization effects. In cirrhotic patients, both plasma albumin concentration and its functional properties are diminished, becoming even more severe depending on the level of the patient's renal failure[33].

The aforementioned situation has been the rationale for the use of albumin in decompensated cirrhosis. The main evidence in favor of its use is in the prevention of renal failure, both in the presence of spontaneous bacterial peritonitis and after a large-volume paracentesis.

In HRS-1, circulatory disorders are established at its highest levels, and by definition, these disorders are not reversed by the administration of albumin alone, the use of which is commonly suggested to expand intravascular volume and to improve cases of prerenal failure, thus disregarding the HRS-1 diagnosis in these patients[3].

Vasoconstrictors are the basis of HRS-1 treatment, and in the majority of well-designed, prospective and randomized studies, they have been associated with the use of albumin as a plasma expander and compared to the isolated use of albumin[9,12]. In these studies, there has been evidence of a significant difference in favor of combined therapy regarding HRS-1 reversal,

improvement of renal function, MBP and diuresis.

The purpose of a meta-analysis performed by Dobre *et al*[11] was to prove the usefulness of terlipressin with or without albumin, compared with placebo with or without albumin. The study showed that HRS-1 reversal using the first alternative was significantly more common, with an OR of 7.47. Of the six studies included in the meta-analysis, only 1 did not use albumin, and it was the oldest (1998) and had the smallest number of subjects[11], proving that the majority of researchers have considered albumin to be a part of the basic treatment for HRS-1 patients.

Regarding the assumption that albumin provides an additional benefit to the use of vasoconstrictors alone, we only found evidence of an observational study designed to answer this question. Seventy-seven percent of the patients who used terlipressin and albumin experienced a resolution of HRS-1, compared to 25% in the group that used terlipressin alone. In addition, the group of patients treated with terlipressin plus albumin showed significant improvement in MBP and a reduction in the activation of the renin-aldosterone system[34].

Along these same lines, the retrospective study by Moreau *et al*[35] assessing the usefulness of terlipressin in HRS-1 showed that the respondent group used albumin in 79% of cases *vs* 68% in the non-respondent group, which was not a significant difference.

There is no evidence available that other fluids (such as crystalloids) can have a similar effect to albumin associated with vasoconstrictors. No studies have been designed for this purpose, and no such studies are likely to be performed because the use of crystalloids increases ascites and, therefore, intra-abdominal pressure, which in turn affects renal perfusion and reduces the likelihood of improvement of renal and circulatory failure. An observational study, in which a large-volume paracentesis with reposition of albumin was performed in HRS-1 patients, showed partial improvement of renal function, supporting the hypothesis that a reduction in intra-abdominal pressure could be useful for renal perfusion recovery[36].

Recommendation: The use of albumin with vasoconstrictors is the therapy of choice for treating HRS-1. The use of albumin without vasoconstrictors is only recommended in the stage prior to HRS-1 diagnosis to exclude patients with prerenal failure (Evidence Level Ⅱ-2, grade of recommendation B, Agreement 4.8 ± 0.3).

Efficacy of the use of a trans-jugular intrahepatic portosystemic shunt

There is scarce evidence for the use of trans-jugular intrahepatic portosystemic shunt (TIPS) in HRS-1. In a study including 16 patients, 6 with HRS-1 and 10 with HRS-2 and Child-Pugh scores of 7-9, a duplication of creatinine clearance in serum and increased sodium concentration excreted in the urine were observed two weeks after the TIPS procedure. Three of the HRS-1 patients required hemodialysis during the progression of the disease, and 12 and 18 d after the TIPS procedure, two patients were able to stop hemodialysis. There was an improvement in renal function, even after 6-8 wk. Three of the 16 HRS-1 and HRS-2 patients did not respond, and they died within a 6-wk period[37]. A prospective, non-randomized, phase Ⅱ study included 41 patients with cirrhosis and HRS without indications for transplantation: 21 with HRS-1 and 20 with HRS-2. Thirty-one of these patients (14 type 1 and 17 type 2) received TIPS and were followed for a mean of 24 mo. The use of TIPS in HRS-1 and HRS-2 patients reduced significantly ($P < 0.001$) the hepatic venous pressure gradient and increased creatinine clearance and sodium excretion. Those patients who received TIPS showed higher survival rates than those who did not. There was only one death related to the procedure (3.2%). It is important to note that the HRS-2 patients had a significantly greater benefit and were identified as a variable independently correlated with survival[38]. Another uncontrolled study assessed 7 patients with cirrhosis and HRS-1. The TIPS procedure was associated with gradual improvements in the glomerular filtration rate (9 to 27 mL/min) and blood urea nitrogen and creatinine reduction. The majority of patients also showed a reduction in the activity of the renin-angiotensin system and in the sympathetic nervous system, suggesting an improvement in hemodynamic parameters. The average survival after the TIPS procedure was approximately 5 mo, which was longer than the survival rate expected for these patients[39].

Unfortunately, many HRS-1 patients are too sick to undergo a TIPS procedure, mainly because the procedure can present complications such as deterioration of hepatic encephalopathy and liver function (increased bilirubin levels), bleeding and intravenous contrast-induced nephropathy[40]. In a study that designed a predictive model for determining the survival rate after a TIPS procedure, patients with HRS-1 due to alcoholic cirrhosis or chronic cholestatic disease showed a 25% mortality rate 90 d after the procedure and a mortality rate of 80% in patients with cirrhosis due to other causes[41].

In general, these results suggest that TIPS could be considered for patients with relatively preserved liver function and as a bridge therapy to LT. However, due to the risks associated with the procedure and the lack of well-designed studies, this procedure should be considered only as a last resource.

Recommendation: Due to the lack of evidence, the consensus considers that the use of TIPS shall not be recommended in HRS-1 patients (Evidence Level Ⅱ-2, grade of recommendation Ⅰ, Agreement 4.7 ± 0.4).

Extracorporeal substitution therapies

Role of renal replacement therapies for the management of acute renal failure associated with HRS-1: If there is no response to proven pharmacological strategies, acute renal failure (ARF) in HRS-1 takes an irreversible course unless the patient undergoes LT. At this point, patients develop oliguria, hydrosaline balance

disorders and severe metabolic disorders that can lead to the prescription of renal replacement therapies (RRTs).

For patients who will not undergo LT, the potential benefit of RRT is controversial due to the high morbi-mortality associated with RRT, basically determined by poor hemodynamic tolerance and/or hemorrhages associated with liver failure complications[42].

For patients who are non-respondent to pharmacological therapy or TIPS, who are waiting for a LT or who are under evaluation to undergo the surgery, the use of RRT is advised as a bridge to LT. In a retrospective study developed by Keller *et al*[43], the survival rate of patients with HRS-1 was 44% in the group that received RRT *vs* 10% in the group that did not receive the therapy. However, this higher survival rate could be related to reduced RRT tolerance, which could increase the number of hospitalizations. In a report of 4 patients who received hemodialysis while waiting for LT, Capling *et al*[44] observed an average survival of 236 d (31 to 460 d). All of the patients survived the initial event and were discharged, but 33% of the days gained were then spent in hospitalization due to intercurrent diseases. The most common cause of hospitalization was hepatic encephalopathy; the authors believe that avoiding lactulose during the days when the patient undergoes dialysis, to prevent diarrhea events, might have been a contributing factor[44].

Efficacy, safety and the best RRT modality in HRS-1 patients have not been systematically assessed. Potential advantages of continuous *vs* intermittent RRT include slower removal of fluids with higher hemodynamic stability and slower control of solute concentrations, which is why many clinicians prefer continuous RRT in patients with hemodynamic instability and in patients with evidence of cerebral edema[45]. In two studies, Davenport and Detry proved that continuous RRT was better tolerated than intermittent hemodialysis in patients with liver failure, evidenced by greater cardiovascular stability, gradual correction of hyponatremia and less variation in intracranial pressure[46,47].

Recommendation: We recommend the initiation of RRT in patients with HRS-1 refractory to pharmacological therapy who are candidates for LT. In patients with hemodynamic instability and/or evidence of cerebral edema, we recommend the use of other continuous RRTs; We recommend maintaining RRT in patients with HRS-1 who are candidates for LT and who must be temporarily removed from the waiting list because they have developed an intercurrent disease (Evidence Level Ⅱ-3, grade of recommendation C, Agreement 4.6 ± 0.5).

Extracorporeal liver support with albumin dialysis (molecular adsorbent recirculating system): The molecular adsorbent recirculating system (MARS) is an extracorporeal liver support that, by means of recirculating albumin dialysis, helps to remove water-soluble substances, as well as protein-bound substances. The removal function has been shown to reduce bilirubin, ammonium, urea nitrogen, creatinine, fatty acids and bile salts, which are all substances that, in high concentrations, are related to liver and renal failure. As expected, the effect is temporary, and if there is no improvement in liver function, these parameters change again in the short term[48,49]. This system does not improve hepatic synthesis; it is used as a depuration system, comparable to renal hemodialysis. In contrast, some small studies have shown an improvement in the hemodynamics of these patients, with increased blood pressure that had been reduced due to the hyperdynamic circulation characteristic of liver failure. The mechanism of the aforementioned benefit would be depuration and the reduction of substances such as renin, angiotensin and aldosterone, which are responsible for the hemodynamic disorders related to liver failure[48]. A recent retrospective, uncontrolled study showed that, of 32 HRS-1 patients receiving MARS therapy for an average of 3.5 ± 1.5 sessions, 13 (40%) experienced an improvement in renal function, but only 9 (28%) showed complete response in the form of renal function recovery. In contrast, of the 15 patients who survived > 28 d, only 9 achieved this stage without transplantation, and of these 9 patients, only 2 showed complete renal response using MARS therapy[50]. Therefore, it has been suggested that MARS therapy is capable of improving HRS-1 through the removal of vasodilators; however, this effect would more probably be caused by MARS's hemofiltration function, which is an effect that is similar to conventional hemodiafiltration.

As mentioned, non-treated HRS-1 patients show high mortality rates in the short term. The effect of MARS therapy in this stage is controversial. There have been three studies that have not shown any benefit in terms of survival[51-53], and another two studies, both from the same author, did not show benefits[49,54].

Finally, a recent (2013) multi-center, randomized study[51] included patients with acute or chronic liver failure and randomized a total of 189 patients to a group with standard medical therapy plus MARS therapy (95 patients) *vs* another group using only standard medical therapy (94 patients); this study observed no benefit in survival at 28 d in the MARS group. A sub-analysis of the HRS-1 patients that were included (48 in the MARS group and 47 in the control group) also did not show differences in the survival rates.

Recommendation: We do not recommend the use of extracorporeal liver support with albumin dialysis (MARS) for the treatment of HRS-1 (Evidence Level Ⅰ, grade of recommendation D, Agreement 4.8 ± 0.3).

Efficacy of LT: Survival and renal function

LT is the therapy of choice for HRS-1 patients because it not only improves renal failure but also improves the underlying diseases, *i.e*., cirrhosis and PHT. Post-transplantation survival in HRS-1 patients seems to be lower than for transplanted patients without HRS-1; however, survival is considerably higher compared with

that in HRS-1 patients without transplantation. In a retrospective study, the survival of HRS-1 transplanted patients after 1 and 3 years was 80.3% and 76.6%, respectively, and it was 90.7% and 85.3%, respectively, for recipients without HRS-1[55].

Although we can consider that treating HRS-1 with vasoconstrictor agents can improve post-transplant results by improving renal function before the procedure, there is no clear evidence of this effect. In a clinical study, 99 patients were randomized to receive terlipressin or placebo. Of these patients, 35% received LT. Subjects receiving albumin plus terlipressin showed a 100% survival rate among transplanted patients and a 34% survival in non-transplanted patients after 6 mo. In contrast, subjects receiving only albumin showed 94% survival in transplanted patients and only 17% survival in non-transplanted patients after 6 mo. The authors concluded that the use of terlipressin has no impact on post-transplant survival. The sole benefit of the use of terlipressin in patients who will undergo transplantation seems to be the facilitation of the use of calcineurin inhibitors post-transplant, reducing the need for anti-IL2 antibodies[56].

The majority of HRS-1 patients experience an improvement in renal function post-transplant; therefore, there seems to be no advantage in performing double liver and renal transplantation *vs* single LT. In a Chinese observational study, 32 HRS-1 patients received transplantation, and of these patients, 8 received dialysis, showing that 94% of the patients recovered renal function in an average of 24 d, with 65% survival after 1 year[57]. In another observational study with 28 patients, with an average MELD score of 30 ± 6, only 58% of patients recovered renal function. Four patients died, of whom 3 showed resolution of HRS-1[58]. However, patients that did not experience any improvement in renal function post-transplant showed poorer survival rates[59].

In a recent retrospective study, 62 HRS-1 patients received transplantation, with an average basal creatinine of 3.35 mg/dL and an average MELD score of 35 ± 1. The progression time of HRS-1 before transplantation was 18 d. Eleven patients continued dialysis after the surgery, and 5 patients died. Survival after 1 year in the patients who recovered renal function was 97% *vs* 60% in the group that did not show any improvement in renal function. After one year, the creatinine levels in the group with HRS-1 resolution were similar to the creatinine levels in the group of transplanted patients without HRS-1. The only factor associated with the non-resolution of HRS-1 after transplantation was the period of time on dialysis pre-transplantation. For each day of dialysis, the patient has a 6% increase in the risk of non-resolution of HRS-1. A patient who is on dialysis for more than 14 d has a 9.2 times greater relative risk of non-resolution of HRS-1[60].

Despite these findings, apart from the duration of dialysis time before transplantation, predictive factors for the improvement of renal function after transplantation have not been clearly established. Patients with ARF requiring dialysis more than two times per week for more than 4 wk must be assessed for double liver and renal transplantation, considering the risk factors at the time of the surgery, such as hypertension, diabetes and older age[60,61].

Recommendation: LT can be considered the definitive treatment for HRS-1 patients. HRS-1 patients must receive treatment with vasopressors before LT because it could improve the subsequent results. Patients requiring dialysis for long periods of time (> 4 wk) must be considered for combined liver-kidney transplantation (Evidence Level Ⅱ-2, grade of recommendation B, Agreement 4.6 ± 0.5).

DISCUSSION

LT is considered the treatment of choice for HRS-1[62]. It is the only therapy able to reverse this condition completely, resolving circulatory dysfunction and the consequences of cirrhosis and liver failure[63]. Thus, survival can be dramatically improved after LT[55]. In fact, the 180 d survival rate was 97% in a recent study[56]. In another recent study, the one- and three-year survival rates were 80.3% and 76.6%, respectively[55]. Interestingly, the impact of pharmacologic treatment on the outcomes after LT was recently evaluated. In the study by Boyer *et al*[56], the use of terlipressin plus albumin had no impact on post-transplant survival. However, this is not an argument for neglecting the importance of the treatment of HRS-1, especially considering that the time elapsed between enlistment and transplantation could be weeks. In this regard, an effort to recover renal function before LT is advisable. Although it seems to be the most frequent scenario, not every patient recovers renal function after LT. In a very recent study, Wong *et al*[64] evaluated the survival of liver recipients who experienced reversal of HRS-1 after LT, compared to the survival of patients who did not. In this study, 75.8% of the recipients had a reversal of HRS-1 after LT. The one-year survival rate after LT was 97% for patients who had a reversal of HRS-1 and 60% for those who did not[64]. Thus, for all of the aforementioned reasons, LT is a desirable approach for HRS-1 patients.

Nonetheless, there are at least two obstacles that render access to LT difficult: (1) the scarcity of liver grafts, which dramatically reduces the likelihood of these patients receiving a transplant as rapidly as they should; and (2) the existence of severe comorbidities or conditions that make LT not plausible. Hence, there is an important role for different therapeutic approaches than could be used as alternatives or "bridges" to LT.

Thus, several therapeutic tools have been evaluated. As expected, the quality of these studies, the efficacy of the interventions, and their availability, costs and adverse effects are, of course, very different. It was the purpose of this panel of experts to determine the treatments with greater efficacy, based on studies with the highest quality available.

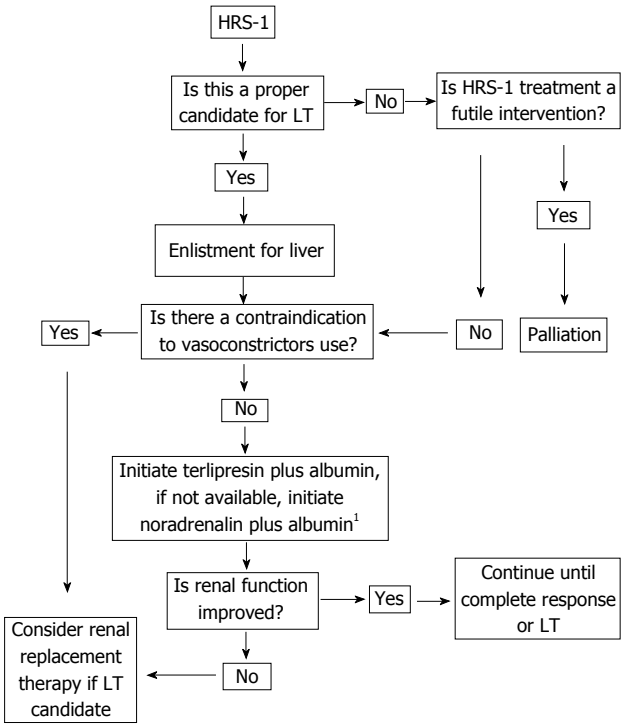

Figure 1 Therapeutic algorithm for the treatment of type 1 hepatorenal syndrome. [1]Doses must be adjusted according to diuresis or creatinine levels. HRS-1: Type 1 hepatorenal syndrome; LT: Liver transplantation.

Based on the available evidence, the expert panel agrees that the best evidence for the treatment of HRS-1 supports the use of vasoconstrictors as a treatment of the choice, specifically terlipressin, based on a recent systematic review[13]. On the other hand, noradrenalin seems to be as effective as terlipressin. In fact, a recent systematic review evaluated the efficacy of noradrenalin compared to terlipressin. Only four studies were included (154 randomized patients). The authors report a similar rate of reversal of HRS-1, 30 d mortality and recurrence. Thus, in this study, its effect on renal function seemed to be completely comparable to that of terlipressin[21], and its use seems to be adequate when terlipressin is not available. Nonetheless, these findings are more difficult to interpret because two studies included patients with HRS-2. In this regard, the expert panel recommends the use of noradrenalin as a second choice if terlipressin is not available. Another strategy based on the use of vasoconstrictors is the combination of octreotide plus midodrine (also in combination with albumin). Very interestingly, a recent study compared the use of terlipressin plus albumin with the combination of octreotide, midodrine and albumin. Notably, the rate of complete response was 55.5% in the terlipressin group and 4.8% in the octreotide-midodrine group ($P < 0.001$)[28]. Based on these results, the panel of experts did not recommend the use of octreotide plus midodrine for the treatment of HRS-1.

The use of vasopressin was not recommended by the expert panel due to the scarcity and poor quality of the evidence, in addition to the incidence of ischemic side effects[31].

Another issue evaluated by the panel was the use of albumin as a plasma expander. Most of the studies that evaluated the use of vasoconstrictors combined them with albumin. However, Ortega *et al*[34] conducted a prospective, non-randomized study that compared the use of terlipressin with and without albumin. A complete response was observed in 77% of patients receiving albumin and in 25% of those who did not receive albumin. In contrast, there is a lack of evidence suggesting that the apparent benefit of using albumin combined with vasoconstrictors cannot be substituted for another colloid or crystalloids. However, considering that the benefit of vasoconstrictors has been proved in combination with albumin, this panel decided to recommend its use every time that vasoconstrictors are indicated.

The use of a TIPS has been tested in only a few patients; however, there have been no randomized, controlled studies, and it has not been compared to the use of vasoconstrictors. In contrast, the associated adverse effects, mostly hepatic encephalopathy, have made the use of the TIPS procedure difficult. For these reasons, the expert panel does not recommend its use.

The MARS has also been tested as an alternative for the treatment of HRS-1. However, its benefits have not been consistently demonstrated. In fact, in a recent randomized, controlled trial, MARS was employed for patients with acute or chronic liver disease, including 95 patients with HRS-1. No benefit on survival was demonstrated[51]. Hence, the panel of experts does not recommend its use.

RRT use is considered controversial in cirrhotic patients with HRS-1 when LT is not considered an option because of the morbidity and mortality associated with the procedure and with liver failure[42]. Although the literature is scarce in this topic, RRT seems to prolong short term survival[43], potentially improving the probability of receiving a liver graft. Thus, although disputable, the expert panel decided to recommend the use of RRT only in those patients listed for LT.

The present consensus is an important effort that intends to organize the available strategies based on the available evidence in the literature, the quality of the evidence and the benefits, adverse effects and availability of the therapeutic tools described. This attempt has been synthesized in the algorithm described in Figure 1. We hope that it will be a useful tool for guiding the management of HRS-1 patients.

COMMENTS

Background

Hepatorenal syndrome (HRS) is a severe condition strictly related to the presence of portal hypertension and ascites. It has a very poor prognosis with a mean survival that only reaches two weeks. Several therapeutics alternatives have been evaluated. Based on the best available evidence the authors attempt to define the best therapeutic choice considering its availability and the clinical characteristics of each patient.

Research frontiers

Although several therapeutic alternatives have been proposed the quality of the

evidence is heterogeneous and it can be difficult to discriminate the best option on each circumstance. A careful evaluation of the evidence is necessary to make appropriate recommendations.

Innovations and breakthroughs

This is the first published consensus about the treatment of HRS. A significant effort has been made to evaluate the quality of the available literature to generate appropriate recommendations.

Applications

The information included on this consensus will be a valuable tool to determine the best therapeutic option for HRS based on the best available evidence, the availability of each intervention and the particular condition of the patient.

Terminology

Delphi-technique method was used to reach consensus. A panel of experts voted on a 1 to 5 Likert scale (where 1 means "totally disagree" and 5 "totally agree"). Approved recommendations (those with average score $\geqslant$ 4 on the Likert scale) are presented; Level of evidence: The quality of the evidence is classified in three types. Thus, type Ⅰ is obtained from well design, randomized trials or systematic reviews. Type Ⅱ is obtained from studies of lower quality (*i.e.*, non-randomized trials, case-control studies or case series). Type Ⅲ is obtained from opinion of authorities on the subject matter based on expertise, expert committees, case reports, pathophysiological studies or basic science studies; Levels of recommendation are classified in five categories (A, B, C, D, I) where A corresponds to the stronger recommendation to support a determined intervention and Ⅰ classifies situations where the evidence is insufficient to generate a recommendation (see Table 3 on the manuscript).

Peer-review

The study is well organized and properly processed. The conclusion is reasonable.

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SYSTEMATIC REVIEWS

Hydatid cyst of the gallbaldder: A systematic review of the literature

Roberto Gómez, Yousef Allaoua, Rafael Colmenares, Sergio Gil, Pilar Roquero, José M Ramia

Roberto Gómez, Yousef Allaoua, Rafael Colmenares, Sergio Gil, Pilar Roquero, Faculty of Medicine, Universidad de Alcalá, 28805 Alcalá de Henares, Spain

José M Ramia, Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario de Guadalajara, 19002 Guadalajara, Spain

Author contributions: Gómez R, Allaoua Y, Comenares R, Gil S and Roquero P analyzed data; Gómez R, Allaoua Y, Comenares R, Gil S, Roquero P and Ramia JM wrote the manuscript; Ramia JM performed research.

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Correspondence to: José M Ramia, MD, PhD, FACS, FRCS, Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario de Guadalajara, C/Donantes de Sangre s/n. 7ª planta, 19002 Guadalajara, Spain. jose_ramia@hotmail.com
Telephone: +34-61-6292056
Fax: +34-94-9209218

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Abstract

AIM

To evaluate all the references about primary gallbladder hidatidosis looking for best treatment evidence.

METHODS

Search: 1966-2015 in MEDLINE, Cochrane Library, SciELO, and Tripdatabase. Key words: "gallabladder hydatid disease" and "gallbladder hydatid cyst". We found 124 papers in our searches but only 14 papers including 16 cases were about hydatid cyst of the gallbladder (GBHC).

RESULTS

Eight cases of GBHC were women and seven men. One not mentioned. Median age was 48.3 years. The most frequent clinical symptom was abdominal pain (94%) usually in the right upper quadrant. Ultrasound was performed in ten patients (62.5%) but in most cases a combination of several techniques was performed. The location of the cysts was intravesicular in five patients. Five patients presented GBHC and liver hydatid cysts. Two patients presented cholelithiasis and one choledocholithiasis. The most frequent surgical technique was cholecystectomy by laparotomy (81.25%). Simultaneous surgery of liver cysts was carried out in five cases. Eleven patients did not present postoperative complications, but one died. The mean hospital stay was seven days. No recurrence of GBHC was recorded.

CONCLUSION

In GBHC, the most frequent symptom is right hypocondrium pain (evidence level V). Best diagnostic methods are ultrasound and computed tomography (level V, grade D). Suggested treatment is open cholecystectomy and postoperative albendazole (level V, grade D) obtaining good clinical results and none relapses.

Key words: Hydatid cyst; Gallbladder; Cholecystectomy; Review; Hydatidosis

Core tip: Systematic review of gallbladder hydatidosis has not previously done. We have performed a systematic search trying to define best diagnostic procedures and best therapeutical strategies.

Gómez R, Allaoua Y, Colmenares R, Gil S, Roquero P, Ramia JM. Hydatid cyst of the gallbaldder: A systematic review of the literature. *World J Hepatol* 2016; 8(25): 1087-1092 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i25/1087.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i25.1087

INTRODUCTION

Hydatid disease is a zoonotic infection found all over the world, which is caused by the larval stage of parasites of the *Echinococcus species*. *Echinococcus granulosus* is the most frequent (95% of cases); other species such as *Echinococcus multilocularis* are rare (5%). Hydatid disease is endemic in cattle-raising regions like the Mediterranean countries, Africa, South America, Middle East, Australia and New Zealand[1,2].

Echinococcus granulosus lives in the intestine of dogs and other wild canines, which are the definitive hosts. Humans are accidentally infected *via* the fecal-oral route. Larval embryos pass through the intestinal wall and reach the liver through the portal system. Subsequently, through the liver and lungs, parasites reach the arterial circulation and may spread through the rest of the organs[1-3]. The larvae can remain and develop into hydatid cyst anywhere in the body, but liver (70%) and lungs (20%) are the most commonly affected sites.

Primary hydatid cyst of the gallbladder (GBHC) is an exceptional location for hydatidosis, and its pathogenesis is not completely clear. While the literature on liver hydatid disease is abundant, references to the primary involvement of the gallbladder are limited to clinical cases and so it is difficult to reach meaningful conclusions[3-16]. In this paper we present a systematic review of the literature on GBHC published to date.

MATERIALS AND METHODS

Search strategy

We introduced the following keywords in the MEDLINE (PubMed), Tripdatabase, SciELO and Cochrane Library databases: "gallbladder hydatid disease (GHD)" and "gallbladder hydatid cyst (GHC)" without restrictions on publication date or author until 31 December 2015[17]. The first selection of papers was made after reading title and abstract, and in case of doubt, after reading the full text. A flowchart is shown in Figure 1.

Our results were as follows: (1) zero results in SciELO; (2) 2 results for both searches (GHD and GHC) in the Cochrane Library: Neither met the inclusion criteria; (3) 21 results for GHD and 17 for GHC in Tripdatabase. After review, none were found to be related to the topic; and (4) 137 results for GHD and 138 for GHC in MEDLINE. Since the overlap between search results was 99%, we used the latter search with 138 results; of them, only 14 (10.14%) met the selection criteria for this study.

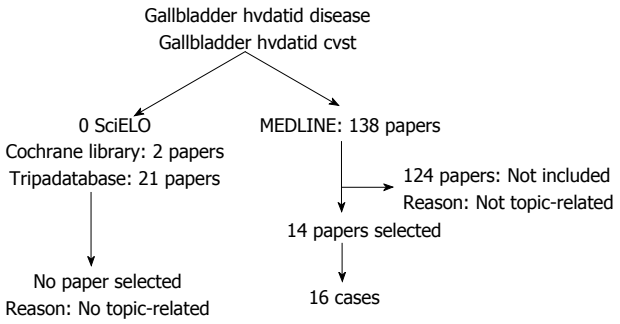

Figure 1 Search flowchart.

These 14 papers included 16 clinical cases covering a wide range of clinical, diagnostic and therapeutic aspects of GBHC. These characteristics are summarized in Tables 1-4.

In the next step, to assess the quality of the selected studies we used the rating scale described by Manterola *et al*[18], which assesses each publication individually depending on the type of study, the size of the sample and whether it is justified, and the methodology used. A mean score of all the selected studies is produced ranging from 6 to 36 points, with a quality cut-off score of 18 points. The mean score in our review was 10.3; however, due to the rarity of GBHC and the few studies of this issue published, we selected all the papers available.

We also carried out a qualitative analysis of the selected papers and their conclusions, based on the classical levels of evidence and grades of recommendation proposed in Cook *et al*[19] and Sackett[20].

RESULTS

Eight cases of GBHC were women and seven men. The sex of one patient was not specified. Median age was 48.3 years (range: 27-76). The most frequent clinical manifestation was abdominal pain (15/16) (94%) (Table 1), in the right upper quadrant in 13 patients) (81.25%), in the epigastrium in four (25%), (three of whom combined upper quadrant pain in right hypochondrium and epigastric pain), and finally diffuse abdominal pain in two (12.5%). In one case, no data on abdominal pain were included (6.25%). Three patients presented vomiting and two had nausea; no information on nausea or vomiting was reported in the rest of patients. Three patients had fever, four were fever-free, and no data on fever were available for the remaining nine patients. Four patients had jaundice, five did not, and no data were available in seven cases. As regards past medical history, two patients had been previously diagnosed with hydatid disease and one had had hepatitis.

On physical examination (Table 1), four patients presented abdominal tenderness, three hepatomegaly,

Table 1 Clinical data

Ref.	Sex	Age	Abdominal pain	Nausea and vomiting	Fever	Jaundice	Abdominal exploration	Past medical history
Noomene *et al*[3], 2013	Male	48	Diffuse		No (36.7 ºC)	Yes	Painful palpation in right hypocondrium	
Ertem *et al*[4], 2012	Male	32	Right hyponcondrium and epigastrium	Nausea	No	No	Painful palpation in right hypocondrium	
Krasniqi *et al*[5], 2010	Female	39	Right hypocondrium (18 mo)	Nausea		No	Painful palpation in right hypocondrium	
Murtaza *et al*[6], 2008	Female	32	Right hyponcondrium and epigastrium (3 mo)		No	No	Hepatomegaly	Liver hydatid surgery 8 yr ago
Sabat *et al*[7], 2008	Female	35	Right hyponcondrium and epigastrium		Yes	Yes		
Wani *et al*[8], 2005	Female	51	Right hyponcondrium					
Pitiakoudis *et al*[9], 2006	Male	60	Right hyponcondrium (10 d)	Vomiting	Yes (38 ºC-39.5 ºC)		Abdominal distension	
Safioleas *et al*[10], 2004	Female	65	Right hyponcondrium and epigastrium	Vomiting				
Safioleas *et al*[10], 2004	Female	51	Right hyponcondrium (6 mo)					
Safioleas *et al*[10], 2004	Male	63	Right hyponcondrium and epigastrium				Normal	
Kumar *et al*[11], 2004	Female	27	Diffuse					Relapsed liver hydatid cyst
Raza *et al*[12], 2003	Male	27	Right hyponcondrium (4 mo)		No	No	Hepatomegaly	
Kapoor *et al*[13], 2000	Male	53	Right hyponcondrium (2 mo)		Yes (high fever, 10 d)	Yes	Abdominal distension, ascitis, gallbladder mass	
Cangiotti *et al*[14], 1994	Male							
Rigas *et al*[15], 1979	Female	65	Right hyponcondrium	Vomiting		No	Normal	
Barón Urbano *et al*[16], 1978	-	76	Right hyponcondrium			Sí	Hepatomegaly, rubi spots in thorax and abdomen	Hepatitis

Table 2 Radiological and analitical studies

Ref.	Alakaline phosphatase (UI/L)	Bilirrubin (mg/dL)	Ultrasound	CT	MRI	Cysts inside gallbladder	Cholelithiasis	Choledocolitihasis	Serology *E. granulosus*
Noomene *et al*[3], 2013	220	7.1	Yes	Yes	Cholangio MRI			Yes	Positive
Ertem *et al*[4], 2012			Yes	Yes	Yes	Yes	No	No	Negative
Krasniqi *et al*[5], 2010			Yes	Yes				No	
Murtaza *et al*[6], 2008	140	10.2	Yes						
Sabat *et al*[7], 2008			Yes	Yes					
Wani *et al*[8], 2005			Yes	Yes			Yes		
Pitiakoudis *et al*[9], 2006		0.9	Yes	Yes	Yes	Yes			
Safioleas *et al*[10], 2004							Dude	Dude	
Safioleas *et al*[10], 2004			Yes						
Safioleas *et al*[10], 2004				Yes		Yes			Positive
Kumar *et al*[11], 2004				Yes		Yes			
Raza *et al*[12], 2003			Yes				Yes		
Kapoor *et al*[13], 2000	465	5.6	Yes			Yes			Positive
Cangiotti *et al*[14], 1994									
Rigas *et al*[15], 1979				Yes				No	
Barón Urbano *et al*[16], 1978	266	8.8							

CT: Computed tomography; MRI: magnetic resonance imaging; *E. granulosus*: *Echinococcus granulosus*.

two abdominal distension, and one a palpable mass. Serological information was available in only five cases (Table 2). Levels of alkaline phosphatase and bilirubin were high in four patients, normal in one, and no information was recorded for the other eleven. In the cases in which they were specified, alkaline phosphatase levels were between 140 and 465 IU/L and bilirubin between 5.6 and 10.2 mg/dL. Echinococcus serology was performed in four cases, being positive in three and negative in one.

Image diagnostic methods are described in Table 2. Abdominal ultrasound (US) was performed in ten patients (62.5%), abdominal computed tomography (CT) in nine (56.25%), and magnetic resonance imaging (MRI) in three (18.75%). In most cases a combination of several techniques was performed: US + CT + MRI in three cases, US + TC in three others; so four cases underwent US alone and three CT alone. The location of the cysts was intravesicular in five patients. Five patients presented

Table 3 Therapeutical strategies

Ref.	Preoperative albendazole	Treatment	Liver hydatidosis	Intraoperative treatment cyst	Intraoperative findings
Noomene *et al*[3], 2013	No	ERCP + Stent Laparoscopy cholecystectomy	No	No	Biliary sludge and stones in ampulla seen in ERCP
Ertem *et al*[4], 2012	No	Cholecystectomy by laparotomy	No	No	Galbladder cyst with inflammatory changes
Krasniqi *et al*[5], 2010	No	Cholecystectomy by laparotomy	Yes Cystopericystectomy	No	Calcified primary gallbladder cyst
Murtaza *et al*[6], 2008	Yes (2 wk)	Subtotal Cholecystectomy by laparotomy	No	Yes	Biliary communication into the cyst closed with sutures
Sabat *et al*[7], 2008	No	Cholecystectomy by laparotomy	No	Yes (aspiration + hypertonic solution cleaning)	-
Wani *et al*[8], 2005	No	Cholecystectomy by laparotomy	No	No	-
Pitiakoudis *et al*[9], 2006	No	Cholecystectomy by laparotomy	No	Yes	-
Safioleas *et al*[10], 2004	No	Cholecystectomy by laparotomy	No	No	5 cm × 4 cm cyst
Safioleas *et al*[10], 2004	No	Cholecystectomy by laparotomy	No	No	3 cm × 4 cm cyst
Safioleas *et al*[10], 2004	No	Cholecystectomy by laparotomy	No	No	5 cm × 4 cm cyst
Kumar *et al*[11], 2004	No	Cholecystectomy by laparotomy	Yes Cysts segment Ⅳ and Ⅷ. Cystopericystectomy segment Ⅳ + PAIR segment Ⅶ	Yes (aspiration + hypertonic solution cleaning) segment Ⅶ cyst	Cyst invading segment Ⅳ. Communication between cyst and galbladder
Raza *et al*[12], 2003	No	Cholecystectomy by laparotomy	Yes Right Lobe Enucleation	No	In gallbladder: Stones and daughter vesicles
Kapoor *et al*[13], 2000	No	NO. ERCP + Stent	No	No	-
Cangiotti *et al*[14], 1994	No	Cholecystectomy by laparotomy	SI. Right lobe. Cystoperycystectomy	No	-
Rigas *et al*[15], 1979	No	Cholecystectomy by laparotomy	No	No	-
Barón Urbano *et al*[16], 1978	No	Cholecystectomy by laparotomy	Yes Segment Ⅳ. Done by thoracotomy	-	Enlarged liver. Cholangitis. Daughter vesicles in cystic conduct lumen

ERCP: Endoscopic retrograde cholangiopancreatography.

GBHC and liver hydatid cysts. Two patients presented cholelithiasis and one choledocholithiasis.

The data on therapeutic management are displayed in Table 3. One patient received preoperative albendazole for two weeks, but no data on the other fifteen were available. The most frequent surgical technique was cholecystectomy by laparotomy (81.25%), performed in 13 patients; laparoscopic cholecystectomy was performed in two cases (12.5%), in one of them a previous endoscopic retrograde cholangiopancreatography (ERCP) was done and received a biliary stent; in the last patient, cholecystectomy was not performed, only ERCP and biliary stenting (6.25%). Cholecystectomies were total in 14 cases (93.3%) and subtotal in the patient treated preoperatively with albendazole (6.7%). Simultaneous surgery of liver hydatid cysts was carried out in five cases: Cystopericystectomy in three cases, enucleation in one, and in the other the surgical technique was not specified except for the fact that access was made by thoracotomy. Eleven patients did not present postoperative complications: One presented fever, atelectasis and pleural effusion, and another multiple organ failure and death. No data regarding postoperative outcome were recorded in three cases. The pathological examination (Table 4) was performed in nine patients. In three, the presence of Echinococcus granulosus was confirmed microscopically.

The mean hospital stay was seven days (range: 1-12 d). Seven patients were treated postoperatively with varying doses of albendazole. In nine cases follow-up after the postoperative period was recorded, for a mean period of 38 mo (range: 1-120 mo); no recurrence of GBHC was recorded.

DISCUSSION

Hydatidosis is a disease caused by the larva of the genus *Echinococcus*, within which *Echinococcus granulosus* is the most common species. Although cases have been diagnosed all over the world as a result of increased intercontinental migration, areas in which the incidence is significantly higher include the Mediterranean Sea,

Table 4 Pathology, postoperative course and follow-up

Ref.	Pathologic study	Stay	Postoperative treatment	Morbidity	Follow-up
Noomene *et al*[3], 2013	Cysts in gallbladder. Chronic inflammation	1	Albendazole 400 mg/d	No	
Ertem *et al*[4], 2012	Cyst in gallbladder	4		No	6 mo
Krasniqi *et al*[5], 2010	Calcified cyst 7 cm × 5 cm located in gallbladder mucosa	7	Albendazole 400 mg/d, 42 d	No	5 yr
Murtaza *et al*[6], 2008				No	2 mo
Sabat *et al*[7], 2008			Albendazole 10 mg/kg, 9 mo	No	
Wani *et al*[8], 2005					
Pitiakoudis *et al*[9], 2006	Echinococcus in gallbladder	12	Albendazole 800 mg/d, 4 mo	No	2 yr
Safioleas *et al*[10], 2004	Echinococcus in gallbladder			No	10 yr
Safioleas *et al*[10], 2004	Cyst with wall of 5 mm. Daughter vesicles	7		No	6 yr
Safioleas *et al*[10], 2004	Calcified cyst with daughter vesicles	10	Albendazole 2 mo	Yes: Fever, atelectasis and pleural effusion	4 yr
Kumar *et al*[11], 2004			Albendazole	No	1 yr
Raza *et al*[12], 2003			Albendazole 10 mg/kg per day	No	1 mo
Kapoor *et al*[13], 2000	Postmortem: Cholangitis, chronic liver obstruction			Yes: Sepsis, Multiorganic failure. Death	
Cangiotti *et al*[14], 1994					
Rigas *et al*[15], 1979	Cyst 5 cm × 4 cm with membranes. *Echinococcus* in gallbladder	9		No	
Barón *et al*[16], 1978					

Africa, South America, Middle East, Australia and New Zealand. Hydatid disease is prevalent in pastoral areas where cattle and dogs are in close contact. Dogs are the definitive hosts; they excrete eggs in their feces, and humans become intermediate hosts through accidental fecal-oral infection[2,21].

The reviews of Dziri *et al*[21,22] and Gomez I Gavara *et al*[1] concluded that many questions about liver hydatidosis still lack evidence-based answers. In 2016, PAIR or surgery, systematic or selective preoperative ERCP, the best surgical approach (conservative or radical), type of technique (laparoscopic or laparotomy), and the use of albendazole all remain topics for debate[1,21,22].

GBHC is an extremely rare entity, even in places where hydatid disease is endemic. Primary involvement is even less common. It is essential to differentiate primary GBHC from secondary invasion of the gallbladder caused by daughter vesicles of primary liver hydatid disease. GBHC can be located within the vesicle or on its outer surface. GBHC pathogenesis is not very well documented; one of the most accepted hypotheses is infestation through the bile duct, although this explanation is unconvincing in cases of superficial cysts, and also often requires prior hepatic involvement. Larval spread through the lymphatic system after intestinal absorption is possible and may explain the intraluminal cysts. Other routes, such as contamination of gallbladder after surgery for hepatic hydatid cyst, should also be considered[3].

In this evidence-based systematic review we have attempted to answer questions about the symptoms, diagnosis and treatment of GBHC. The main limitation is the lack of published series; all the reviewed papers are clinical cases, and so we are unable to reach an acceptable level of evidence. The most common symptom in GBHC is pain in the right upper quadrant[4-10,12-16]. Suspicion of GBHC is established by ultrasound and/or CT[3-13,15]. The involvement of the gallbladder is usually an incidental finding in patients being examined for liver hydatid cysts[4-6,8,10-12,14-16]. The most common therapeutic approach is cholecystectomy by laparotomy and postoperative albendazole[4-12,14-16], Few cases present postoperative complications, and the recurrence of hydatid disease is practically zero[3-12,15].

In conclusion, three main conclusions can be drawn regarding the clinical diagnosis and treatment of GBHC: (1) the most common clinical finding is right upper quadrant pain with a very low level of evidence (level V, grade D recommendation); (2) the most useful diagnostic methods are diagnostic ultrasound and CT with a very low level of evidence (level V, grade D recommendation); and (3) the recommended treatment is cholecystectomy by laparotomy plus albendazole in the postoperative period. This strategy achieves good results: There is no postoperative recurrence in the subsequent months of follow-up, with a very low level of evidence (level V, grade D recommendation). To our knowledge, this is the first literature review that focuses on the clinical, diagnostic and therapeutic aspects of GBHC. The lack of published cases on the topic and the fact that all the papers included deal with clinical cases impeded us from achieving a higher level of evidence in the results. More studies are needed, especially randomized controlled trials, in order to reach meaningful conclusions.

COMMENTS

Background

Primary gallbladder hidatidosis is an unfrequent disease. No systematic reviews have been done before.

Research frontiers

Obtaining best clinical evidence to treat primary gallbladder hydatidosis.

Applications

Future cases and publications will have a systematic review to treat these

patients.

Peer-review

Hydatid disease of the gallbladder is very rare, from this point of view this systematic review has some interest.

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