ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2016 February 8; 8(4): 207-264

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

Editorial Board

2014-2017

The *World Journal of Hepatology* Editorial Board consists of 469 members, representing a team of worldwide experts in hepatology. They are from 53 countries, including Algeria (1), Argentina (6), Armenia (1), Australia (1), Austria (4), Bangladesh (2), Belgium (3), Botswana (2), Brazil (13), Bulgaria (2), Canada (3), Chile (1), China (98), Czech Repoublic (1), Denmark (2), Egypt (12), France (6), Germany (19), Greece (11), Hungary (5), India (15), Indonesia (2), Iran (4), Israel (1), Italy (52), Japan (35), Jordan (1), Malaysia (2), Mexico (3), Moldova (1), Netherlands (3), Nigeria (1), Pakistan (1), Philippines (2), Poland (1), Portugal (2), Qatar (1), Romania (6), Russia (2), Saudi Arabia (4), Singapore (1), South Korea (11), Spain (20), Sri Lanka (1), Sudan (1), Sweden (1), Switzerland (1), Thailand (4), Turkey (21), Ukraine (3), United Kingdom (17), and United States (56).

China

Guang-Wen Cao, *Shanghai*
En-Qiang Chen, *Chengdu*
Gong-Ying Chen, *Hangzhou*
Jin-lian Chen, *Shanghai*
Jun Chen, *Changsha*
Alfred Cheng, *Hong Kong*
Chun-Ping Cui, *Beijing*
Shuang-Suo Dang, *Xi'an*
Ming-Xing Ding, *Jinhua*
Zhi-Jun Duang, *Dalian*
He-Bin Fan, *Wuhan*
Xiao-Ming Fan, *Shanghai*
James Yan Yue Fung, *Hong Kong*
Yi Gao, *Guangzhou*
Zuo-Jiong Gong, *Wuhan*
Zhi-Yong Guo, *Guangzhou*
Shao-Liang Han, *Wenzhou*
Tao Han, *Tianjin*
Jin-Yang He, *Guangzhou*
Ming-Liang He, *Hong Kong*
Can-Hua Huang, *Chengdu*
Bo Jin, *Beijing*
Shan Jin, *Hohhot*
Hui-Qing Jiang, *Shijiazhuang*
Wan-Yee Joseph Lau, *Hong Kong*
Guo-Lin Li, *Changsha*
Jin-Jun Li, *Shanghai*
Qiang Li, *Jinan*
Sheng Li, *Jinan*
Zong-Fang Li, *Xi'an*
Xu Li, *Guangzhou*
Xue-Song Liang, *Shanghai*
En-Qi Liu, *Xi'an*
Pei Liu, *Shenyang*
Zhong-Hui Liu, *Changchun*
Guang-Hua Luo, *Changzhou*
Yi Lv, *Xi'an*
Guang-Dong Pan, *Liuzhou*
Wen-Sheng Pan, *Hangzhou*
Jian-Min Qin, *Shanghai*
Wai-Kay Seto, *Hong Kong*
Hong Shen, *Changsha*
Xiao Su, *Shanghai*
Li-Ping Sun, *Beijing*
Wei-Hao Sun, *Nanjing*
Xue-Ying Sun, *Harbin*
Hua Tang, *Tianjin*
Ling Tian, *Shanghai*
Eric Tse, *Hong Kong*
Guo-Ying Wang, *Changzhou*
Yue Wang, *Beijing*
Shu-Qiang Wang, *Chengdu*
Mary MY Waye, *Hong Kong*
Hong-Shan Wei, *Beijing*
Danny Ka-Ho Wong, *Hong Kong*
Grace Lai-Hung Wong, *Hong Kong*
Bang-Fu Wu, *Dongguan*
Feng Wu, *Chongqing*
Xiong-Zhi Wu, *Tianjin*
Chun-Fang Xu, *Suzhou*
Rui-An Xu, *Quanzhou*
Rui-Yun Xu, *Guangzhou*
Wei-Li Xu, *Shijiazhuang*
Shi-Ying Xuan, *Qingdao*
Ming-Xian Yan, *Jinan*
Lv-Nan Yan, *Chengdu*
Jin Yang, *Hangzhou*
Ji-Hong Yao, *Dalian*
Winnie Yeo, *Hong Kong*
Zheng Zeng, *Beijing*
Qi Zhang, *Hangzhou*
Shi-Jun Zhang, *Guangzhou*
Xiao-Lan Zhang, *Shijiazhuang*
Xiao-Yong Zhang, *Guangzhou*
Xin-Chen Zhang, *Harbin*
Yong Zhang, *Xi'an*
Hong-Chuan Zhao, *Hefei*
Ming-Hua Zheng, *Wenzhou*
Yu-Bao Zheng, *Guangzhou*
Ren-Qian Zhong, *Shanghai*
Fan Zhu, *Wuhan*
Xiao Zhu, *Dongguan*

Czech Repoublic

Kamil Vyslouzil, *Olomouc*

Denmark

Henning Gronbaek, *Aarhus*
Christian Mortensen, *Hvidovre*

Egypt

Ihab T Abdel-Raheem, *Damanhour*
NGB G Bader EL Din, *Cairo*
Hatem Elalfy, *Mansoura*
Mahmoud M El-Bendary, *Mansoura*
Mona El SH El-Raziky, *Cairo*
Mohammad El-Sayed, *Cairo*
Yasser M Fouad, *Minia*
Mohamed AA Metwally, *Benha*
Hany Shehab, *Cairo*
Mostafa M Sira, *Shebin El-koom*
Ashraf Taye, *Minia*
MA Ali Wahab, *Mansoura*

France

Laurent Alric, *Toulouse*
Sophie Conchon, *Nantes*
Daniel J Felmlee, *Strasbourg*
Herve Lerat, *Creteil*
Dominique Salmon, *Paris*
Jean-Pierre Vartanian, *Paris*

Germany

Laura E Buitrago-Molina, *Hannover*
Enrico N De Toni, *Munich*
Oliver Ebert, *Muenchen*
Rolf Gebhardt, *Leipzig*
Janine V Hartl, *Regensburg*
Sebastian Hinz, *Kiel*
Benjamin Juntermanns, *Essen*
Roland Kaufmann, *Jena*
Viola Knop, *Frankfurt*
Veronika Lukacs-Kornek, *Homburg*
Benjamin Maasoumy, *Hannover*
Jochen Mattner, *Erlangen*
Nadja M Meindl-Beinker, *Mannheim*
Ulf P Neumann, *Aachen*
Margarete Odenthal, *Cologne*
Yoshiaki Sunami, *Munich*
Christoph Roderburg, *Aachen*
Frank Tacke, *Aachen*
Yuchen Xia, *Munich*

Greece

Alex P Betrosian, *Athens*
George N Dalekos, *Larissa*
Ioanna K Delladetsima, *Athens*
Nikolaos K Gatselis, *Larissa*
Stavros Gourgiotis, *Athens*
Christos G Savopoulos, *Thessaloniki*
Tania Siahanidou, *Athens*
Emmanouil Sinakos, *Thessaloniki*
Nikolaos G Symeonidi, *Thessaloniki*
Konstantinos C Thomopoulos, *Larissa*
Konstantinos Tziomalos, *Thessaloniki*

Hungary

Gabor Banhegyi, *Budapest*
Peter L Lakatos, *Budapest*
Maria Papp, *Debrecen*
Ferenc Sipos, *Budapest*
Zsolt J Tulassay, *Budapest*

India

Deepak N Amarapurkar, *Mumbai*
Girish M Bhopale, *Pune*
Sibnarayan Datta, *Tezpur*
Nutan D Desai, *Mumbai*
Sorabh Kapoor, *Mumbai*
Jaswinder S Maras, *New Delhi*
Nabeen C Nayak, *New Delhi*
C Ganesh Pai, *Manipal*
Amit Pal, *Chandigarh*
K Rajeshwari, *New Delhi*
Anup Ramachandran, *Vellore*
D Nageshwar Reddy, *Hyderabad*
Shivaram P Singh, *Cuttack*
Ajith TA, *Thrissur*
Balasubramaniyan Vairappan, *Pondicherry*

Indonesia

Cosmas RA Lesmana, *Jakarta*
Neneng Ratnasari, *Yogyakarta*

Iran

Seyed M Jazayeri, *Tehran*
Sedigheh Kafi-Abad, *Tehran*
Iradj Maleki, *Sari*
Fakhraddin Naghibalhossaini, *Shiraz*

Israel

Stephen DH Malnick, *Rehovot*

Italy

Francesco Angelico, *Rome*

Alfonso W Avolio, *Rome*
Francesco Bellanti, *Foggia*
Marcello Bianchini, *Modena*
Guglielmo Borgia, *Naples*
Mauro Borzio, *Milano*
Enrico Brunetti, *Pavia*
Valeria Cento, *Roma*
Beatrice Conti, *Rome*
Francesco D'Amico, *Padova*
Samuele De Minicis, *Fermo*
Fabrizio De Ponti, *Bologna*
Giovan Giuseppe Di Costanzo, *Napoli*
Luca Fabris, *Padova*
Giovanna Ferraioli, *Pavia*
Andrea Galli, *Florencee*
Matteo Garcovich, *Rome*
Edoardo G Giannini, *Genova*
Rossano Girometti, *Udine*
Alessandro Granito, *Bologna*
Alberto Grassi, *Rimini*
Alessandro Grasso, *Savona*
Salvatore Gruttadauria, *Palermo*
Francesca Guerrieri, *Rome*
Quirino Lai, *Aquila*
Andrea Lisotti, *Bologna*
Marcello F Maida, *Palermo*
Lucia Malaguarnera, *Catania*
Andrea Mancuso, *Palermo*
Luca Maroni, *Ancona*
Francesco Marotta, *Milano*
Pierluigi Marzuillo, *Naples*
Sara Montagnese, *Padova*
Giuseppe Nigri, *Rome*
Claudia Piccoli, *Foggia*
Camillo Porta, *Pavia*
Chiara Raggi, *Rozzano (MI)*
Maria Rendina, *Bari*
Maria Ripoli, *San Giovanni Rotondo*
Kryssia I Rodriguez-Castro, *Padua*
Raffaella Romeo, *Milan*
Amedeo Sciarra, *Milano*
Antonio Solinas, *Sassari*
Aurelio Sonzogni, *Bergamo*
Giovanni Squadrito, *Messina*
Salvatore Sutti, *Novara*
Valentina Svicher, *Rome*
Luca Toti, *Rome*
Elvira Verduci, *Milan*
Umberto Vespasiani-Gentilucci, *Rome*
Maria A Zocco, *Rome*

Japan

Yasuhiro Asahina, *Tokyo*
Nabil AS Eid, *Takatsuki*
Kenichi Ikejima, *Tokyo*
Shoji Ikuo, *Kobe*
Yoshihiro Ikura, *Takatsuki*
Shinichi Ikuta, *Nishinomiya*
Kazuaki Inoue, *Yokohama*
Toshiya Kamiyama, *Sapporo*
Takanobu Kato, *Tokyo*
Saiho Ko, *Nara*
Haruki Komatsu, *Sakura*
Masanori Matsuda, *Chuo-city*
Yasunobu Matsuda, *Niigata*
Yoshifumi Nakayama, *Kitakyushu*
Taichiro Nishikawa, *Kyoto*
Satoshi Oeda, *Saga*
Kenji Okumura, *Urayasu*
Michitaka Ozaki, *Sapporo*
Takahiro Sato, *Sapporo*
Junichi Shindoh, *Tokyo*
Ryo Sudo, *Yokohama*
Atsushi Suetsugu, *Gifu*
Haruhiko Sugimura, *Hamamatsu*
Reiji Sugita, *Sendai*
Koichi Takaguchi, *Takamatsu*
Shinji Takai, *Takatsuki*
Akinobu Takaki, *Okayama*
Yasuhito Tanaka, *Nagoya*
Takuji Tanaka, *Gifu City*
Atsunori Tsuchiya, *Niigata*
Koichi Watashi, *Tokyo*
Hiroshi Yagi, *Tokyo*
Taro Yamashita, *Kanazawa*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashihara*

Jordan

Kamal E Bani-Hani, *Zarqa*

Malaysia

Peng Soon Koh, *Kuala Lumpur*
Yeong Yeh Lee, *Kota Bahru*

Mexico

Francisco J Bosques-Padilla, *Monterrey*
María de F Higuera-de la Tijera, *Mexico City*
José A Morales-Gonzalez, *México City*

Moldova

Angela Peltec, *Chishinev*

Netherlands

Wybrich R Cnossen, *Nijmegen*
Frank G Schaap, *Maastricht*
Fareeba Sheedfar, *Groningen*

Nigeria

CA Asabamaka Onyekwere, *Lagos*

Pakistan

Bikha Ram Devrajani, *Jamshoro*

Philippines

Janus P Ong, *Pasig*
JD Decena Sollano, *Manila*

Poland

Jacek Zielinski, *Gdansk*

Portugal

Rui T Marinho, *Lisboa*
Joao B Soares, *Braga*

Qatar

Reem Al Olaby, *Doha*

Romania

Bogdan Dorobantu, *Bucharest*
Liana Gheorghe, *Bucharest*
George S Gherlan, *Bucharest*
Romeo G Mihaila, *Sibiu*
Bogdan Procopet, *Cluj-Napoca*
Streba T Streba, *Craiova*

Russia

Anisa Gumerova, *Kazan*
Pavel G Tarazov, *St.Petersburg*

Saudi Arabia

Abdulrahman A Aljumah, *Riyadh*
Ihab MH Mahmoud, *Riyadh*
Ibrahim Masoodi, *Riyadh*
Mhoammad K Parvez, *Riyadh*

Singapore

Ser Yee Lee, *Singapore*

South Korea

Young-Hwa Chung, *Seoul*
Dae-Won Jun, *Seoul*
Bum-Joon Kim, *Seoul*
Do Young Kim, *Seoul*
Ji Won Kim, *Seoul*
Moon Young Kim, *Wonu*
Mi-Kyung Lee, *Suncheon*
Kwan-Kyu Park, *Daegu*
Young Nyun Park, *Seoul*
Jae-Hong Ryoo, *Seoul*
Jong Won Yun, *Kyungsan*

Spain

Ivan G Marina, *Madrid*
Juan G Acevedo, *Barcelona*
Javier Ampuero, *Sevilla*
Jaime Arias, *Madrid*
Andres Cardenas, *Barcelona*
Agustin Castiella, *Mendaro*
Israel Fernandez-Pineda, *Sevilla*
Rocio Gallego-Duran, *Sevilla*
Rita Garcia-Martinez, *Barcelona*

World Journal of Hepatology

Contents

Three issues per month Volume 8 Number 4 February 8, 2016

World Journal of Hepatology
Volume 8 Number 4 February 8, 2016

Contents

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8[th], 18[th], and 28[th] of each month)

Xiu-Xia Song, Vice Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
February 8, 2016

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i4.207

World J Hepatol 2016 February 8; 8(4): 207-210
ISSN 1948-5182 (online)

EDITORIAL

Inflammasome activation in decompensated liver cirrhosis

José M González-Navajas

José M González-Navajas, FISABIO Biomedical Research Foundation, Hospital General Universitario de Alicante, 03010 Alicante, Spain

José M González-Navajas, Networked Biomedical Research Center for Hepatic and Digestive Disease (CIBERehd), Instituto de Salud Carlos III, 28029 Madrid, Spain

Author contributions: González-Navajas JM solely contributed to this article.

Supported by Grant PI13/00315 from the Instituto de Salud Carlos Ⅲ (co-financed by FEDER funds); and grants UGP-14-123 and UGP-14-248 from FISABIO Research Foundation.

Conflict-of-interest statement: The author declares no conflict of interest.

Correspondence to: José M González-Navajas, PhD, FISABIO Biomedical Research Foundation, Hospital General Universitario de Alicante, Av. Pintor Baeza, 12, 03010 Alicante, Spain. gonzalez_josnav@gva.es
Telephone: +34-965-913928
Fax: +34-965-913922

Received: January 19, 2015
Peer-review started: January 20, 2015
First decision: March 6, 2015
Revised: November 2, 2015
Accepted: January 16, 2016
Article in press: January 19, 2016
Published online: February 8, 2016

Abstract

Inflammation participates in the pathogenesis of many liver diseases, including liver cirrhosis. Certain inflammatory citokines, such as interleukin (IL)-1β and IL-18, are produced after the activation of a multiprotein complex known as the inflammasome. Activation of the inflammasome has been documented in several liver diseases, but its role in the development and progression of liver cirrhosis or the complications associated with this disease is still largely unknown. We have recently studied the impact of the inflammasome in the sterile inflammatory response that takes place in the ascitic fluid of patients with decompensated cirrhosis, providing evidence that activation of the absent in melanoma 2 (AIM2) inflammasome is an important response in these patients. Ascitic fluid-derived macrophages were able to mount a very robust AIM2-mediated response even in the absence of a priming signal, which is usually required for the full activation of all the inflammasomes. In addition, high level of inflammasome activation in these patients was associated with a higher degree of liver disease and an increased incidence of spontaneous bacterial peritonitis. These results may help explain the exacerbated inflammatory response that usually occurs in patients with decompensated cirrhosis in the absence of detectable infections. Thus, inflammasomes should be considered as possible therapeutic targets in sterile inflammatory complications in patients with cirrhosis.

Key words: Cirrhosis; Ascites; Inflammasome; Absent in melanoma 2; Interleukin-1β

Core tip: In this Editorial I discuss the involvement of the inflammasome in the inflammatory reactions that occur in patients with liver cirrhosis and ascites. I focus on a recent work in which we observed that the absent in melanoma 2 inflammasome is highly activated in the ascitic fluid of patients with advanced cirrhosis and that its activation is linked to the severity of liver disease. These findings are important for the understanding of the sterile inflammatory reactions in these patients, and could have important therapeutic implications.

González-Navajas JM. Inflammasome activation in decompensated liver cirrhosis. *World J Hepatol* 2016; 8(4): 207-210 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i4/207.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i4.207

Liver cirrhosis is the result of a long pathologic process initiated by chronic infection with hepatitis B virus or hepatitis C virus (HCV), excessive alcohol consumption, accumulation of fat in liver cells, and other metabolic alterations. The most important complications of liver cirrhosis include intestinal bleeding, encephalopathy, and ascites, and the development of any of these complications is clinically known as decompensated cirrhosis. Ascites is the most common cause of hepatic decompensation, and usually precedes the others. Decompensation of cirrhosis is usually associated with a systemic inflammatory response characterized by activation of innate immune cells and elevated expression of pro-inflammatory cytokines [tumor necrosis factor α, interleukin (IL)-1β, IL-6] in the ascitic fluid. This inflammatory response is usually the result of bacterial translocation from the intestinal lumen to extra-intestinal sites, such as mesenteric lymph nodes and ascitic fluid. Bacterial translocation does not necessarily mean bacterial infection, since the translocating bacteria is often killed by the innate immune system. However, the solely presence of molecules of microbial origin [such as lipopolysaccharide (LPS) or bacterial DNA] is sufficient to mount a sterile inflammatory response in the ascitic fluid in the absence of active infection[1-3].

Since its first description in 2002 by Martinon *et al*[4], the inflammasome has been a key subject of research in multiple inflammatory diseases. Very comprehensive reviews of the expression, activation, and function of the inflammasomes have been published elsewhere[5-7], and therefore these topics are discussed here only briefly. The inflammasome is a cytosolic multiprotein complex that controls the activation of the enzyme caspase-1[4,6]. Once activated, caspase-1 mediates the maturation and release of pro-inflammatory cytokines such as IL-1β and IL-18. Caspase-1 activity can also result in a highly inflammatory form of cell death called "pyroptosis" in some cells[8], which occurs most frequently upon infection with intracellular pathogens[9]. Inflammasomes are assembled upon recognition of pathogen-associated molecular patterns (PAMPs), as well as host-derived signals known as damage-associated molecular patterns (DAMPs) that are released as a result of tissue damage or cellular stress. Several members of the NLR family (nucleotide-binding and oligomerization domain and leucine-rich-repeat-containing proteins) have been reported to exhibit inflammasome activity, including NLRP1, NLRP3, NLRP6 or NLRC4. In addition to NLRs, the HIN-200 domain-containing protein absent in melanoma 2 (AIM2) has also the ability to induce inflammasome activation. Full activation of the inflammasome requires two different signals. The first signal is provided by the activation of pattern recognition receptors, such as Toll-like receptors, resulting in the accumulation of inactive pro-IL-1β and pro-IL-18 inside the cell. The second signal is then provided by the activation of NLRPs or AIM2 by different danger signals[5-7]. For example, NLRP3 is activated by a wide range of PAMPs and DAMPs (*e.g.*, toxins, uric acid, ATP), whereas AIM2 is activated only by double-stranded DNA (dsDNA) of any origin[10,11] (Figure 1).

Recent studies have suggested that the inflammasome also plays an important role in chronic liver disease[12]. For example, the inflammasome is activated in response to HCV infection[13], in drug-induced liver injury[14], or in the pathogenesis of non-alcoholic steatohepatitis[15,16]. However, the inflammasome-mediated response in decompensated cirrhosis was unexplored until publication of our recent study by Lozano-Ruiz *et al*[17]. In this study we show that activation of the inflammasome is an important response in the ascitic fluid of cirrhotic patients. Macrophages from ascitic fluid showed high levels of pro-IL-1β and pro-IL-18 mRNA, constitutive activation of caspase-1 and enhanced expression of AIM2 protein and mRNA when compared to blood-derived macrophages from the same patients. Moreover, contrary to blood macrophages, activation of the AIM2 inflammasome did not require a priming signal in these cells, demonstrating the pre-activated state of the inflammasome in the ascitic fluid. This pre-activated state of the AIM2 inflammasome was associated with the presence of bacterial DNA fragments in the ascitic fluid of these patients, suggesting that translocation of bacteria and their products could be responsible for this priming[17].

It was previously shown that bacterial translocation and inflammation increases depending on the degree of liver damage and the clinical stage of the disease[18]. Thus, it was conceivable that the severity of liver disease could affect the extent of inflammasome activation in cirrhosis. Indeed, activation of caspase-1 and AIM2-mediated production of IL-1β and IL-18 were increased in patients with Child-Pugh C score, compared to those with Child-Pugh B. Additionally, high level of IL-18 in ascitic fluid showed a significant association with the occurrence of spontaneous bacterial peritonitis (SBP) in these patients independently of the Child-Pugh score, suggesting that increased inflammasome activation might be a marker of increased risk of SBP.

In summary, these findings are important for the understanding of the sterile inflammatory reactions in patients with advanced cirrhosis. In these patients, complications associated with high mortality are normally accompanied by excessive inflammation, and therefore our results could have important translational implications. We propose that a two-hit process could explain the exacerbated inflammasome activation in advanced cirrhosis (Figure 2). First, bacterial translocation would lead to an abnormal influx of exogenous PAMPs (*e.g.*, LPS or bacterial DNA) that induce a pre-activation state of the inflammasome in ascitic fluid cells.

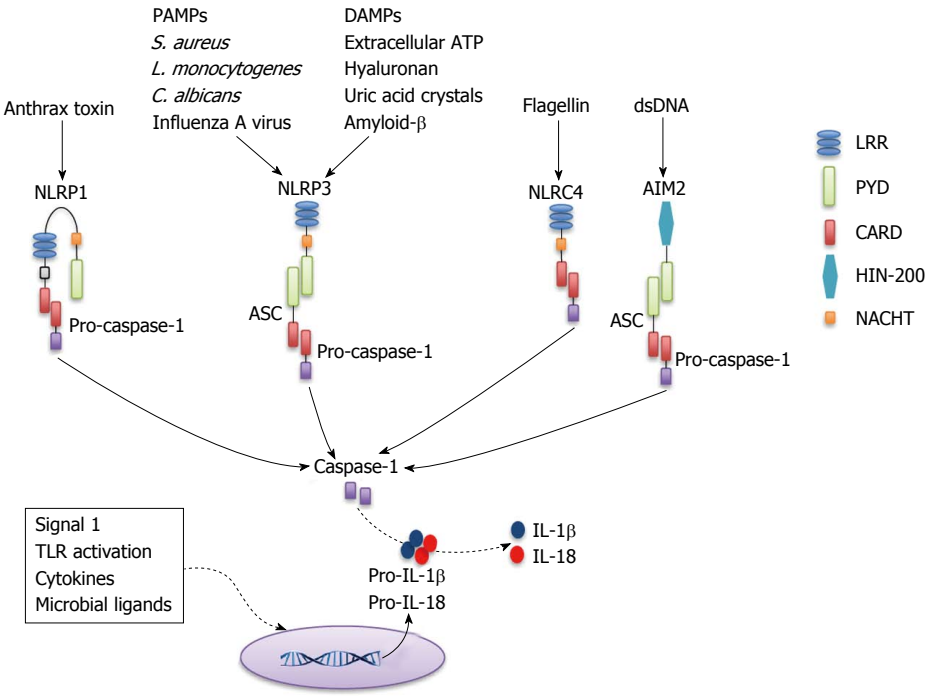

Figure 1 Basic representation of inflammasome activation. Inflammasomes are formed after NLR or PYHIN family members recognize signals associated with tissue damage or infection. Receptors that have a CARD domain can recruit pro-caspase-1 directly (*e.g.*, NLRC4), whereas those that contain a PYD domain (*e.g.*, NLRP3 and AIM2) recruit pro-caspase-1 through the accessory protein ASC (which contains a PYD and a CARD). NLRP1 contains a CARD and can bypass the requirement for ASC, but also contains a PYD and its interaction with ASC enhances the activity of the NLRP1 inflammasome. CARD: Caspase-1 recruitment domain; PYD: Pyrin domain; ASC: Apoptosis-associated speck-like protein containing a CARD; LRR: Leucine rich repeat; HIN-200: Hematopoietic interferon-inducible nuclear antigen with 200 amino-acid repeat; PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; AIM2: Absent in melanoma 2; dsDNA: Double-stranded DNA; IL: Interleukin; *S. aureus*: *Staphylococcus aureus*; *L. monocytogenes*: *Listeria monocytogenes*; *C. albicans*: *Candida albicans*; TLR: Toll-like receptor.

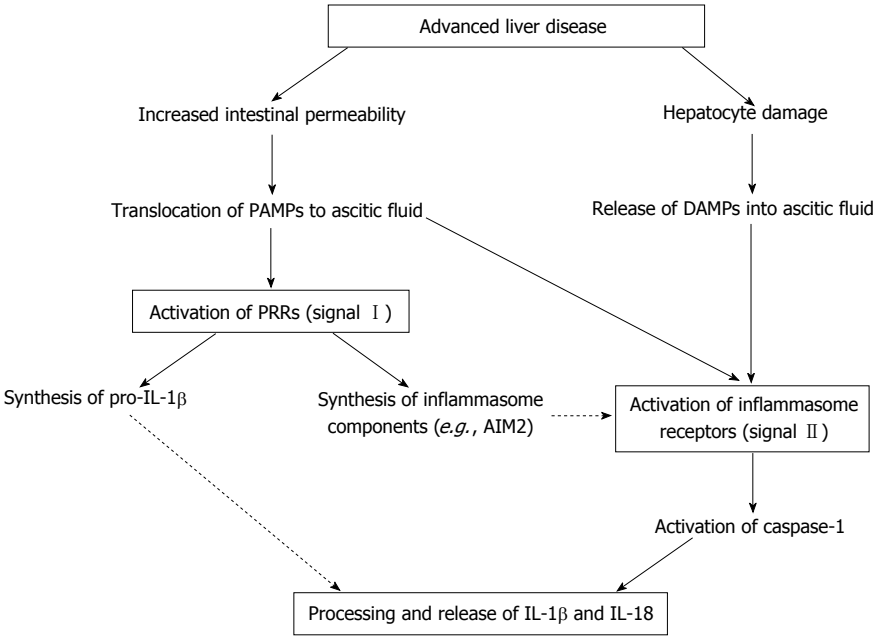

Figure 2 Theoretical mechanism of inflammasome activation in ascitic fluid. Advanced cirrhosis is typically associated with overgrowth of intestinal bacteria and increased intestinal permeability, which results in the translocation of bacterial products (*e.g.*, DNA or LPS) to the ascitic fluid. The presence of these PAMPs activates PRRs in innate immune cells of the ascitic fluid, inducing the synthesis of IL-1β and IL-18 precursors and inflammasome components (signal Ⅰ). At the same time, continuous liver damage (*e.g.*, by virus or alcohol) would result in hepatocyte death and release of DAMPs (*e.g.*, host dsDNA). These DAMPs (and probably new translocation events of PAMPs from the intestinal lumen) would activate inflammasome-forming receptors such as AIM2 (providing signal Ⅱ), which in turn results in the activation of caspase-1 and the maturation and release of IL-1β and IL-18 into the ascitic fluid. IL: Interleukin; PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; AIM2: Absent in melanoma 2; dsDNA: Double-stranded DNA; PRRs: Pattern recognition receptors; LPS: Lipopolysaccharide.

Second, endogenous DAMPs released from damaged liver cells (*e.g.*, host dsDNA) would provide the second signal for the activation of the AIM2 inflammasome and the promotion of inflammation in the absence of active infection[17]. However, some questions remain that need to be further clarified. For example, it is not clear whether the inflammasome contributes to, or is a consequence of, cirrhosis progression. In addition, the use of the inflammasome as a therapeutic target in cirrhosis needs to be carefully addressed. Several IL-1β blocking agents are currently approved and used in patients suffering from different inflammatory diseases[19], but the increased risk of infections would argue against using these immunosuppressive drugs in certain situations, such as in SBP. Therefore, more studies are needed to determine the exact role of the inflammasome in the pathogenesis of advanced cirrhosis and its potential use as a therapeutic target for the treatment or prevention of inflammatory complications.

REFERENCES

1 **Francés R**, Zapater P, González-Navajas JM, Muñoz C, Caño R, Moreu R, Pascual S, Bellot P, Pérez-Mateo M, Such J. Bacterial DNA in patients with cirrhosis and noninfected ascites mimics the soluble immune response established in patients with spontaneous bacterial peritonitis. *Hepatology* 2008; **47**: 978-985 [PMID: 18306221 DOI: 10.1002/hep.22083]

2 **González-Navajas JM**, Bellot P, Francés R, Zapater P, Muñoz C, García-Pagán JC, Pascual S, Pérez-Mateo M, Bosch J, Such J. Presence of bacterial-DNA in cirrhosis identifies a subgroup of patients with marked inflammatory response not related to endotoxin. *J Hepatol* 2008; **48**: 61-67 [PMID: 17998145 DOI: 10.1016/j.jhep.2007.08.012]

3 **Zapater P**, Francés R, González-Navajas JM, de la Hoz MA, Moreu R, Pascual S, Monfort D, Montoliu S, Vila C, Escudero A, Torras X, Cirera I, Llanos L, Guarner-Argente C, Palazón JM, Carnicer F, Bellot P, Guarner C, Planas R, Solá R, Serra MA, Muñoz C, Pérez-Mateo M, Such J. Serum and ascitic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. *Hepatology* 2008; **48**: 1924-1931 [PMID: 19003911 DOI: 10.1002/hep.22564]

4 **Martinon F**, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell* 2002; **10**: 417-426 [PMID: 12191486 DOI: 10.1016/S1097-2765(02)00599-3]

5 **Schroder K**, Tschopp J. The inflammasomes. *Cell* 2010; **140**: 821-832 [PMID: 20303873 DOI: 10.1016/j.cell.2010.01.040]

6 **Rathinam VA**, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. *Nat Immunol* 2012; **13**: 333-342 [PMID: 22430786 DOI: 10.1038/ni.2237]

7 **Strowig T**, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature* 2012; **481**: 278-286 [PMID: 22258606 DOI: 10.1038/nature10759]

8 **Bergsbaken T**, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. *Nat Rev Microbiol* 2009; **7**: 99-109 [PMID: 19148178 DOI: 10.1038/nrmicro2070]

9 **Case CL**, Shin S, Roy CR. Asc and Ipaf Inflammasomes direct distinct pathways for caspase-1 activation in response to Legionella pneumophila. *Infect Immun* 2009; **77**: 1981-1991 [PMID: 19237518 DOI: 10.1128/IAI.01382-08]

10 **Fernandes-Alnemri T**, Yu JW, Datta P, Wu J, Alnemri ES. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. *Nature* 2009; **458**: 509-513 [PMID: 19158676 DOI: 10.1038/nature07710]

11 **Hornung V**, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Latz E, Fitzgerald KA. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* 2009; **458**: 514-518 [PMID: 19158675 DOI: 10.1038/nature07725]

12 **Szabo G**, Csak T. Inflammasomes in liver diseases. *J Hepatol* 2012; **57**: 642-654 [PMID: 22634126 DOI: 10.1016/j.jhep.2012.03.035]

13 **Burdette D**, Haskett A, Presser L, McRae S, Iqbal J, Waris G. Hepatitis C virus activates interleukin-1β via caspase-1-inflammasome complex. *J Gen Virol* 2012; **93**: 235-246 [PMID: 21994322 DOI: 10.1099/vir.0.034033-0]

14 **Imaeda AB**, Watanabe A, Sohail MA, Mahmood S, Mohamadnejad M, Sutterwala FS, Flavell RA, Mehal WZ. Acetaminophen-induced hepatotoxicity in mice is dependent on Tlr9 and the Nalp3 inflammasome. *J Clin Invest* 2009; **119**: 305-314 [PMID: 19164858 DOI: 10.1172/JCI35958]

15 **Kamari Y**, Shaish A, Vax E, Shemesh S, Kandel-Kfir M, Arbel Y, Olteanu S, Barshack I, Dotan S, Voronov E, Dinarello CA, Apte RN, Harats D. Lack of interleukin-1α or interleukin-1β inhibits transformation of steatosis to steatohepatitis and liver fibrosis in hypercholesterolemic mice. *J Hepatol* 2011; **55**: 1086-1094 [PMID: 21354232 DOI: 10.1016/j.jhep.2011.01.048]

16 **Henao-Mejia J**, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JI, Hoffman HM, Flavell RA. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 2012; **482**: 179-185 [PMID: 22297845 DOI: 10.1038/nature10809]

17 **Lozano-Ruiz B**, Bachiller V, García-Martínez I, Zapater P, Gómez-Hurtado I, Moratalla A, Giménez P, Bellot P, Francés R, Such J, González-Navajas JM. Absent in melanoma 2 triggers a heightened inflammasome response in ascitic fluid macrophages of patients with cirrhosis. *J Hepatol* 2015; **62**: 64-71 [PMID: 25173967 DOI: 10.1016/j.jhep.2014.08.027]

18 **Cirera I**, Bauer TM, Navasa M, Vila J, Grande L, Taurá P, Fuster J, García-Valdecasas JC, Lacy A, Suárez MJ, Rimola A, Rodés J. Bacterial translocation of enteric organisms in patients with cirrhosis. *J Hepatol* 2001; **34**: 32-37 [PMID: 11211904 DOI: 10.1016/S0168-8278(00)00013-1]

19 **Hoffman HM**, Wanderer AA. Inflammasome and IL-1beta-mediated disorders. *Curr Allergy Asthma Rep* 2010; **10**: 229-235 [PMID: 20425006 DOI: 10.1007/s11882-010-0109-z]

P- Reviewer: Liu ZH, Tsuchiya A, Uchiyama H
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i4.211

World J Hepatol 2016 February 8; 8(4): 211-225
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Basic Study

Lack of hepcidin expression attenuates steatosis and causes fibrosis in the liver

Sizhao Lu, Robert G Bennett, Kusum K Kharbanda, Duygu Dee Harrison-Findik

Sizhao Lu, Robert G Bennett, Department of Biochemistry, University of Nebraska Medical Center, Omaha, NE 68198-5870, United States

Robert G Bennett, Division of Endocrinology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198-4130, United States

Robert G Bennett, Kusum K Kharbanda, Nebraska-Western Iowa VA Health Care System, Omaha, NE 68105, United States

Kusum K Kharbanda, Duygu Dee Harrison-Findik, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198-2000, United States

Author contributions: Lu S contributed to study design, data acquisition and drafting of the manuscript; Harrison-Findik DD obtained funding, contributed to study concept and supervision, and critical revision of the manuscript; Bennett RG and Kharbanda K helped with technical support and critical reading of the manuscript.

Supported by NIH grant No. R01AA017738 (to Harrison-Findik DD); and University of Nebraska Medical Center Graduate Assistantship/Fellowship (to Lu S).

Institutional animal care and use committee statement: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of University of Nebraska Medical Center (IACUC protocol No. 03-075-10-FC).

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Correspondence to: Duygu Dee Harrison-Findik, DVM, PhD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Nebraska Medical Center, 92000 UNMC, Omaha, NE 68198-2000, United States. dufindik@gmail.com
Telephone: +1-402-5596209
Fax: +1-402-5599004

Received: August 2, 2015
Peer-review started: August 3, 2015
First decision: September 29, 2015
Revised: October 14, 2015
Accepted: November 13, 2015
Article in press: November 13, 2015
Published online: February 8, 2016

Abstract

AIM: To investigate the role of key iron-regulatory protein, hepcidin in non-alcoholic fatty liver disease (NAFLD).

METHODS: Hepcidin (*Hamp1*) knockout and floxed control mice were administered a high fat and high sucrose (HFS) or a regular control diet for 3 or 7 mo. Steatosis, triglycerides, fibrosis, protein and gene expression in mice livers were determined by histological and biochemical techniques, western blotting and real-time polymerase chain reaction.

RESULTS: Knockout mice exhibited hepatic iron accumulation. Despite similar weight gains, HFS feeding induced hepatomegaly in floxed, but not knockout, mice. The livers of floxed mice exhibited higher levels of steatosis, triglycerides and c-Jun N-terminal kinase (JNK) phosphorylation than knockout mice. In contrast, a significant increase in fibrosis was observed in knockout mice livers within 3 mo of HFS administration. The hepatic gene expression levels of sterol regulatory

element-binding protein-1c and fat-specific protein-27, but not peroxisome proliferator-activated receptor-alpha or microsomal triglyceride transfer protein, were attenuated in HFS-fed knockout mice. Knockout mice fed with regular diet displayed increased carnitine palmitoyltransferase-1a and phosphoenolpyruvate carboxykinase-1 but decreased glucose-6-phosphatase expression in the liver. In summary, attenuated steatosis correlated with decreased expression of lipogenic and lipid storage genes, and JNK phosphorylation. Deletion of *Hamp1* alleles *per se* modulated hepatic expression of beta-oxidation and gluconeogenic genes.

CONCLUSION: Lack of hepcidin expression inhibits hepatic lipid accumulation and induces early development of fibrosis following high fat intake. Hepcidin and iron may play a role in the regulation of metabolic pathways in the liver, which has implications for NAFLD pathogenesis.

Key words: *Hamp*; Iron; Non-alcoholic steatohepatitis; Metabolic genes; Steatosis; Non-alcoholic fatty liver disease; Steatohepatitis

Core tip: Due to obesity epidemic the incidence of non-alcoholic fatty liver disease (NAFLD) is on the rise. Iron contributes to disease severity and the expression of key iron regulatory hormone, hepcidin is modulated in NAFLD patients. The underlying mechanisms are unknown. We have generated hepcidin knockout mice with iron overload phenotype. This study investigates the role of hepcidin in NAFLD by using high fat and high sucrose-fed knockout mice as an experimental model of NAFLD. Our findings showed attenuated steatosis and early fibrosis development suggesting a role for hepcidin in the regulation of metabolic processes in the liver, and in NAFLD.

Lu S, Bennett RG, Kharbanda KK, Harrison-Findik DD. Lack of hepcidin expression attenuates steatosis and causes fibrosis in the liver. *World J Hepatol* 2016; 8(4): 211-225 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i4/211.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i4.211

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disease ranging from simple benign steatosis to non-alcoholic steatohepatitis (NASH). NASH, a more aggressive form of disease, is characterized by the presence of lobular inflammation, fibrosis, hepatocellular ballooning and Mallory-Denk bodies[1,2]. NASH with progressive fibrosis can progress to cirrhosis and end stage liver disease[1,3,4].

The precise mechanisms of NASH development are not well understood. Although a so-called "two-hit hypothesis"[5] has been widely adopted[6,7], NASH can also develop in the absence of insulin resistance and simple benign steatosis (*i.e.*, initial hit)[8]. The potential candidates regarded as the "second hit" include oxidative stress, inflammation and changes in mitochondrial function[7,9-12]. Iron is also considered as a "second hit" in liver injury[13] and a role for iron has been reported in NASH pathogenesis. Patients with NAFLD/NASH frequently display elevated serum iron indices and hepatic iron content[14,15]. A strong correlation between hepatic iron content and the level of liver fibrosis in NAFLD/NASH patients has been shown[16-18]. Phlebotomy has also been suggested to alleviate insulin resistance in NAFLD patients[19].

The mechanisms by which iron contributes to NAFLD/NASH pathogenesis have mainly been attributed to oxidative stress, which can induce lipid peroxidation[20] and ultimately the activation of fibrotic signaling[21]. Studies with genetic haemochromatosis (GH) patients have shown the association of primary iron overload with fibrogenesis[22]. By using dietary experimental models, some studies have also suggested a reverse connection between iron and steatosis in rat livers[23,24]. In contrast, another study with a mouse dietary model of iron and high fat failed to show any significant effect of iron on steatosis[25]. The consequences of altered iron homeostasis for lipid metabolism in the liver are therefore unclear.

In this study, we employed hepcidin knockout mice with iron overload phenotype as an experimental model to further study the role of iron metabolism in NAFLD/NASH. Hepcidin is the central regulator of iron homeostasis, which is primarily synthesized in hepatocytes as a circulatory protein[26]. Unlike humans, which express only one hepcidin gene, *HAMP*, mice express two hepcidin genes, hepcidin (*Hamp1*) and *Hamp2*[27]. *Hamp1*, the human equivalent of mouse hepcidin gene, is by itself sufficient to regulate iron metabolism[28,29]. Hepcidin controls iron homeostasis by decreasing iron absorption from the absorptive enterocytes in the duodenum and the release of iron from the macrophages[30]. The lack of hepcidin expression in knockout mice and in human iron disorders results in iron accumulation both in the liver and other organs[30-32]. GH patients also display impaired hepcidin expression[33]. Although changes in both serum and liver hepcidin expression levels have been reported in NAFLD/NASH patients[14,34-38], the significance of hepcidin in disease pathogenesis is unknown. Our findings in this study with *Hamp1* knockout mice administered a high fat diet for different time points suggest a role for hepcidin in NAFLD/NASH pathogenesis. This mouse model may also serve as a novel experimental model of NAFLD/NASH.

MATERIALS AND METHODS

Animal studies

Animal experiments were approved by the Institutional

Table 1 SYBR green real-time quantitative polymerase chain reaction primer sequences of mouse genes

Mouse genes	Forward primer (5'-3')	Reverse primer (5'-3')
Mttp	CTCTTGGCAGTGCTTTTTCTCT	GAGCTTGTATAGCCGCTCATT
Cpt1a	CTCCGCCTGAGCCATGAAG	CACCAGTGATGATGCCATTCT
Fsp27	ATGAAGTCTCTCAGCCTCCTG	AAGCTGTGAGCCATGATGC
G6pc	CGACTCGCTATCTCCAAGTGA	GTTGAACCAGTCTCCGACCA
Pck1	CTGCATAACGGTCTGGACTTC	CAGCAACTGCCCGTACTCC
Pparα	AGAGCCCCATCTGTCCTCTC	ACTGGTAGTCTGCAAAACCAAA
Srebp-1c	GCAGCCACCATCTAGCCTG	CAGCAGTGAGTCTGCCTTGAT
Gapdh	GTGGAGATTGTTGCCATCAACGA	CCCATTCTCGGCCTTGACTGT

Animal Care and Use Committee at the University of Nebraska Medical Center. *Hamp1* floxed mice and ubiquitous *Hamp1* knockout mice, lacking hepcidin expression in all the organs, were generated, as published previously[29]. All mice are on C57BL/6J genetic background. *Hamp* floxed mice have been donated to the Jackson Laboratory (Catalog No. 026872, 026873).

Male mice (4-6-wk-old) were randomly separated into groups to feed with custom-made regular control (17.2% kcal from fat, 100 g/kg sucrose) or high fat and high sucrose (HFS) [42% kcal from fat (54% saturated, 9.7% trans-fat), 0.4% cholesterol, 340 g/kg sucrose] diets for 3 or 7 mo (Harlan Laboratories; TD.97184; TD.120654). Water was given ad libitum, and contained sucrose (40 g/L) with HFS-fed groups to imitate the western diet with fat and soda consumption.

Liver histology

Formalin-fixed, paraffin-embedded liver tissues were sectioned and stained with hematoxylin and eosin at UNMC Histology Core Facility. To determine fibrosis, sections were stained with Picrosirius Red, as published previously[39] and histomorphometric analyses were performed using ImageJ ROI manager software.

Quantification of liver triglycerides

Triglycerides were isolated, as described[40] and quantified using a commercial kit (Thermo Scientific DMA kit 2750) according to manufacturer's instructions.

Real-time polymerase chain reaction

cDNA was synthesized from liver tissue RNA with Superscript Ⅱ reverse transcriptase (Invitrogen), as described[41]. Real-time polymerase chain reaction (PCR) reactions were performed using iTaq Universal SYBR Green Supermix (Bio-Rad) with a StepOnePlus instrument (Life Technologies). Glyceraldehyde 3-phosphate dehydrogenase (*Gapdh*) gene was used as the endogenous control and gene amplification was calculated using comparative Ct method, as described[41]. Primer sequences are shown in Table 1.

Western blotting

Western blots using whole liver tissue lysate proteins were performed, as published previously[41]. Antibodies were obtained commercially (Cell Signaling, Sigma) and immune-reactive bands were detected by the ImmunStar™ kits (Bio-Rad).

Statistical analysis

The significance of differences between groups was determined by Student's *t*-test or one-way ANOVA by using SPSS software. A value of $P < 0.05$ was accepted as statistically significant.

RESULTS

To study the interaction of hepcidin-induced iron overload and lipid metabolism, ubiquitous *Hamp1* knockout and floxed control mice were administered either high fat and HFS or regular (control) diets, as described in Material and Methods. Since NAFLD/NASH progression can occur over a long period of time, mice were fed up to 7 mo. We have previously shown that the deletion of both *Hamp1* alleles induces significant iron overload in the livers of *Hamp1* knockout mice by using inductively coupled mass spectrometry (ICP-MS)[29]. ICP-MS analysis did not detect any significant level of iron in the livers of homozygous *Hamp1* floxed control mice. Gradual iron deposition was also indicated macroscopically by the darker color of knockout mice livers compared to those of floxed control mice (Figure 1).

Macroscopic analyses have confirmed that HFS intake induced hepatomegaly and more pronounced visceral fat accumulation in floxed control mice compared to knockout mice (Figure 1). In agreement, the liver weights of floxed mice were significantly higher (3.5 ± 0.46 g) than those of knockout mice (2.42 ± 0.54 g) particularly following 7 mo of HFS administration (Figure 2A and B). However, HFS intake induced similar increases in body weights in both floxed (Figure 2C) and knockout (Figure 2D) mice after either 3 or 7 mo-long feeding, as compared to respective controls fed with regular diet.

To further understand these discrepancies between floxed and knockout mice, histological analysis were performed. Hematoxylin and eosin staining of livers showed significantly higher levels of steatosis in floxed than in knockout mice both after 3 and 7 mo-long HFS feeding (Figure 3). The quantification of hepatic triglycerides further confirmed that HFS intake signifi-

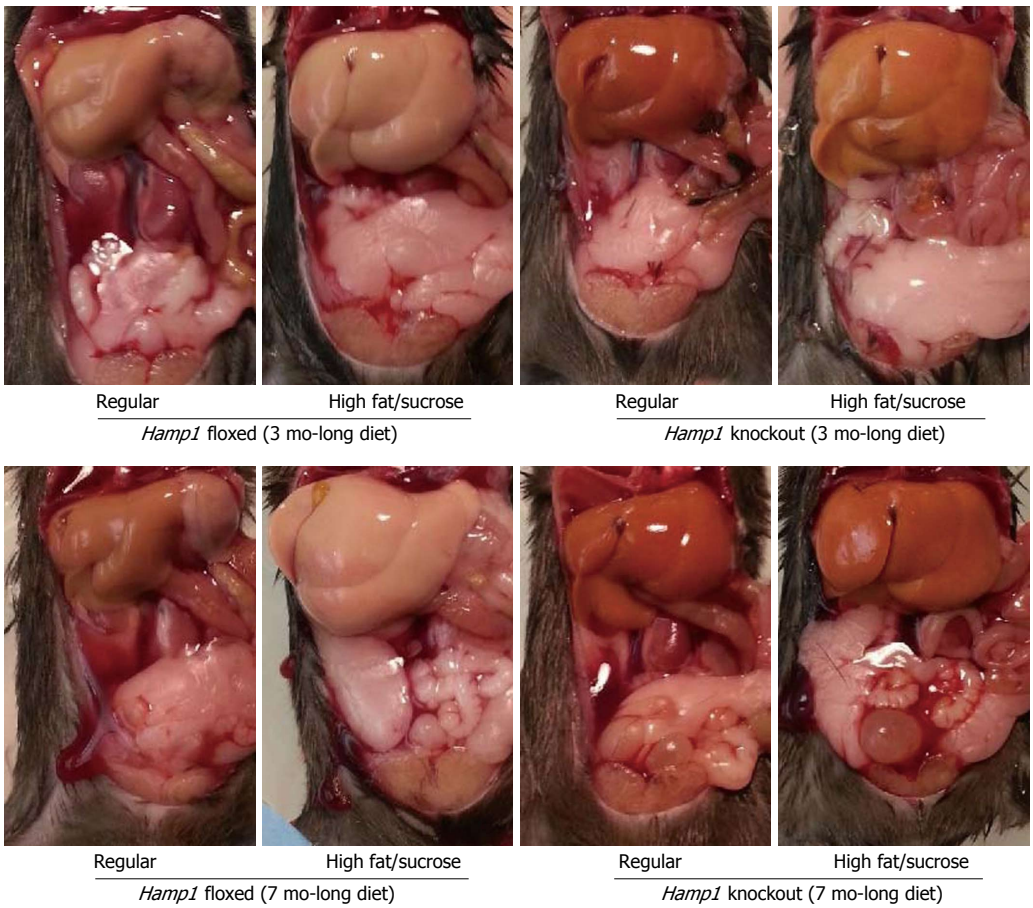

Figure 1 Macroscopic changes in *Hamp1* floxed and knockout mice fed with either a high fat and high sucrose or a regular control diet for 3 or 7 mo. Representative images showing the abdominal cavity of mice were obtained with a digital camera (Nikon).

cantly increased hepatic triglyceride content to different extents in floxed and knockout mice (Figure 4). At the end of 3 mo-long high fat intake, the level of hepatic triglyceride accumulation was 2.85-fold higher in floxed mice compared to knockout mice (1876.64 ± 370.84 and 657.98 ± 186.89 μmol/L per 100 g BW) (Figure 4A). Seven mo-long feeding yielded 2.07-fold higher hepatic triglyceride content in floxed than in knockout mice (1837.71 ± 118.12 and 886.91 ± 89.51 μmol/L per 100 g BW) (Figure 4B).

Sirius Red staining of liver sections showed that knockout, but not floxed, mice developed fibrosis within 3 mo of high fat intake (Figure 5A). The deletion of both *Hamp1* alleles per se has also caused weaker but significant level of fibrosis in the livers of knockout mice (Figure 5A). Quantification by ImageJ analysis has shown a 2.56-fold higher level of fibrosis in the livers of high fat-fed knockout than regular diet-fed knockout mice at 3 mo (Figure 5B) In contrast to 3 mo, 7 mo of high fat intake induced fibrosis in the livers of floxed mice (Figure 6A). Compared to 3 mo, regular diet feeding for 7 mo slightly increased the level of fibrosis in knockout mice livers (Figure 6A). Knockout mice with 7 mo-long high fat intake developed the highest level of fibrosis, as shown by Image J quantification (Figure 6B). The hepatic expression patterns of alpha smooth muscle actin (αSMA) protein, a marker for hepatic stellate cell activation, were in agreement with our histological analysis. Three months-long HFS feeding elevated liver αSMA expression in knockout, but not floxed, mice, as shown by Western blotting (Figure 7A). The deletion of *Hamp1* alleles by itself increased hepatic αSMA expression (Figure 7A). In contrast to 3 mo, 7 mo-long high fat intake increased αSMA expression in the livers of both floxed and knockout mice (Figure 7A).

Studies with JNK knockout mice fed with methionine-choline-deficient diet (MCD) diets have indicated a role for c-Jun N-terminal kinase (JNK) in steatosis[42]. JNK is activated by phosphorylation on serine residues[43]. The expression levels of phosphorylated JNK protein in the livers of *Hamp1* transgenic mice were therefore determined by western blotting using specific anti-phospho JNK antibodies (Figure 7B). Three-month-long high fat intake significantly stimulated JNK phosphorylation in the livers of floxed, but not knockout, mice (Figure 7B). In contrast, the effect of high fat intake on JNK phosphorylation in the liver was weakened by 7 mo-long feeding (Figure 7B).

To further investigate the underlying mechanisms of attenuated fat accumulation in the livers of knockout mice with high fat intake, mRNA expression levels of genes, which are known to be involved in lipid meta-

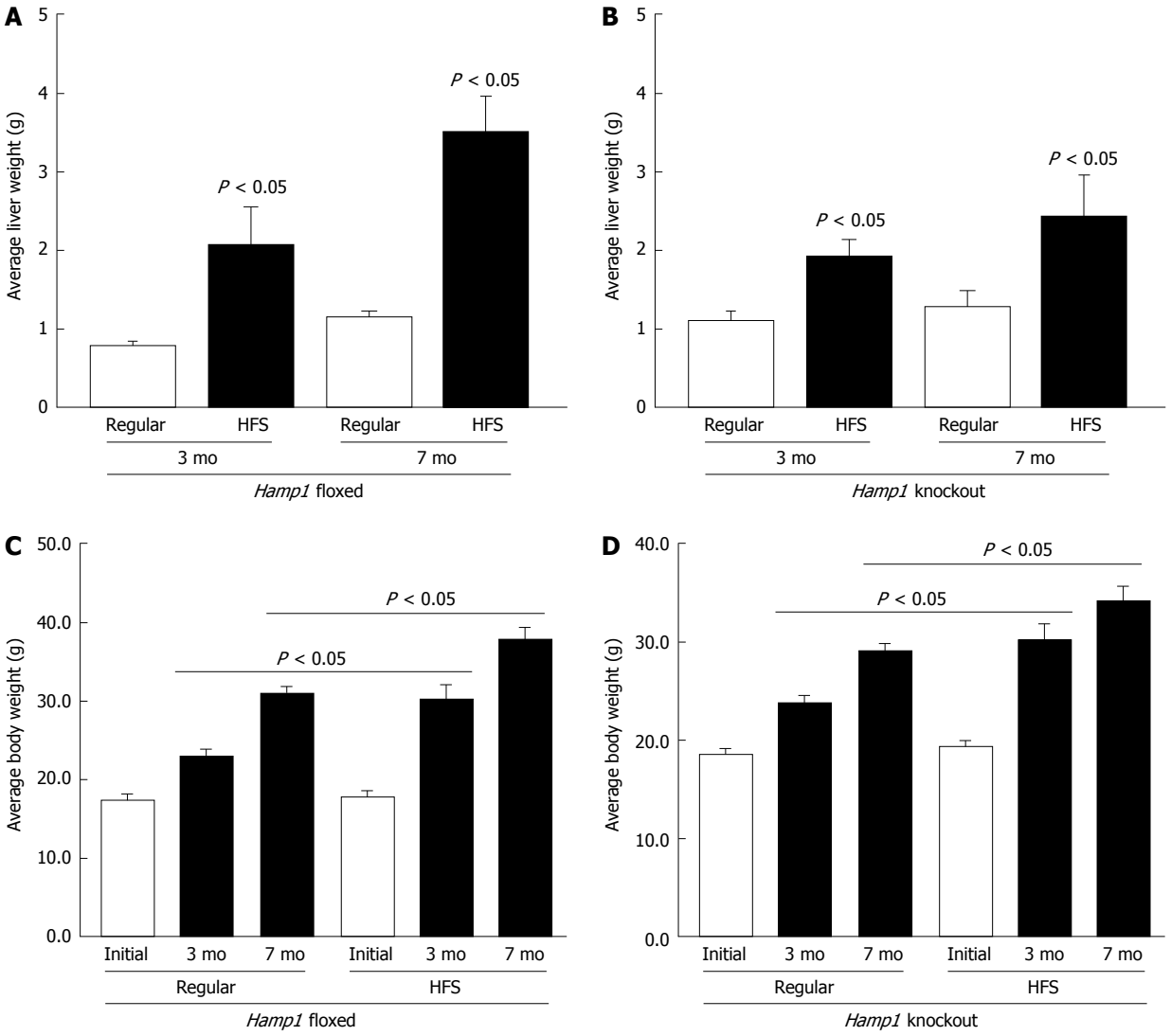

Figure 2 Liver and body weights of *Hamp1* floxed and knockout mice fed with high fat or regular diets. Average liver (A and B) and body (C and D) weights of floxed (A and C) and knockout (B and D) mice prior to (initial) and after feeding with high fat and sucrose (HFS) or regular control diets for 3 or 7 mo are shown as gram weight.

bolism, were examined by real-time PCR (Figure 8). The transcription factor, sterol regulatory element-binding protein-1c (Srebp-1c) is involved in *de novo* lipogenesis and its expression is also regulated at the transcriptional level[44,45]. The deletion of *Hamp1* alleles did not significantly alter basal hepatic expression levels of *Srebp-1c* (Figure 8A and B). Three months of high fat intake stimulated *Srebp-1c* expression by 13.39-fold in floxed and 7.40-fold knockout mice compared to controls (Figure 8A). In contrast, 7 mo of high fat intake elevated *Srebp-1c* expression only by 3.72-fold in floxed mice (Figure 8B). Furthermore, 7 mo-long high fat feeding did not significantly alter liver *Srebp-1c* expression in knockout mice (Figure 8B).

Fat-specific protein-27 (Fsp27) protein is involved in lipid droplet formation[46]. HFS feeding for 3 and 7 mo significantly induced *Fsp27* expression in the livers of floxed mice by 3.83- and 5.36-fold, respectively compared to regular diet-fed floxed mice (Figure 8C and D). The livers of knockout mice fed with HFS for 3 or 7 mo displayed significantly lower induction of *Fsp27* expression than floxed mice, which was more prominent at 7 mo (Figure 8C and D). Liver *Fsp27* expression was not significantly altered in knockout mice fed with regular diets for 3 or 7 mo compared to respective floxed controls (Figure 8C and D).

Microsomal triglyceride transfer protein (Mttp) protein is responsible for the production and secretion of VLDL particles[47]. The mRNA expression level of Mttp in the liver was not significantly altered in floxed and knockout mice after 3 mo of high fat intake (Figure 8E). However, high fat exposure for 7 mo significantly suppressed *Mttp* expression in the livers of both floxed and knockout mice (Figure 8F).

Changes in fatty acid oxidation in the liver play an important role in NAFLD pathogenesis. Peroxisome proliferator-activated receptor-alpha (Pparα) activates the transcription of genes involved in the regulation of

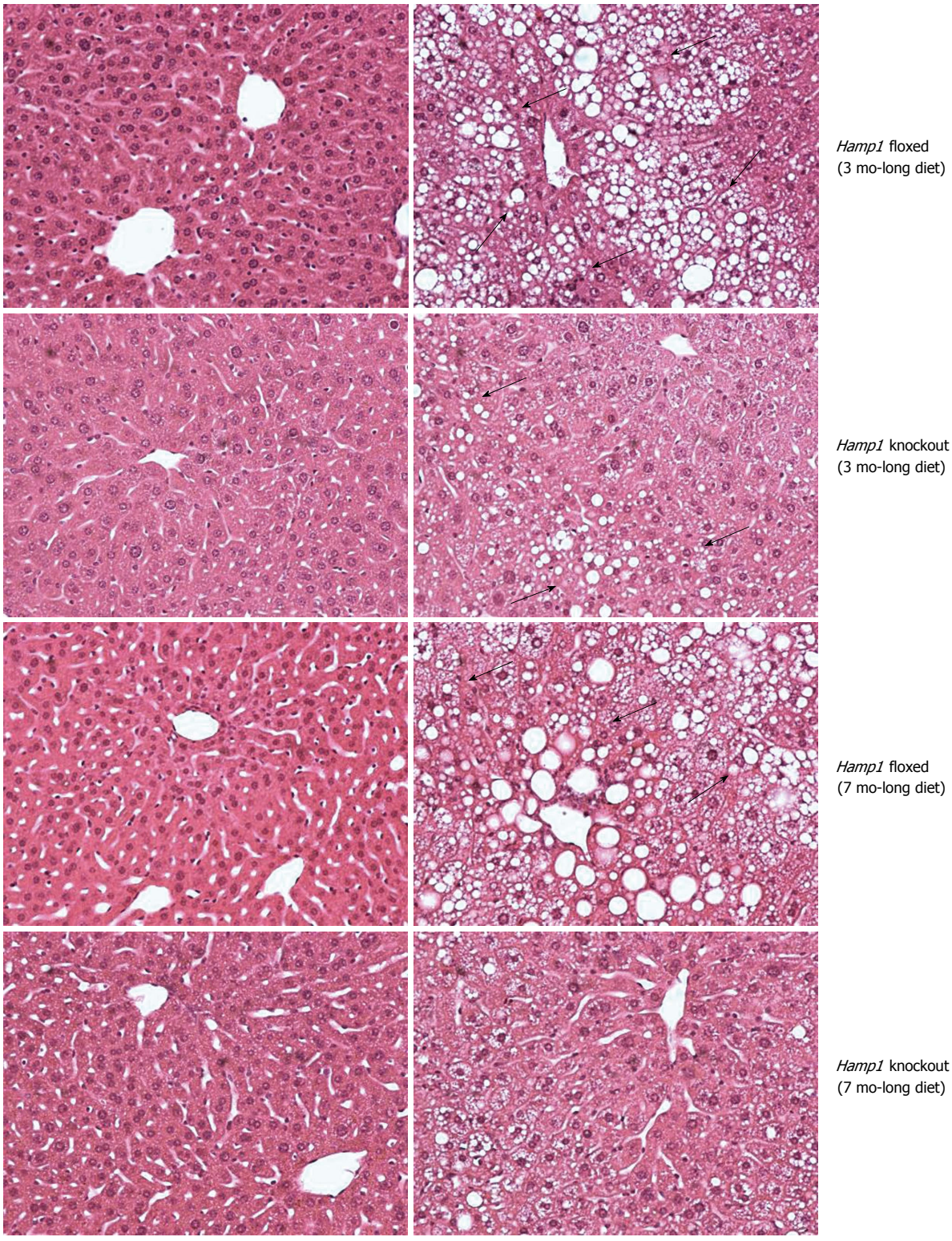

Figure 3 Liver histology in *Hamp1* floxed and knockout mice fed high fat or regular diets. Liver sections from floxed and knockout mice fed with high fat and sucrose (HFS) or regular diets for 3 and 7 mo were stained with hemotoxylin and eosin. Representative images obtained with a Nikon Eclipse E400 light microscope are shown (20 ×). Arrows indicate steatosis.

fatty acid β-oxidation[48]. The mRNA expression levels of Pparα were up-regulated at similar levels in the livers of both floxed and knockout mice within 3 mo of high fat feeding (Figure 9A). In contrast, the livers of floxed and knockout mice with 7 mo of high fat exposure displayed significantly inhibited Pparα expression (Figure 9B). Carnitine palmitoyltransferase-1 (Cpt1) is the rate-limiting enzyme in mitochondrial β-oxidation pathway[49].

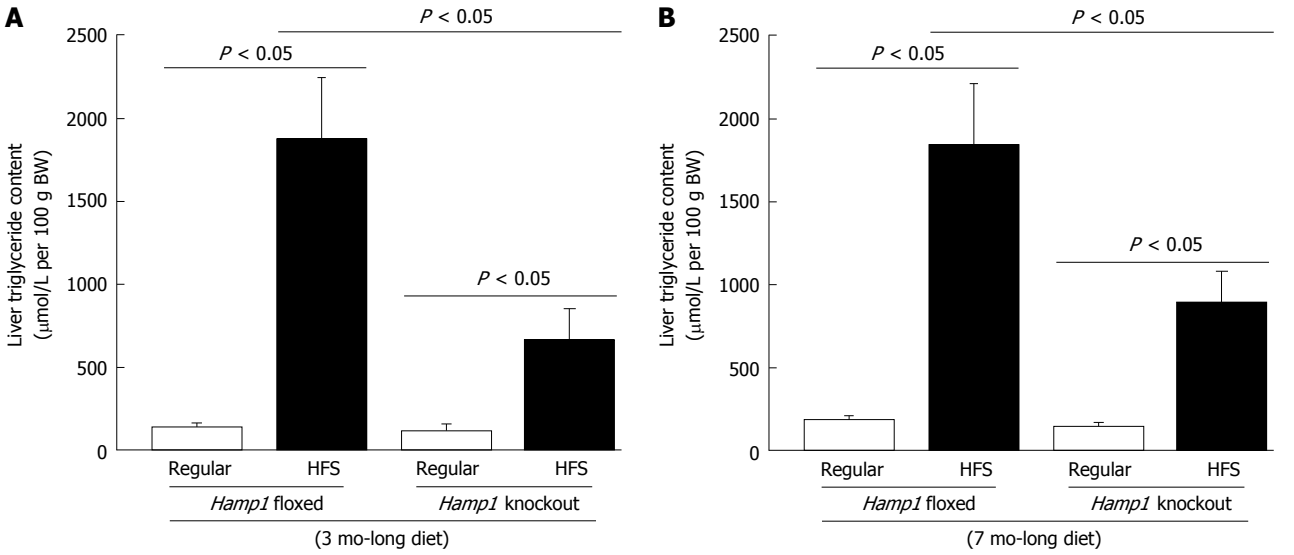

Figure 4 Liver triglyceride content in *Hamp1* floxed and knockout mice fed high fat or regular diets. Hepatic triglyceride content in floxed and knockout mice fed with regular or high fat sucrose (HFS) diets for 3 (A) or 7 (B) mo was quantified using 50 mg of wet liver tissue. Liver triglyceride amount was expressed as μmol per liver per 100 g body weight (μmol/L per 100 g BW).

Three month-long high fat administration did not exert a significant effect on hepatic *Cpt1a* expression in floxed and knockout mice (Figure 9C). On the other hand, the livers of knockout mice fed with regular diet for 7 mo expressed higher *Cpt1a* levels compared to floxed mice fed under similar conditions, suggesting a role for gradual iron deposition (Figure 9D). Seven month-long high fat intake did not alter hepatic *Cpt1a* expression in floxed mice (Figure 9D). In contrast, long-term high fat exposure significantly suppressed *Cpt1a* expression in the livers of knockout mice compared to knockout controls (Figure 9D).

Both phosphoenolpyruvate carboxykinase-1 (Pck1) and glucose-6-phosphatase (G6pc) are involved in gluconeogenesis. Similar to *Cpt1a*, the deletion of *Hamp1* alleles significantly up-regulated basal *Pck1* mRNA expression in the liver. In contrast, the absence of hepcidin expression suppressed basal hepatic *G6pc* mRNA expression (Figure 9E-H). Both 3 and 7 mo-long high fat exposure significantly inhibited *Pck1* and *G6pc* mRNA expression in the livers of both floxed and knockout mice (Figure 9E-H).

DISCUSSION

Changes in iron metabolism contribute to liver injury[22,50]. The deposition of iron in the liver correlates with disease severity in NAFLD patients[15]. The mechanisms by which excess iron contribute to NAFLD pathogenesis is unclear. Although inconclusive, some studies suggested a role for iron in the regulation of lipid metabolism[23-25]. Since hepcidin is the central regulator of iron metabolism, we investigated its role in fatty liver disease. We and others showed iron accumulation in *Hamp1* knockout mice[29,31,51]. *Hamp1* knockout mice were administered high fat diets for different time periods to generate pathological features in the liver, which are representative of NAFLD/NASH[2]. Collectively, our findings showed a strong correlation between hepcidin and lipid metabolism, and fibrosis in the liver.

The absence of hepcidin expression in *Hamp1* knockout mice exerted an inhibitory effect on hepatic lipid accumulation. This effect was not due to altered rates of diet consumption or weight gain and suggests the involvement of regulatory mechanisms. Previous studies showed a converse relationship between iron and lipid metabolism[22,23]. Since lack of hepcidin expression causes iron overload, elevated hepatic iron content may have interfered with fat accumulation in HFS-fed knockout mice. Furthermore, our findings suggest a role for JNK in this process. Namely, we showed a direct correlation between JNK phosphorylation and steatosis levels in floxed mice livers. In contrast, the livers of *Hamp1* knockout mice did not display significant JNK phosphorylation. Of note, the deletion of JNK1 reverses steatosis[52,53] and JNK is activated by phosphorylation[43]. Hepcidin-mediated changes in JNK activation may therefore be associated with attenuated steatosis in *Hamp1* knockout mice, particularly in early stages of high fat exposure.

Besides iron and JNK, altered metabolic gene expression in high fat-fed knockout mice may play a role in the inhibition of lipid accumulation. This is supported by our findings, which showed that the hepatic expression level of genes involved in lipogenesis and lipid storage do not adequately respond to high fat intake in *Hamp1* knockout mice. Namely, *Srebp-1c* and *Fsp27* expression were blunted in the livers of HFS-fed knockout, but not floxed, mice. These findings are significant because *Srebp-1c* and *Fsp27* expression are regulated at mRNA level[54]. Furthermore, the deletion of *Hamp1* alleles did not alter their basic expression levels.

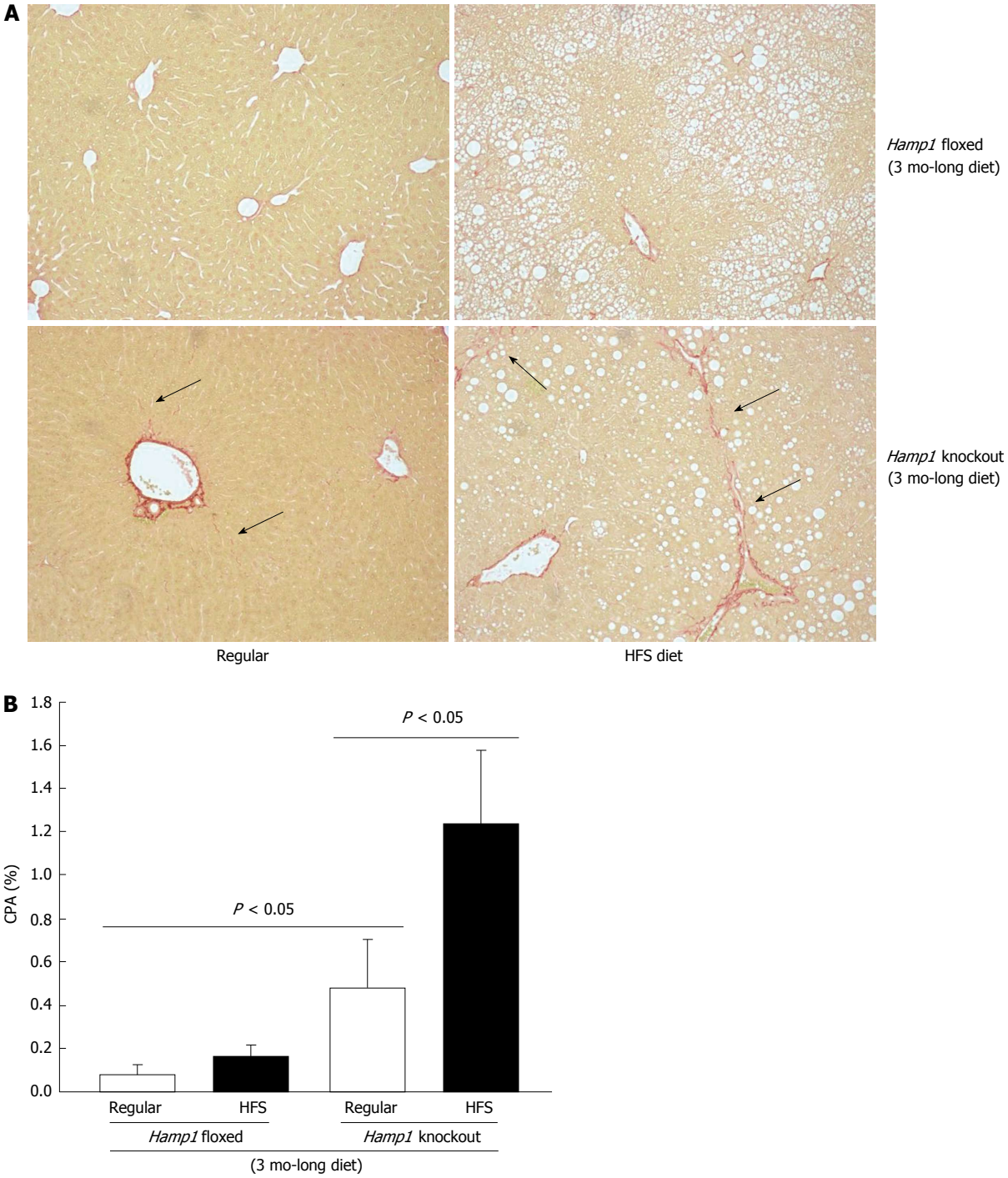

Figure 5 Fibrosis in *Hamp1* floxed or knockout mice fed high fat or regular diets for 3 mo. A: Fibrosis in the livers of floxed and knockout mice fed on regular or high fat sucrose (HFS) diets for 3 mo was detected by Sirius Red staining of tissue sections. Representative images obtained with Nikon Eclipse E400 light microscope are shown; B: 10 independent images (10 x) taken from each group were quantified using ImageJ ROI manager software. The collagen proportional area (CPA) was determined by calculating the percentage of collagen-occupied pixels against the total pixel values.

Iron-deficient rodents have been reported to display elevated lipogenic gene expression, which indirectly supports our findings[55-57]. Hepatic lipid homeostasis is also regulated by lipid export *via* VLDL secretion. The hepatic expression levels of *Mttp*, which is important in this process, were comparable between control and knockout mice. Our findings therefore suggest that decreased lipogenesis and lipid storage, but not increased lipid secretion, might lead to attenuated steatosis in high fat-fed *Hamp1* knockout mice.

Increased mitochondrial β-oxidation alleviates extra-hepatic fat burden in NAFLD by disposing of excess lipids[58]. Pparα, which induces the transcription of genes involved in β-oxidation, is itself regulated at the transcriptional level[59,60]. However, Pparα is not expected to contribute to liver pathology in *Hamp1*

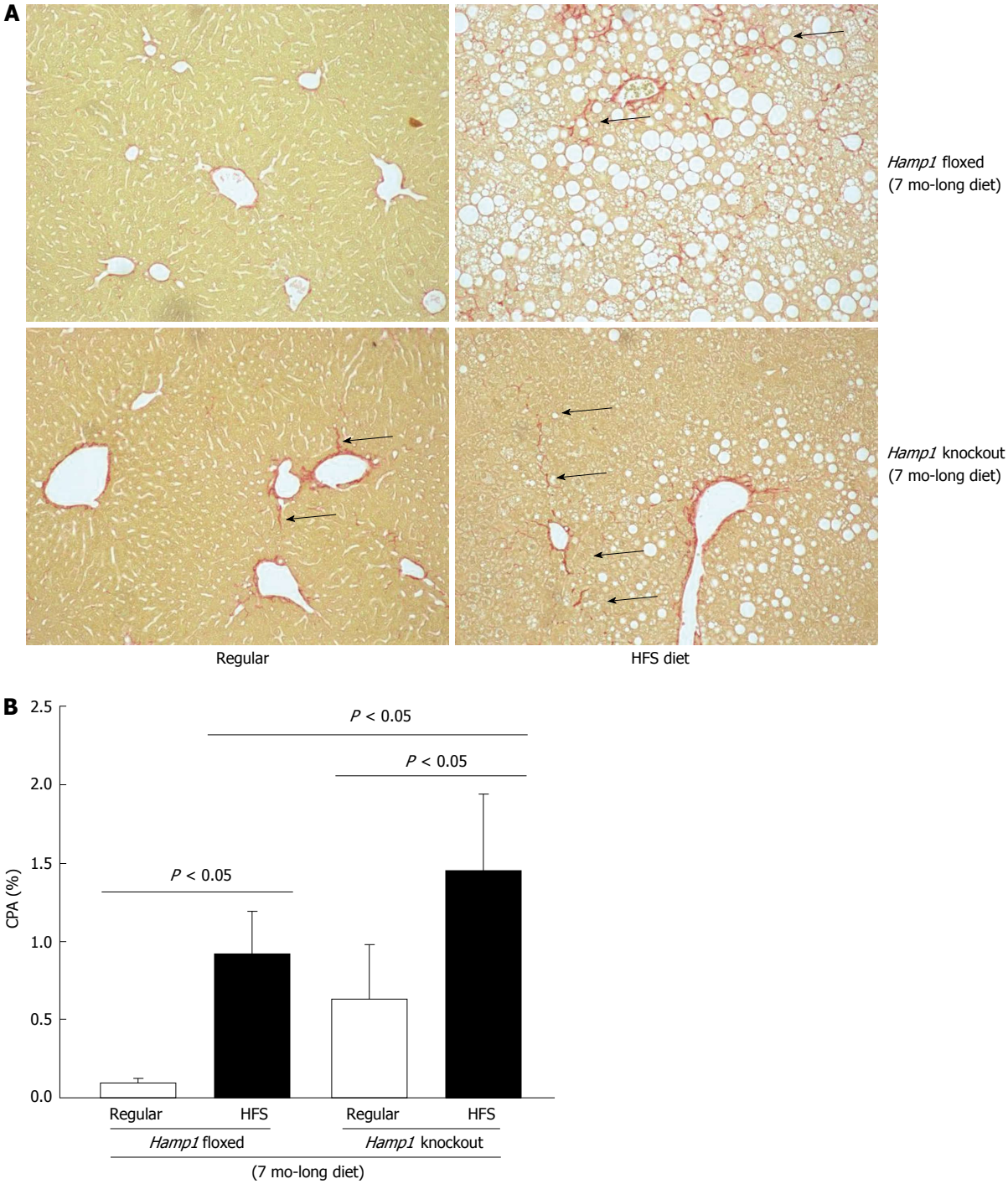

Figure 6 Fibrosis in *Hamp1* floxed or knockout mice fed high fat or regular diets for 7 mo. Liver fibrosis in floxed and knockout mice fed on regular or high fat sucrose (HFS) diets for 7 mo was detected (A) and quantified (B), as described above. CPA: Collagen proportional area.

knockout mice because HFS-fed floxed and knockout mice livers displayed similar levels of Pparα expression. Cpt1 is the rate-limiting enzyme in β-oxidation. Long-term high fat intake significantly suppressed *Cpt1a* expression only in knockout mice livers suggesting a role for it in attenuated steatosis in *Hamp1* knockout mice. Interestingly, *Hamp1* deletion by itself elevated hepatic *Cpt1a* expression. Besides β-oxidation, mitochondria is also important for iron metabolism[61]. It is feasible that iron accumulation caused by *Hamp1* deletion modulates metabolic gene expression in mitochondria. Of note, mitochondrial changes contribute to NAFLD/NASH pathology[11]. *Hamp1* deletion also altered the expression of gluconeogenic genes, *Pck1* and *G6pc*. Hepcidin serves as a gluconeogenic sensor in mice during starvation[62]. The reasons for the differential regulation of *Pck1* and *G6pc* expression in knockout mice livers are unclear. *Pck1* and *G6pc* are however regulated by various transcription factors including Foxo1[54] and iron regulates Foxo1 in adipocytes[63]. The net effect of hepcidin and

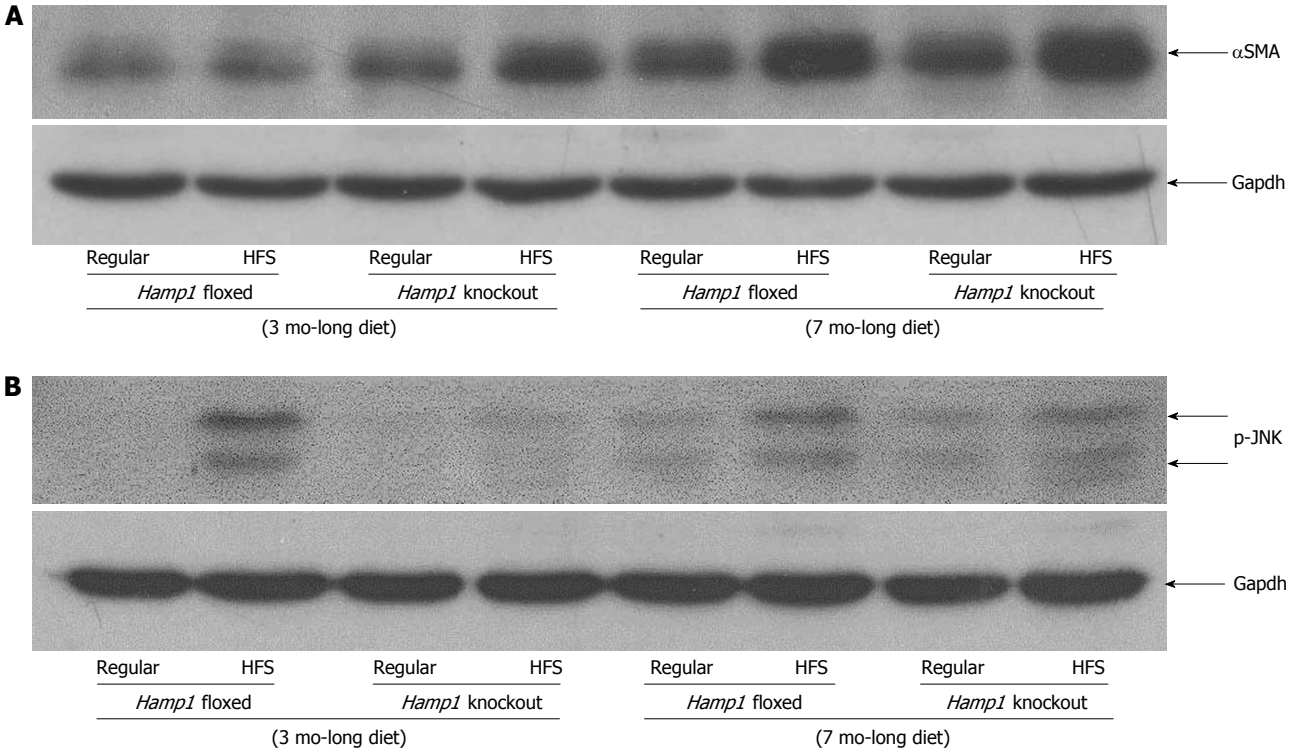

Figure 7 Protein expression levels of phosphorylated Jun N-terminal kinase and alpha smooth muscle actin in *Hamp1* floxed and knockout mice fed with high fat or regular diets for 3 or 7 mo. The expression levels of alpha smooth muscle actin (αSMA) (A) and phosphorylated Jun N-terminal kinase (p-JNK) (B) proteins in the livers of floxed and knockout mice fed with regular or high fat sucrose (HFS) diets for 3 or 7 mo was determined by western blotting, as described in Material and Methods. An anti-gapdh antibody was used as control to determine equal protein loading; Gapdh: Glyceraldehyde 3-phosphate dehydrogenase.

iron on metabolic processes in the liver requires further investigation.

Despite amelioration of steatosis, high fat administration caused injury in the livers of *Hamp1* knockout mice. In fact, knockout mice displayed an earlier and more pronounced development of fibrosis compared to control mice. Previous studies using MCD experimental models have shown that iron supplementation attenuates steatosis and triggers fibrosis[24,64]. Of note, MCD diet does not reproduce the metabolic changes observed in NAFLD/NASH patients and induces weight loss[65,66]. On the other hand, most high fat diet models induce metabolic changes but not fibrosis[66,67]. Furthermore, introduction of iron in the diet can create secondary effects by up-regulating liver hepcidin synthesis and thereby inhibiting the expression of iron exporter, ferroportin[68-70]. This will then lead to sequestration of iron in Kupffer cells and trigger inflammation. These artefacts are avoided in in our experimental system because iron accumulation is directly caused by the lack of hepcidin expression. Our high fat-fed *Hamp1* knockout mice, which develop early fibrosis, may therefore be an advantageous NAFLD/NASH model.

Simple steatosis is considered to be a benign condition in NAFLD patients. *In vivo* and *in vitro* studies have also shown this to be a beneficial process because triglycerides synthesis protects the liver from lipotoxicity induced by free fatty acid accumulation[64,71]. The decreased level of steatosis in synergy with iron might be responsible for early fibrosis development in the livers of HFS-fed *Hamp1* knockout mice.

In summary, our findings strongly suggest a role for hepcidin in the regulation of hepatic lipid and carbohydrate metabolism. There are currently a limited number of NASH experimental models[66]. *Hamp1* knockout mice will therefore be useful to investigate the molecular mechanisms of metabolic processes and fibrosis in NASH pathogenesis.

Lack of hepcidin expression due to the deletion of *Hamp1* alleles inhibited lipid accumulation in the liver following a high fat and high sucrose diet administration. Lack of c-jun kinase phosphorylation and the changes in the expression of metabolic genes, which are involved in lipogenesis and lipid storage, played a role in attenuated steatosis observed in hepcidin knockout mice. Knockout mice developed fibrosis within 3 mo of high fat exposure, which was more prominent at 7 mo. Deletion of *Hamp1* alleles by itself modulated hepatic expression of genes involved in mitochondrial fatty acid oxidation and gluconeogenesis. In summary, hepcidin is associated with the regulation of metabolic processes in the liver and the lack of hepcidin expression triggers early fibrosis development. High fat-fed hepcidin knockout mice may therefore serve as a useful animal model to study different aspects of fatty liver disease pathogenesis.

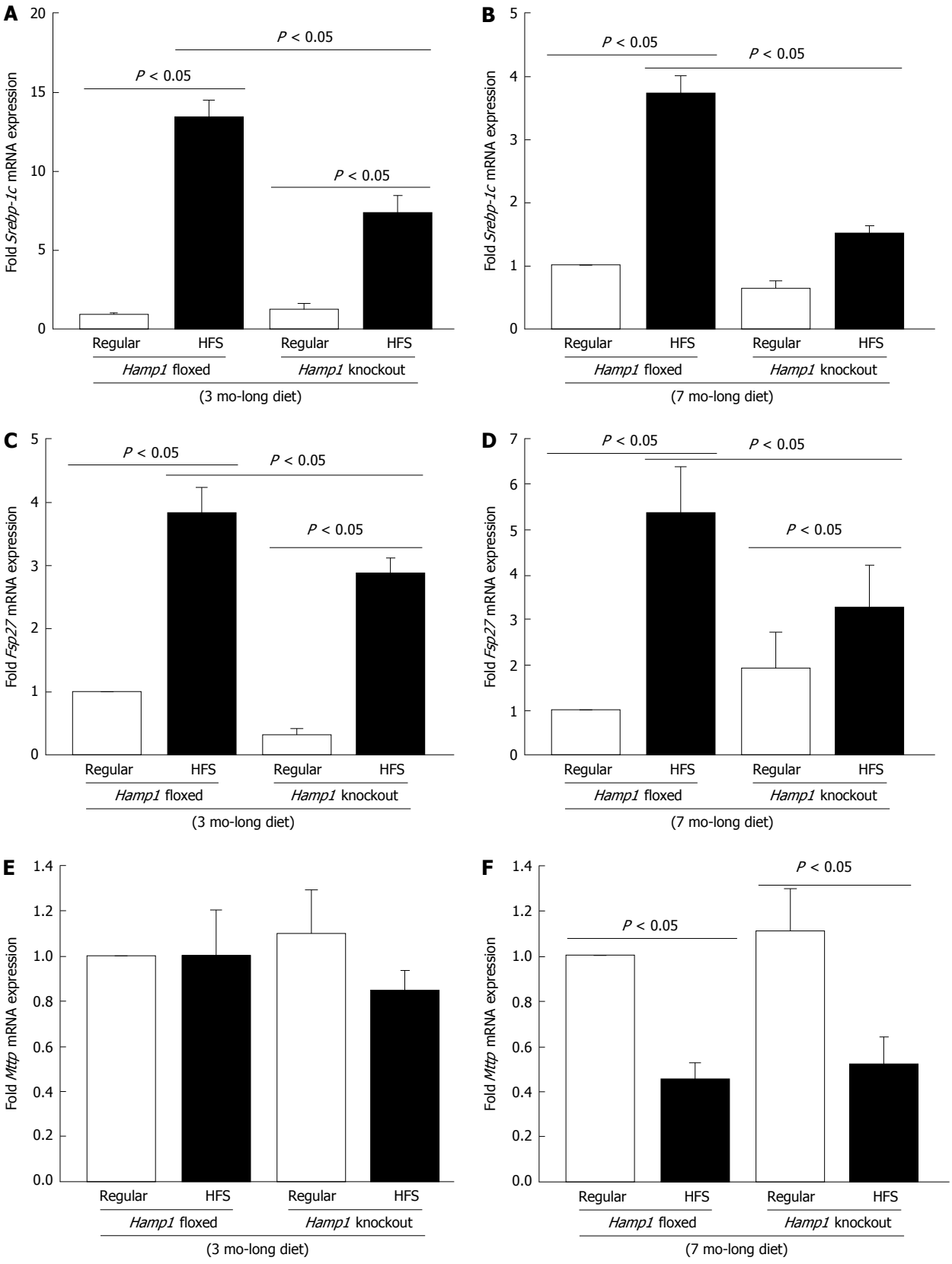

Figure 8 Expression of genes involved in lipogenesis, lipid storage and secretion. The mRNA expression levels of *Srebp-1c* (A and B), *Fsp27* (C and D), and *Mttp* (E and F) in the livers of floxed and knockout mice fed with regular and high fat sucrose (HFS) diets, was determined by real-time polymerase chain reaction. Gene expression in high fat-fed floxed or knockout and regular diet-fed knockout mice for 3 (A, C and E) or 7 mo (B, D and F) was expressed as fold change of that in floxed mice fed with a regular diet for the same time period.

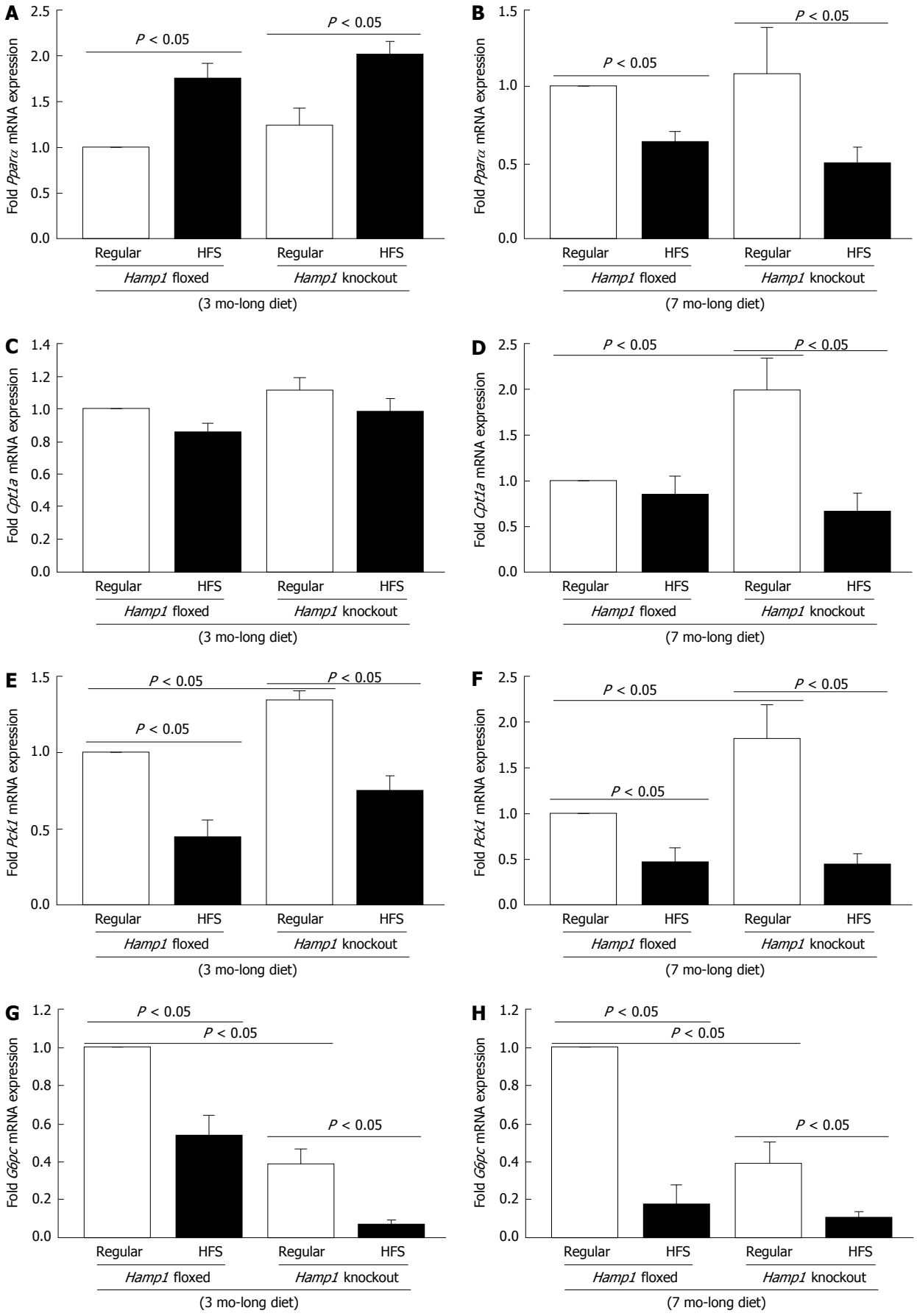

Figure 9 Expression of genes involved in β-oxidation and gluconeogenesis. The mRNA expression levels of *Pparα* (A and B), *Cpt1a* (C and D), *Pck1* (E and F) and *G6pc* (G and H), in the livers of *Hamp1* floxed and knockout mice fed with regular and high fat sucrose (HFS) diets, was determined by real-time polymerase chain reaction. Gene expression in high fat-fed floxed or knockout and regular diet-fed knockout mice for 3 (A, C, E and G) or 7 mo (B, D, F and H) was expressed as fold change of that in floxed mice fed with a regular diet for the same time period.

COMMENTS

Background

Obesity-related metabolic syndrome and its hepatic manifestation, non-alcoholic fatty liver disease (NAFLD) are important public health problems. Hepcidin, synthesized primarily by the liver, is the key iron-regulatory hormone. The authors have previously shown a role for hepcidin in alcoholic liver disease. Hepcidin expression is modulated in NAFLD patients but its significance is unknown. Furthermore, there are only a few animal models of NAFLD, which resemble human disease pathology. The authors are one of the few laboratories with hepcidin transgenic mice models, which were employed in this study to investigate NAFLD pathogenesis.

Research frontiers

NAFLD is a wide spectrum of disease ranging from simple benign fat accumulation (steatosis) to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation (steatohepatitis) and fibrosis in the liver. A correlation between hepatic iron levels and disease severity in NAFLD/NASH patients has been clearly demonstrated. Since hepcidin is the central iron regulator, it is essential to understand its role in NAFLD/NASH.

Innovations and breakthroughs

The previously published studies with hepcidin knockout mice generated in the laboratory have demonstrated significant iron accumulation in the liver. To establish a novel NAFLD/NASH experimental model, hepcidin knockout mice were fed with a high fat diet for different time periods. By showing that hepcidin is directly involved in lipid storage and fibrogenesis in the liver following high fat intake, the authors underlined the importance of hepcidin and iron homeostasis in NAFLD/NASH pathogenesis.

Applications

This study indicated a role for hepcidin in the regulation of metabolic processes and early fibrosis development in the liver. These findings will further understanding of the mechanisms involved in NAFLD/NASH progression and liver fibrosis. Furthermore, the high fat-fed hepcidin knockout mice, as a novel experimental NAFLD/NASH model, can be useful in the search for functional biomarkers and therapeutics for NAFLD/NASH.

Terminology

Hepcidin is essential for systemic iron homeostasis. Chronic high fat intake and obesity ultimately lead to metabolic syndrome, which is characterized by dyslipidemia and insulin resistance. Obesity also impairs metabolic functions and histology of the liver causing fat accumulation (steatosis), inflammation (steatohepatitis) and scar tissue formation (fibrogenesis), as observed in patients with NAFLD/NASH.

Peer-review

This manuscript investigated the role of key iron-regulatory protein, hepcidin in non-alcoholic fatty liver disease in hepcidin (*Hamp1*) knockout and floxed control mice administered a high fat and high sucrose or a regular control diet for 3 or 7 mo. The authors suggest that *Hamp1* and iron may play a role in the regulation of metabolic pathways in the liver, which has implications for NAFLD pathogenesis. This manuscript was well designed *in vivo* experiments and well written with all the results obtained.

REFERENCES

1 **Anstee QM**, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 330-344 [PMID: 23507799 DOI: 10.1038/nrgastro.2013.41]

2 **Brunt EM**, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999; **94**: 2467-2474 [PMID: 10484010 DOI: 10.1111/j.1572-0241.1999.01377.x]

3 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/hep.21327]

4 **Hernandez-Gea V**, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol* 2011; **6**: 425-456 [PMID: 21073339 DOI: 10.1146/annurev-pathol-011110-130246]

5 **Day CP**, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998; **114**: 842-845 [PMID: 9547102 DOI: 10.1016/S0016-5085(98)70599-2]

6 **Wree A**, Broderick L, Canbay A, Hoffman HM, Feldstein AE. From NAFLD to NASH to cirrhosis-new insights into disease mechanisms. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 627-636 [PMID: 23958599 DOI: 10.1038/nrgastro.2013.149]

7 **Basaranoglu M**, Basaranoglu G, Sentürk H. From fatty liver to fibrosis: a tale of "second hit". *World J Gastroenterol* 2013; **19**: 1158-1165 [PMID: 23483818 DOI: 10.3748/wjg.v19.i8.1158]

8 **Tiniakos DG**, Vos MB, Brunt EM. Nonalcoholic fatty liver disease: pathology and pathogenesis. *Annu Rev Pathol* 2010; **5**: 145-171 [PMID: 20078219 DOI: 10.1146/annurev-pathol-121808-102132]

9 **Malaguarnera M**, Di Rosa M, Nicoletti F, Malaguarnera L. Molecular mechanisms involved in NAFLD progression. *J Mol Med* (Berl) 2009; **87**: 679-695 [PMID: 19352614 DOI: 10.1007/s00109-009-0464-1]

10 **Takaki A**, Kawai D, Yamamoto K. Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). *Int J Mol Sci* 2013; **14**: 20704-20728 [PMID: 24132155 DOI: 10.3390/ijms141020704]

11 **Dowman JK**, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. *QJM* 2010; **103**: 71-83 [PMID: 19914930 DOI: 10.1093/qjmed/hcp158]

12 **Fabbrini E**, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology* 2010; **51**: 679-689 [PMID: 20041406 DOI: 10.1002/hep.23280]

13 **O'Brien J**, Powell LW. Non-alcoholic fatty liver disease: is iron relevant? *Hepatol Int* 2012; **6**: 332-341 [PMID: 22020821 DOI: 10.1007/s12072-011-9304-9]

14 **Martinelli N**, Traglia M, Campostrini N, Biino G, Corbella M, Sala C, Busti F, Masciullo C, Manna D, Previtali S, Castagna A, Pistis G, Olivieri O, Toniolo D, Camaschella C, Girelli D. Increased serum hepcidin levels in subjects with the metabolic syndrome: a population study. *PLoS One* 2012; **7**: e48250 [PMID: 23144745 DOI: 10.1371/journal.pone.0048250]

15 **Aigner E**, Weiss G, Datz C. Dysregulation of iron and copper homeostasis in nonalcoholic fatty liver. *World J Hepatol* 2015; **7**: 177-188 [PMID: 25729473 DOI: 10.4254/wjh.v7.i2.177]

16 **Valenti L**, Fracanzani AL, Bugianesi E, Dongiovanni P, Galmozzi E, Vanni E, Canavesi E, Lattuada E, Roviaro G, Marchesini G, Fargion S. HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2010; **138**: 905-912 [PMID: 19931264 DOI: 10.1053/j.gastro.2009.11.013]

17 **Nelson JE**, Wilson L, Brunt EM, Yeh MM, Kleiner DE, Unalp-Arida A, Kowdley KV. Relationship between the pattern of hepatic iron deposition and histological severity in nonalcoholic fatty liver disease. *Hepatology* 2011; **53**: 448-457 [PMID: 21274866 DOI: 10.1002/hep.24038]

18 **Nelson JE**, Brunt EM, Kowdley KV; Nonalcoholic Steatohepatitis Clinical Research Network. Lower serum hepcidin and greater parenchymal iron in nonalcoholic fatty liver disease patients with C282Y HFE mutations. *Hepatology* 2012; **56**: 1730-1740 [PMID: 22611049 DOI: 10.1002/hep.25856]

19 **Valenti L**, Fracanzani AL, Dongiovanni P, Bugianesi E, Marchesini G, Manzini P, Vanni E, Fargion S. Iron depletion by phlebotomy improves insulin resistance in patients with nonalcoholic fatty liver disease and hyperferritinemia: evidence from a case-control study. *Am J Gastroenterol* 2007; **102**: 1251-1258 [PMID: 17391316 DOI: 10.1111/j.1572-0241.2007.01192.x]

20 **Browning JD**, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest* 2004; **114**: 147-152 [PMID: 15254578 DOI: 10.1172/JCI22422]

21 **Ahmed U**, Latham PS, Oates PS. Interactions between hepatic iron and lipid metabolism with possible relevance to steatohepatitis. *World J Gastroenterol* 2012; **18**: 4651-4658 [PMID: 23002334 DOI: 10.3748/wjg.v18.i34.4651]

22 **Ramm GA**, Crawford DH, Powell LW, Walker NI, Fletcher LM, Halliday JW. Hepatic stellate cell activation in genetic haemochromatosis. Lobular distribution, effect of increasing hepatic iron and response to phlebotomy. *J Hepatol* 1997; **26**: 584-592 [PMID: 9075666 DOI: 10.1016/S0168-8278(97)80424-2]

23 **Cunnane SC**, McAdoo KR. Iron intake influences essential fatty acid and lipid composition of rat plasma and erythrocytes. *J Nutr* 1987; **117**: 1514-1519 [PMID: 3116180]

24 **Kirsch R**, Sijtsema HP, Tlali M, Marais AD, Hall Pde L. Effects of iron overload in a rat nutritional model of non-alcoholic fatty liver disease. *Liver Int* 2006; **26**: 1258-1267 [PMID: 17105592 DOI: 10.1111/j.1478-3231.2006.01329.x]

25 **Choi JS**, Koh IU, Lee HJ, Kim WH, Song J. Effects of excess dietary iron and fat on glucose and lipid metabolism. *J Nutr Biochem* 2013; **24**: 1634-1644 [PMID: 23643521 DOI: 10.1016/j.jnutbio.2013.02.004]

26 **Ganz T**, Nemeth E. Hepcidin and iron homeostasis. *Biochim Biophys Acta* 2012; **1823**: 1434-1443 [PMID: 22306005 DOI: 10.1016/j.bbamcr.2012.01.014]

27 **Pigeon C**, Ilyin G, Courselaud B, Leroyer P, Turlin B, Brissot P, Loréal O. A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. *J Biol Chem* 2001; **276**: 7811-7819 [PMID: 11113132 DOI: 10.1074/jbc.M008923200]

28 **Lou DQ**, Nicolas G, Lesbordes JC, Viatte L, Grimber G, Szajnert MF, Kahn A, Vaulont S. Functional differences between hepcidin 1 and 2 in transgenic mice. *Blood* 2004; **103**: 2816-2821 [PMID: 14604961 DOI: 10.1182/blood-2003-07-2524]

29 **Lu S**, Seravalli J, Harrison-Findik D. Inductively coupled mass spectrometry analysis of biometals in conditional Hamp1 and Hamp1 and Hamp2 transgenic mouse models. *Transgenic Res* 2015; **24**: 765-773 [PMID: 25904410 DOI: 10.1007/s11248-015-9879-3]

30 **Ganz T**. Systemic iron homeostasis. *Physiol Rev* 2013; **93**: 1721-1741 [PMID: 24137020 DOI: 10.1152/physrev.00008.2013]

31 **Lesbordes-Brion JC**, Viatte L, Bennoun M, Lou DQ, Ramey G, Houbron C, Hamard G, Kahn A, Vaulont S. Targeted disruption of the hepcidin 1 gene results in severe hemochromatosis. *Blood* 2006; **108**: 1402-1405 [PMID: 16574947 DOI: 10.1182/blood-2006-02-003376]

32 **Nemeth E**, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004; **306**: 2090-2093 [PMID: 15514116 DOI: 10.1126/science.1104742]

33 **van Dijk BA**, Laarakkers CM, Klaver SM, Jacobs EM, van Tits LJ, Janssen MC, Swinkels DW. Serum hepcidin levels are innately low in HFE-related haemochromatosis but differ between C282Y-homozygotes with elevated and normal ferritin levels. *Br J Haematol* 2008; **142**: 979-985 [PMID: 18557745 DOI: 10.1111/j.1365-2141.2008.07273.x]

34 **Bekri S**, Gual P, Anty R, Luciani N, Dahman M, Ramesh B, Iannelli A, Staccini-Myx A, Casanova D, Ben Amor I, Saint-Paul MC, Huet PM, Sadoul JL, Gugenheim J, Srai SK, Tran A, Le Marchand-Brustel Y. Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. *Gastroenterology* 2006; **131**: 788-796 [PMID: 16952548 DOI: 10.1053/j.gastro.2006.07.007]

35 **Aigner E**, Theurl I, Theurl M, Lederer D, Haufe H, Dietze O, Strasser M, Datz C, Weiss G. Pathways underlying iron accumulation in human nonalcoholic fatty liver disease. *Am J Clin Nutr* 2008; **87**: 1374-1383 [PMID: 18469261]

36 **Senates E**, Yilmaz Y, Colak Y, Ozturk O, Altunoz ME, Kurt R, Ozkara S, Aksaray S, Tuncer I, Ovunc AO. Serum levels of hepcidin in patients with biopsy-proven nonalcoholic fatty liver disease. *Metab Syndr Relat Disord* 2011; **9**: 287-290 [PMID: 21417913 DOI: 10.1089/met.2010.0121]

37 **Hamza RT**, Hamed AI, Kharshoum RR. Iron homeostasis and serum hepcidin-25 levels in obese children and adolescents: relation to body mass index. *Horm Res Paediatr* 2013; **80**: 11-17 [PMID: 23817203 DOI: 10.1159/000351941]

38 **Sam AH**, Busbridge M, Amin A, Webber L, White D, Franks S, Martin NM, Sleeth M, Ismail NA, Daud NM, Papamargaritis D, Le Roux CW, Chapman RS, Frost G, Bloom SR, Murphy KG. Hepcidin levels in diabetes mellitus and polycystic ovary syndrome. *Diabet Med* 2013; **30**: 1495-1499 [PMID: 23796160 DOI: 10.1111/dme.12262]

39 **Junqueira LC**, Bignolas G, Brentani RR. Picrosirius staining plus polarization microscopy, a specific method for collagen detection in tissue sections. *Histochem J* 1979; **11**: 447-455 [PMID: 91593]

40 **Folch J**, Lees M, Sloane stanley GH. A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem* 1957; **226**: 497-509 [PMID: 13428781]

41 **Harrison-Findik DD**, Klein E, Crist C, Evans J, Timchenko N, Gollan J. Iron-mediated regulation of liver hepcidin expression in rats and mice is abolished by alcohol. *Hepatology* 2007; **46**: 1979-1985 [PMID: 17763462 DOI: 10.1002/hep.21895]

42 **Czaja MJ**. JNK regulation of hepatic manifestations of the metabolic syndrome. *Trends Endocrinol Metab* 2010; **21**: 707-713 [PMID: 20888782 DOI: 10.1016/j.tem.2010.08.010]

43 **Ip YT**, Davis RJ. Signal transduction by the c-Jun N-terminal kinase (JNK)--from inflammation to development. *Curr Opin Cell Biol* 1998; **10**: 205-219 [PMID: 9561845 DOI: 10.1016/S0955-0674(98)80143-9]

44 **Chen G**, Liang G, Ou J, Goldstein JL, Brown MS. Central role for liver X receptor in insulin-mediated activation of Srebp-1c transcription and stimulation of fatty acid synthesis in liver. *Proc Natl Acad Sci USA* 2004; **101**: 11245-11250 [PMID: 15266058 DOI: 10.1073/pnas.0404297101]

45 **Amemiya-Kudo M**, Shimano H, Yoshikawa T, Yahagi N, Hasty AH, Okazaki H, Tamura Y, Shionoiri F, Iizuka Y, Ohashi K, Osuga J, Harada K, Gotoda T, Sato R, Kimura S, Ishibashi S, Yamada N. Promoter analysis of the mouse sterol regulatory element-binding protein-1c gene. *J Biol Chem* 2000; **275**: 31078-31085 [PMID: 10918064 DOI: 10.1074/jbc.M005353200]

46 **Gong J**, Sun Z, Li P. CIDE proteins and metabolic disorders. *Curr Opin Lipidol* 2009; **20**: 121-126 [PMID: 19276890 DOI: 10.1097/MOL.0b013e328328d0bb]

47 **Hussain MM**, Nijstad N, Franceschini L. Regulation of microsomal triglyceride transfer protein. *Clin Lipidol* 2011; **6**: 293-303 [PMID: 21808658 DOI: 10.2217/clp.11.21]

48 **Berger J**, Moller DE. The mechanisms of action of PPARs. *Annu Rev Med* 2002; **53**: 409-435 [PMID: 11818483 DOI: 10.1146/annurev.med.53.082901.104018]

49 **Bartlett K**, Eaton S. Mitochondrial beta-oxidation. *Eur J Biochem* 2004; **271**: 462-469 [PMID: 14728673 DOI: 10.1046/j.1432-1033.2003.03947.x]

50 **Lunova M**, Goehring C, Kuscuoglu D, Mueller K, Chen Y, Walther P, Deschemin JC, Vaulont S, Haybaeck J, Lackner C, Trautwein C, Strnad P. Hepcidin knockout mice fed with iron-rich diet develop chronic liver injury and liver fibrosis due to lysosomal iron overload. *J Hepatol* 2014; **61**: 633-641 [PMID: 24816174 DOI: 10.1016/j.jhep.2014.04.034]

51 **Nicolas G**, Bennoun M, Devaux I, Beaumont C, Grandchamp B, Kahn A, Vaulont S. Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. *Proc Natl Acad Sci USA* 2001; **98**: 8780-8785 [PMID: 11447267 DOI: 10.1073/pnas.151179498]

52 **Schattenberg JM**, Singh R, Wang Y, Lefkowitch JH, Rigoli RM, Scherer PE, Czaja MJ. JNK1 but not JNK2 promotes the development of steatohepatitis in mice. *Hepatology* 2006; **43**: 163-172 [PMID: 16374858 DOI: 10.1002/hep.20999]

53 **Singh R**, Wang Y, Xiang Y, Tanaka KE, Gaarde WA, Czaja MJ. Differential effects of JNK1 and JNK2 inhibition on murine steatohepatitis and insulin resistance. *Hepatology* 2009; **49**: 87-96 [PMID: 19053047 DOI: 10.1002/hep.22578]

54 **Rui L**. Energy metabolism in the liver. *Compr Physiol* 2014; **4**: 177-197 [PMID: 24692138 DOI: 10.1002/cphy.c130024]

55 **Sherman AR**. Lipogenesis in iron-deficient adult rats. *Lipids* 1978; **13**: 473-478 [PMID: 692295]

56 **Sherman AR**, Guthrie HA, Wolinsky I, Zulak IM. Iron deficiency hyperlipidemia in 18-day-old rat pups: effects of milk lipids, lipoprotein lipase, and triglyceride synthesis. *J Nutr* 1978; **108**: 152-162 [PMID: 619036]

57 **Davis MR**, Rendina E, Peterson SK, Lucas EA, Smith BJ, Clarke SL. Enhanced expression of lipogenic genes may contribute to hyperglycemia and alterations in plasma lipids in response to dietary iron deficiency. *Genes Nutr* 2012; **7**: 415-425 [PMID: 22228222 DOI: 10.1007/s12263-011-0278-y]

58 **Begriche K**, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. *Mitochondrion* 2006; **6**: 1-28 [PMID: 16406828 DOI: 10.1016/j.mito.2005.10.004]

59 **Pawlak M**, Lefebvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *J Hepatol* 2015; **62**: 720-733 [PMID: 25450203 DOI: 10.1016/j.jhep.2014.10.039]

60 **Pineda Torra I**, Jamshidi Y, Flavell DM, Fruchart JC, Staels B. Characterization of the human PPARalpha promoter: identification of a functional nuclear receptor response element. *Mol Endocrinol* 2002; **16**: 1013-1028 [PMID: 11981036 DOI: 10.1210/mend.16.5.0833]

61 **Richardson DR**, Lane DJ, Becker EM, Huang ML, Whitnall M, Suryo Rahmanto Y, Sheftel AD, Ponka P. Mitochondrial iron trafficking and the integration of iron metabolism between the mitochondrion and cytosol. *Proc Natl Acad Sci USA* 2010; **107**: 10775-10782 [PMID: 20495089 DOI: 10.1073/pnas.0912925107]

62 **Vecchi C**, Montosi G, Garuti C, Corradini E, Sabelli M, Canali S, Pietrangelo A. Gluconeogenic signals regulate iron homeostasis via hepcidin in mice. *Gastroenterology* 2014; **146**: 1060-1069 [PMID: 24361124 DOI: 10.1053/j.gastro.2013.12.016]

63 **Gabrielsen JS**, Gao Y, Simcox JA, Huang J, Thorup D, Jones D, Cooksey RC, Gabrielsen D, Adams TD, Hunt SC, Hopkins PN, Cefalu WT, McClain DA. Adipocyte iron regulates adiponectin and insulin sensitivity. *J Clin Invest* 2012; **122**: 3529-3540 [PMID: 22996660 DOI: 10.1172/JCI44421]

64 **Yamaguchi K**, Yang L, McCall S, Huang J, Yu XX, Pandey SK, Bhanot S, Monia BP, Li YX, Diehl AM. Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis. *Hepatology* 2007; **45**: 1366-1374 [PMID: 17476695 DOI: 10.1002/hep.21655]

65 **Larter CZ**, Yeh MM. Animal models of NASH: getting both pathology and metabolic context right. *J Gastroenterol Hepatol* 2008; **23**: 1635-1648 [PMID: 18752564 DOI: 10.1111/j.1440-1746.2008.05543.x]

66 **Schattenberg JM**, Galle PR. Animal models of non-alcoholic steatohepatitis: of mice and man. *Dig Dis* 2010; **28**: 247-254 [PMID: 20460919 DOI: 10.1159/000282097]

67 **Imajo K**, Yoneda M, Kessoku T, Ogawa Y, Maeda S, Sumida Y, Hyogo H, Eguchi Y, Wada K, Nakajima A. Rodent models of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Int J Mol Sci* 2013; **14**: 21833-21857 [PMID: 24192824 DOI: 10.3390/ijms141121833]

68 **Ramos E**, Kautz L, Rodriguez R, Hansen M, Gabayan V, Ginzburg Y, Roth MP, Nemeth E, Ganz T. Evidence for distinct pathways of hepcidin regulation by acute and chronic iron loading in mice. *Hepatology* 2011; **53**: 1333-1341 [PMID: 21480335 DOI: 10.1002/hep.24178]

69 **Feng Q**, Migas MC, Waheed A, Britton RS, Fleming RE. Ferritin upregulates hepatic expression of bone morphogenetic protein 6 and hepcidin in mice. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G1397-G1404 [PMID: 22517766 DOI: 10.1152/ajpgi.00020.2012]

70 **Corradini E**, Meynard D, Wu Q, Chen S, Ventura P, Pietrangelo A, Babitt JL. Serum and liver iron differently regulate the bone morphogenetic protein 6 (BMP6)-SMAD signaling pathway in mice. *Hepatology* 2011; **54**: 273-284 [PMID: 21488083 DOI: 10.1002/hep.24359]

71 **Listenberger LL**, Han X, Lewis SE, Cases S, Farese RV, Ory DS, Schaffer JE. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. *Proc Natl Acad Sci USA* 2003; **100**: 3077-3082 [PMID: 12629214 DOI: 10.1073/pnas.0630588100]

P- Reviewer: Yu DY **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Liu SQ

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i4.226

World J Hepatol 2016 February 8; 8(4): 226-230
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Total hepatectomy and liver transplantation as a two-stage procedure for fulminant hepatic failure: A safe procedure in exceptional circumstances

Rebeca Sanabria Mateos, Niamh M Hogan, Dimitri Dorcaratto, Helen Heneghan, Venkatesh Udupa, Donal Maguire, Justin Geoghegan, Emir Hoti

Rebeca Sanabria Mateos, Niamh M Hogan, Dimitri Dorcaratto, Helen Heneghan, Venkatesh Udupa, Donal Maguire, Justin Geoghegan, Emir Hoti, Hepatobiliary and Liver Transplant Surgical Unit, St. Vincent's University Hospital, Dublin 4, Ireland

Author contributions: Sanabria Mateos R designed and performed the research and wrote the paper; Hogan NM supervised the report; Dorcaratto D designed the research and contributed to the analysis; Heneghan H and Udupa V supervised the report; Maguire D, Geoghegan J and Hoti E provided clinical advice and supervised the report.

Institutional review board statement: This study was reviewed and approved by St. Vincent's University Hospital Institutional Review Board.

Informed consent statement: Patients were not required to give informed consent because the analyses use anonymous clinical data.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Correspondence to: Dr. Rebeca Sanabria Mateos, Hepatobiliary and Liver Transplant Unit, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland. rebecasanabria@gmail.com
Telephone: +353-1-2214000

Received: November 3, 2015
Peer-review started: November 3, 2015
First decision: December 4, 2015
Revised: December 17, 2015
Accepted: January 16, 2016
Article in press: January 19, 2016
Published online: February 8, 2016

Abstract

AIM: To evaluate the outcomes of two-stage liver transplant at a single institution, between 1993 and March 2015.

METHODS: We reviewed our institutional experience with emergency hepatectomy followed by transplantation for fulminant liver failure over a twenty-year period. A retrospective review of a prospectively maintained liver transplant database was undertaken at a national liver transplant centre. Demographic data, clinical presentation, preoperative investigations, cardiocirculatory parameters, operative and postoperative data were recorded.

RESULTS: In the study period, six two-stage liver transplants were undertaken. Indications for transplantation included acute paracetamol poisoning (n = 3), fulminant hepatitis A (n = 1), trauma (n = 1) and exertional heat stroke (n = 1). Anhepatic time ranged from 330 to 2640 min. All patients demonstrated systemic inflammatory response syndrome in the first post-operative week and the incidence of sepsis was high at 50%. There was one mortality, secondary to cardiac arrest 12 h following re-perfusion. Two patients required re-transplantation secondary to arterial thrombosis. At a median follow-up of 112 mo, 5 of 6 patients are alive and without evidence of graft dysfunciton.

CONCLUSION: Two-stage liver transplantation represents a safe and potentially life-saving treatment for carefully selected exceptional cases of fulminant hepatic failure.

Key words: Two-stage liver transplantation; Fulminant hepatic failure; Liver transplant; Survival

Core tip: We share our experience with selected cases of emergency total hepatectomy followed by liver transplantation for fulminant hepatic failure. This involves initial haemodynamic stabilization by recipient hepatectomy, creating a temporary porto-caval shunt to permit venous drainage during a variable anhepatic phase, then orthotopic transplantation once a suitable donor graft is available.

Sanabria Mateos R, Hogan NM, Dorcaratto D, Heneghan H, Udupa V, Maguire D, Geoghegan J, Hoti E. Total hepatectomy and liver transplantation as a two-stage procedure for fulminant hepatic failure: A safe procedure in exceptional circumstances. *World J Hepatol* 2016; 8(4): 226-230 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i4/226.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i4.226

INTRODUCTION

Liver transplantation is the treatment of choice for acute or chronic end-stage liver disease. In cases of acute liver failure, often the only life-saving intervention is a super-urgent liver transplantation. However, immediate allocation of a donor organ is not always achievable. Without urgent hepatectomy, some patients with fulminant hepatic failure develop a toxic hepatic syndrome with potentially catastrophic haemorrhage[1]. Toxic liver syndrome is defined as complete liver necrosis associated with critical multi-organ dysfunction[2]. In this grave circumstance, these critically-ill patients may benefit from a two-stage approach to transplantation; with urgent explantation of the toxic liver and creation of a temporary portocaval shunt, followed by transplantation as soon as a donor organ becomes available[2]. First reported in 1988 by Ringe *et al*[2] for a patient with primary graft failure causing multi-organ dysfunction, the goal of the first stage of this technique is haemodynamic and metabolic stabilisation. Subsequent to Ringe's description of this novel approach to retransplantation for primary graft failure, a wider variety of indications for this technique have been sporadically reported including liver trauma, spontaneous hepatic rupture, haemolysis elevated liver enzymes and low platelet syndrome associated with preeclampsia, and acute deterioration of chronic liver disease[2-11]. During the first stage of these two-stage transplantations, the inferior vena cava is retained and a porto-caval anastomosis allows systemic and portal venous drainage during the subsequent anhepatic period[2-11]. Once an allograft becomes available, the second stage involves orthotopic liver transplantation using a modified piggyback technique without veno-venous bypass[2-11].

MATERIALS AND METHODS

A retrospective review of a prospectively maintained database was undertaken to identify all patients who underwent two-stage liver transplantation at a single institution (a National Liver Transplant Unit) between January 1993 and March 2015. Demographic data, clinical presentation, preoperative investigations, operative details, postoperative course, and histopathological results were recorded. Data collection and analyses were performed with Statistical Package for the Social Sciences (version 16.0) (SPSS, Chicago, IL, United States). Descriptive statistics were computed for all variables. The Kolmogorov-Smirnov test was used to determine the variables' distribution. For nonparametric data, continuous variables are presented as median values (and range) and the Mann-Whitney *U* test was used for any two sample comparisons. Dichotomous variables were compared using the χ^2 test. All tests were two tailed and results with a *P*-value of < 0.05 were considered statistical significant.

RESULTS

During the study period, six cases of two-stage liver transplantation were undertaken in our centre. There was a male preponderance (4 males, 2 females). Median age at presentation was 28 years (range 20-47). Two patients had a past medical history of depression, no other co-morbidities were present. The most common indication for super-urgent transplantation was extensive liver necrosis secondary to paracetamol overdose ($n = 3$). One patient developed fulminant liver failure secondary to Hepatitis A infection. One patient had extensive haemorrhage secondary to liver trauma, and one patient developed exertional heat stroke causing ischemic hepatitis while running the final stages of an ultra-marathon. Five of six patients had evidence of toxic liver syndrome, as previously defined. The median model end stage liver disease was 39.50 (range 28-40). All patients had hypoglycemia and metabolic acidosis. In 50% of these cases, haemofiltration was initiated prior to hepatectomy, and all patients were intubated and mechanically ventilated before the procedure. The liver trauma case was the only patient who did not demonstrate signs of encephalopathy. Features of cerebral edema were present in 50% of cases. The anhepatic time ranged from 330 and 2640 min. In two patients, the hepatectomy was performed when a donor graft had been accepted for harvest but was not yet available. In one case, the hepatectomy was

Table 1 Transplant details and patient survival

	Sex, age	Indication	MELD	Toxic liver syndrome	CVVH	Hptc before graft availability	Inotrope requirements	Anhepatic phase (h)	Survival (mo)
1	F, 26	Paracetamol overdose	39	Yes	No	Yes	Yes	7	116
2	M, 41	Heat stroke	40	Yes	Yes	Yes	Yes	16	22
3	M, 47	Fulminant hepatits A	40	Yes	Yes	No	Yes	5.5	12 h
4	M, 20	Paracetamol overdose	40	Yes	No	No	No	5.8	107
5	F, 30	Paracetamol overdose	36	Yes	Yes	Yes	Yes	44	108
6	M, 21	Liver trauma	28	No	No	Yes	No	15	106

MELD: Model end stage liver disease; CVVH: Continous venoveno hemodyalisis; Hptc: Hepatectomy.

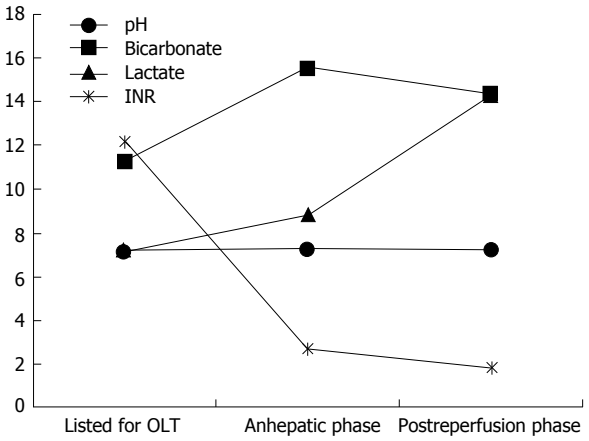

Figure 1 Evolution of coagulation and gasometry parameters at all three stages of the procedure. INR: International normalized ratio; pH: Potential of hydrogen; OLT: Orthotopic liver transplant.

undertaken prior to acceptance of a donor organ due to uncontrollable haemorrhage in the recipient and the patient was listed as "super-urgent" for transplantation. For the remaining three patients the hepatectomy was performed at the time of listing the patinet for superurgent transplantation (Table 1).

All patients underwent total hepatectomy and end-to side portocaval anastomosis with temporary abdominal closure as the first of a two-stage transplantation. During the anhepatic phase, patients were managed in the intensive care unit and received haemofiltration with plasma separation treatment. Orthotopic liver transplantation was then performed as soon as an allograft became available. In all cases, histological evaluation of the native liver confirmed the indication for emergency liver transplantation (total liver necrosis regardless the etiology). The use of noradrenaline was required in 4 patients before total hepatectomy with a median of 67 μg/min (range 50-200). During the anhepatic period the inotropic requirements increased to 74 μg/min (10-120), however inotropic requirements decreased immediately after reperfusion of the donor grafts, with a median noradrenaline requirement of 26 μg/min (range 5-60).

Arterial blood gasometry parameters demonstrated increased levels of lactate during the anhepatic phase from a median of 7.2 mmol/L pre-hepatectomy to 8.8 mmol/L. However their acidosis improved during the anhepatic phase as reflected by an increase in pH from median of 7.14 to 7.25, and an increase in bicarbonate from 11.3 to 15.6 mmol/L (Figure 1). Coagulation parameters pre-hepatectomy, during the anhepatic phase, and post transplant are shown in Table 2. During graft implantation, median blood loss was 8.5 L (range 2.5-43 L). All patients received transfusion of blood products, pools of platelets (median of 4 pools), plasma products (median of 9.5 units) and packed red cells (median 8.5 units). During the anhepatic phase, three patient developed ventricular tachycardia which was treated with amiodarone infusion. One patient (liver trauma case) required repeated cardioversions during the anhepatic phase as well as after reperfusion of the donor graft.

All patients (n = 6) fulfilled criteria for the diagnosis of systemic inflammatory response syndrome in the first post-transplant week, with 50% having a source of sepsis identified which required anti-microbial treatment with a single broad-spectrum agent. The median time to extubation was 7 d (range 5-15), haemodialysis duration was 20 d (range 6-28) and median hospital stay was 33 d (range 2-210). Two patients required re-transplantation secondary to arterial thrombosis (33%). One of these patients necessitated right hemicolectomy secondary to ileocolic arterial ischemia as well as the early hepatic artery thrombosis which required re-transplantation. There was a single mortality which was due to cardiac arrest and occurred 12 h after reperfusion of the graft, with a median follow-up of 112 mo.

DISCUSSION

Acute liver failure is a rapidly devastating pathology due to its potential to precipitate multi-organ failure, sepsis and cerebral oedema. Despite advances in supportive care, liver transplantation remains the only potentially life-saving treatment. Although fulminant hepatic failure (FHF) in not a common indication for orthotopic liver transplantation, these patients nonetheless represent a significant challenge for transplant surgeons. Data suggests that the most important prognostic indicators for patients with FHF undergoing transplantation are the degree of encephalopathy, patient's age, the etiology of FHF, and the time to transplantation with the majority of

Table 2 Biochemical data pre and post transplant

No. of patient		Dose NA	pH	Bicarbonate (mmol/L)	Lactate (mmol/L)	INR	Sodium (mmol/L)	Potasium (mmol/L)
	Before Hptc	70	7.14	11.30	5.32	11.25	133	3.9
1	Anhepatic	80	7.24	17.20	7.3	2.50	133	3.7
	Post reperfusion	60	7.27	16.40	6	1.85	135	5.4
	Before Hptc	64	7.15	13.30	9.20	15.80	136	5.5
2	Anhepatic	80	7.26	14.00	11	3.33	137	4.5
	Post reperfusion	20	7.20	14.60	10	2.27	145	3.9
	Before Hptc	50	7.06	14.70	10.20	13	138	4.8
3	Anhepatic	36	7.17	13.30	10	1.75	143	4.9
	Post reperfusion	48	7.12	13.80	10.5	1.75	146	5.0
	Before Hptc	None	7.34	11.10	5.30	17	133	3.6
4	Anhepatic	10	7.34	20.70	4.20	2.90	133	3.6
	Post reperfusion	5	7.32	18.60	3.7	1.64	136	3.8
	Before Hptc	200	7.16	11.30	12.00	6.3	148	3.7
5	Anhepatic	68	7.26	18.00	12.30	3.01	141	4.2
	Post reperfusion	32	7.19	14.00	6.7	2.47	144	5.20
	Before Hptc	None	7.02	10.70	3.30	10.59	151	5.0
6	Anhepatic	120	6.91	13.50	7.7	2.46	146	4.3
	Post reperfusion	10	7.01	12.70	7.7	1.61	144	3.8
	Before Hptc	67	7.14	11.3	7.26	12.12	137	4.35
		(50-200)	(7.02-7.34)	(10.70-14.7)	(3.3-12)	(6.3-17)	(133-152)	(3.6-5.5)
Median	Anhepatic	74	7.25	15.6	8.85	2.7	139	4.3
range		(10-120)	(6.91-7.34)	(13.30-20.70)	(4.2-12.3)	(1.75-3.33)	(133-146)	(3.6-4.9)
	Post reperfusion	26	7.19	14.3	14.3	1.8	144	4.45
		(5-60)	(7.01-7.32)	(12.7-18.60)	(12.7-18.60)	(1.61-2.47)	(135-146)	(3.8-5.4)

INR: International normalized ratio; pH: Potential of hydrogen; NA: Noradrenaline; Hptc: Hepatectomy.

authors concurring that transplantation within 48-72 h is critical to reduce mortality[1].

The anhepatic state requires considerable expertise in critical care to manage these gravely ill patients. In addition to cardiorespiratory support, haemofiltration and plasma separation are essential to prevent the development of severe lactate acidosis. The longest anhepatic period compatible with life is reported to be 66 h, which was recorded in a child with liver graft non-function after transplantation[12]. Herein we report a maximum anhepatic time of 44 h, in a patient who survived despite requiring re-transplantation secondary to hepatic artery thrombosis.

The number of cases of two-stage transplantation reported in the literature is scant and therefore survival rates vary widely[2-11]. However, advances in surgical techniques and supportive care appear to have exerted a beneficial effect on survival over time. In his seminal work almost two decades ago, Ringe *et al*[2,3] reported 32 patients treated with two-stage transplantation with 24 mortalities (75% mortality). In 2001, Domínguez Fernández *et al*[7] reported their outcomes from a series of eight patients who underwent emergency hepatectomy for FHF. Two patients died before a donor liver became available. A further five of six patients who underwent transplantation after an anhepatic period died postoperatively secondary to primary nonfunction or sepsis causing multiorgan failure (87.5% mortality). Herein, we report a series of six patients with a single death (16.6% mortality).

In conclusion, we report a series of cases of two-stage liver transplantation, which is a potentially life-saving procedure in carefully selected patients in exceptional clinical circumstances.

COMMENTS

Background

In the setting of fulminant liver failure, immediate donor graft allocation for life-saving transplant may not always be possible and a two-stage approach may be necessary. This involves initial haemodynamic stabilisation by recipient hepatectomy - creating a temporary porto-caval shunt to allow circulation during a variable anhepatic phase. Once an allograft becomes available, orthotopic transplantation is undertaken using the standard technique. In this study, the authors evaluated the outcomes of two-stage liver transplant at a single institution, between 1993 and March 2015.

Research frontiers

In cases of acute liver failure, the only life-saving procedure is frequently an emergency liver transplantation. However, immediate allocation of a donor organ is not always possible, particularly in the acute setting. Without urgent removal of the native liver, patients with fulminant hepatic failure, regardless of aetiology, can develop a life-threatening toxic hepatic syndrome. The results of this study suggest that in carefully selected patients a two-stage approach to super-urgent liver transplantation has utility, and can salvage these patients from the multi-organ failure arising from a toxic liver.

Innovations and breakthroughs

In this study, two-stage liver transplantation appears to be a valuable, albeit exceptional, approach to the management of fulminant liver failure with associated toxic liver syndrome. The authors report a series of six patients treated with emergency hepatectomy and temporary portocaval shunt, followed by urgent orthotopic liver transplantation once a suitable donor graft became available. There was a single perioperative mortality in this series. Although two of the surviving five patients subsequently required re-transplantation for hepatic artery thrombosis, all are alive and without evidence of current graft dysfunction at a median follow-up of 112 mo. The number of cases of two-stage transplantation reported in the literature is scant, therefore mortality and

morbidity rates are largely unknown. This report contributes such data to the transplant literature.

Applications

This study suggests that two-stage liver transplantation is a potentially life-saving procedure in carefully selected patients and in exceptional clinical circumstances.

Terminology

Toxic liver syndrome: A critical systemic inflammatory syndrome-like response defined as complete liver necrosis associated with critical multi-organ dysfuntion. Two-stage liver transplantation: A procedure which involves emergency hepatectomy and end-to-side portocaval anastmosis in the first stage, followed by liver transplantation when a donor organ becomes available in the second stage.

Peer-review

The authors of this paper evaluated the outcomes of two-stage liver transplantation as an exceptional procedure in carefully selected patients with fulminant hepatic failure. Further reports of such cases are necessary to better evaluate its safety and utility in the management of acute liver failure.

REFERENCES

1 **Gotthardt D**, Riediger C, Weiss KH, Encke J, Schemmer P, Schmidt J, Sauer P. Fulminant hepatic failure: etiology and indications for liver transplantation. *Nephrol Dial Transplant* 2007; **22** Suppl 8: viii5-viii8 [PMID: 17890263 DOI: 10.1093/ndt/gfm650]

2 **Ringe B**, Pichlmayr R, Lübbe N, Bornscheuer A, Kuse E. Total hepatectomy as temporary approach to acute hepatic or primary graft failure. *Transplant Proc* 1988; **20**: 552-557 [PMID: 3279648]

3 **Ringe B**, Lübbe N, Kuse E, Frei U, Pichlmayr R. Total hepatectomy and liver transplantation as two-stage procedure. *Ann Surg* 1993; **218**: 3-9 [PMID: 8328827 DOI: 10.1097/00000658-199307000-00002]

4 **Rozga J**, Podesta L, LePage E, Hoffman A, Morsiani E, Sher L, Woolf GM, Makowka L, Demetriou AA. Control of cerebral oedema by total hepatectomy and extracorporeal liver support in fulminant hepatic failure. *Lancet* 1993; **342**: 898-899 [PMID: 8105168 DOI: 10.1016/0140-6736(93)91947-K]

5 **So SK**, Barteau JA, Perdrizet GA, Marsh JW. Successful retransplantation after a 48-hour anhepatic state. *Transplant Proc* 1993; **25**: 1962-1963 [PMID: 8385827]

6 **Oldhafer KJ**, Bornscheuer A, Frühauf NR, Frerker MK, Schlitt HJ, Ringe B, Raab R, Pichlmayr R. Rescue hepatectomy for initial graft non-function after liver transplantation. *Transplantation* 1999; **67**: 1024-1028 [PMID: 10221488]

7 **Domínguez Fernández E**, Lange K, Lange R, Eigler FW. Relevance of two-stage total hepatectomy and liver transplantation in acute liver failure and severe liver trauma. *Transpl Int* 2001; **14**: 184-190 [PMID: 11499909 DOI: 10.1111/j.1432-2277.2001.tb00039.x]

8 **Erhard J**, Lange R, Niebel W, Scherer R, Kox WJ, Philipp T, Eigler FW. Acute liver necrosis in the HELLP syndrome: successful outcome after orthotopic liver transplantation. A case report. *Transpl Int* 1993; **6**: 179-181 [PMID: 8499073 DOI: 10.1111/j.1432-2277.1993.tb00643.x]

9 **Chiumello D**, Gatti S, Caspani L, Savioli M, Fassati R, Gattinoni L. A blunt complex abdominal trauma: total hepatectomy and liver transplantation. *Intensive Care Med* 2002; **28**: 89-91 [PMID: 11819007 DOI: 10.1007/s00134-001-1162-9]

10 **Heneghan HM**, Nazirawan F, Dorcaratto D, Fiore B, Boylan JF, Maguire D, Hoti E. Extreme heatstroke causing fulminant hepatic failure requiring liver transplantation: a case report. *Transplant Proc* 2014; **46**: 2430-2432 [PMID: 24998305 DOI: 10.1016/j.transproceed.2013.12.055]

11 **Guirl MJ**, Michael J, Weinstein JS, Goldstein RM, Levy MF, Klintmalm GB. "Two-stage total hepatectomy and liver transplantation for acute deterioration of chronic liver disease: A new bridge to transplantation. *Liver Transpl* 2004; **10**: 564-570 [PMID: 15048803 DOI: 10.1002/lt.20134]

12 **Hammer GB**, So SK, Al-Uzri A, Conley SB, Concepcion W, Cox KL, Berquist WE, Esquivel CO. Continuous venovenous hemofiltration with dialysis in combination with total hepatectomy and portocaval shunting. Bridge to liver transplantation. *Transplantation* 1996; **62**: 130-132 [PMID: 8693530 DOI: 10.1097/00007890-199607150-00026]

P- Reviewer: Ferraioli G, He ST, Savopoulos CG
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i4.231

World J Hepatol 2016 February 8; 8(4): 231-262
ISSN 1948-5182 (online)

SYSTEMATIC REVIEWS

Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy

Mihajlo Gjeorgjievski, Mitchell S Cappell

Mihajlo Gjeorgjievski, Mitchell S Cappell, Division of Gastroenterology and Hepatology, William Beaumont Hospital, Royal Oak, MI 48073, United States

Mitchell S Cappell, Oakland University William Beaumont School of Medicine, Royal Oak, MI 48073, United States

Author contributions: Gjeorgjievski M and Cappell MS are equal authors; they contributed equally to conceiving and planning this project, to performing the systematic review, to retrieving and analyzing the data from the literature, to writing the manuscript, and to editing of the final manuscript.

Conflict-of-interest statement: None for all authors. This paper does not discuss any confidential pharmaceutical industry data reviewed by Cappell MS as a consultant for the United States Food and Drug Administration (FDA) Advisory Committee on Gastrointestinal Drugs. Cappell MS is a member of the speaker's bureau for AstraZeneca. This paper does not discuss any drug manufactured or marketed by AstraZeneca.

Data sharing statement: The paper has no original data or original statistics presented. No additional data are, therefore, available.

Correspondence to: Mitchell S Cappell, MD, PhD, Chief, Division of Gastroenterology and Hepatology, William Beaumont Hospital, MOB #602, 3535 West Thirteen Mile Road, Royal Oak, MI 48073, United States. mscappell@yahoo.com
Telephone: +1-248-5511227
Fax: +1-248-551758

Received: October 2, 2015
Peer-review started: October 4, 2015
First decision: November 4, 2015
Revised: November 30, 2015
Accepted: January 16, 2016
Article in press: January 19, 2016
Published online: February 8, 2016

Abstract

AIM: To describe the pathophysiology, clinical presentation, natural history, and therapy of portal hypertensive gastropathy (PHG) based on a systematic literature review.

METHODS: Computerized search of the literature was performed *via* PubMed using the following medical subject headings or keywords: "portal" and "gastropathy"; or "portal" and "hypertensive"; or "congestive" and "gastropathy"; or "congestive" and "gastroenteropathy". The following criteria were applied for study inclusion: Publication in peer-reviewed journals, and publication since 1980. Articles were independently evaluated by each author and selected for inclusion by consensus after discussion based on the following criteria: Well-designed, prospective trials; recent studies; large study populations; and study emphasis on PHG.

RESULTS: PHG is diagnosed by characteristic endoscopic findings of small polygonal areas of variable erythema surrounded by a pale, reticular border in a mosaic pattern in the gastric fundus/body in a patient with cirrhotic or non-cirrhotic portal hypertension. Histologic findings include capillary and venule dilatation, congestion, and tortuosity, without vascular fibrin thrombi or inflammatory cells in gastric submucosa. PHG is differentiated from gastric antral vascular ectasia by a different endoscopic appearance. The etiology of PHG is inadequately understood. Portal hypertension is necessary but insufficient to develop PHG because many patients have portal hypertension without PHG.

PHG increases in frequency with more severe portal hypertension, advanced liver disease, longer liver disease duration, presence of esophageal varices, and endoscopic variceal obliteration. PHG pathogenesis is related to a hyperdynamic circulation, induced by portal hypertension, characterized by increased intrahepatic resistance to flow, increased splanchnic flow, increased total gastric flow, and most likely decreased gastric mucosal flow. Gastric mucosa in PHG shows increased susceptibility to gastrotoxic chemicals and poor wound healing. Nitrous oxide, free radicals, tumor necrosis factor-alpha, and glucagon may contribute to PHG development. Acute and chronic gastrointestinal bleeding are the only clinical complications. Bleeding is typically mild-to-moderate. Endoscopic therapy is rarely useful because the bleeding is typically diffuse. Acute bleeding is primarily treated with octreotide, often with concomitant proton pump inhibitor therapy, or secondarily treated with vasopressin or terlipressin. Nonselective β-adrenergic receptor antagonists, particularly propranolol, are used to prevent bleeding after an acute episode or for chronic bleeding. Iron deficiency anemia from chronic bleeding may require iron replacement therapy. Transjugular-intrahepatic-portosystemic-shunt and liver transplantation are highly successful ultimate therapies because they reduce the underlying portal hypertension.

CONCLUSION: PHG is important to recognize in patients with cirrhotic or non-cirrhotic portal hypertension because it can cause acute or chronic GI bleeding that often requires pharmacologic therapy.

Key words: Portal hypertensive gastropathy; Congestive gastropathy; Portal hypertension; Cirrhosis; Cirrhotic; Chronic liver disease; Nonvariceal upper gastrointestinal bleeding; Esophageal varices; Hepatic fibrosis

Core tip: Portal hypertensive gastropathy (PHG) is diagnosed by characteristic endoscopic findings of variably erythematous, small, polygonal areas surrounded by a whitish, reticular border in a mosaic pattern in the gastric fundus/body in a patient with portal hypertension of any etiology. The pathophysiology of PHG is inadequately understood. Portal hypertension is a prerequisite to develop PHG. PHG increases in frequency with increasing portal hypertension, liver disease progression, duration of liver disease, presence of esophageal varices, and endoscopic variceal obliteration. Pathogenesis is related to a hyperdynamic circulation induced by portal hypertension. Gastric mucosa in PHG exhibits greater susceptibility to gastrotoxic chemicals and poor wound healing. Acute or chronic gastrointestinal bleeding are the only clinical complications. Bleeding is typically mild-to-moderate and rarely fatal. Endoscopic therapy is rarely useful. Pharmacotherapy for acute bleeding includes octreotide with concomitant proton-pump-inhibitor therapy, or alternatively vasopressin. Nonselective β-adrenergic receptor antagonists, particularly propranolol, are used to prevent re-bleeding after acute bleeding or for chronic bleeding. Transjugular-intrahepatic-portosystemic-shunt and liver transplantation is ultimate therapies because they treat the underlying portal hypertension.

Gjeorgjievski M, Cappell MS. Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy. *World J Hepatol* 2016; 8(4): 231-262 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i4/231.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i4.231

INTRODUCTION

Portal hypertensive gastropathy (PHG) is an important, but underappreciated, cause of morbidity in patients with cirrhotic or non-cirrhotic portal hypertension. Researchers have recently intensely focused on this inadequately understood disease. However, the research studies have been published in a wide spectrum of journals including basic or biomedical journals not readily accessible to clinicians and a review incorporating the recent basic and clinical advances in this rapidly evolving subject is needed. This work systematically reviews this entity including pathophysiology, clinical presentation, natural history, and established, evolving, or experimental therapy, with a focus on data relevant to clinicians and an emphasis on recent data. This work aims to describe what is known about the disease and to expose gaps, requiring further research, in our current understanding of this disease.

MATERIALS AND METHODS

Computerized search of the literature was performed *via* PubMed using the following medical subject headings or keywords: "portal" and "gastropathy"; or "portal" and "hypertensive"; or "congestive" and "gastropathy"; or "congestive" and "gastroenteropathy". The following criteria were applied for study inclusion: Publication in peer-reviewed journals, and publication since 1980, except for publications from 1957-1980 of historical significance reviewed in the history section. Articles were independently evaluated by each author and selected for inclusion by consensus after a thorough discussion based on the following criteria: Well-designed, prospective trials; recent studies; large study populations; and study emphasis on PHG. However, data from retrospective series, reviews from internationally recognized authorities, and even case reports were included when prospective trials were unavailable.

RESULTS

History

Palmer[1], in 1957, proposed that the pathogenesis of erosive gastritis in cirrhotic patients was different than that in non-cirrhotic patients and that erosive gastritis

Table 1 Rates of portal hypertensive gastropathy in patients with portal hypertension

Ref.	Analyzed patients	Total number	No. (%) with PHG	No. (%) with mild PHG	No. (%) with severe PHG
McCormack *et al*[3]	Portal hypertension	127	65 (51%)	37 (29%)	28 (22%)
Sarin *et al*[5]	Portal hypertension	136	10 (7%)		
DeWeert *et al*[6]	Non-alcoholic liver disease	81	23 (28%)	Not reported	Not reported
McCormick *et al*[7]	Portal hypertension	93 endoscopies in 74 patients	85 endoscopies (91%)	6 (6%), moderate 61 (66%)	18 (19%)
Sarin *et al*[8]	Portal hypertension	107	4 (3.7%) (only cirrhotic)	Not reported	Not reported
Parikh *et al*[9]	Portal hypertension	118	71 (60%)	41 (58%)	30 (42%)
Sarin *et al*[10]	Portal hypertension with prior variceal bleeding	967	86 (9%)	56 (5.8%)	30 (3.1%)
Itha *et al*[11]	EHPVO in children	163	(12%)	Not reported	Not reported
Rana *et al*[12]	Portal hypertension	41	27 (66%)	19 (46%)	8 (20%)
El-Rifai *et al*[13]	Portal hypertension	24	14 (58%)	10 (42%) - moderate	4 (16%)
Sogaard *et al*[14]	Portal vein thrombosis	67	28 (42%)	Not reported	Not reported
Figueiredo *et al*[15]	Portal hypertension; cirrhosis	36	27 (75%)		5 (46%)
Erden *et al*[16]	Portal hypertension	57	15 (26.3%)	Not reported	Not reported
Duché *et al*[17]	Children, portal hypertension with biliary atresia	125	27 (21%)	Not reported	Not reported
Aydoğan *et al*[18]	Portal hypertension	51	30 (58%)	Not reported	Not reported
dos Santos *et al*[19]	Portal hypertension	43	22 (51%)	Not reported	Not reported
Pantham *et al*[20]	Esophageal varices undergoing TEE	24	12 (50%)	Not reported	Not reported
Abdollahi *et al*[21]	Autoimmune hepatitis	60	27 (45%)	Not reported	Not reported
de Alcantara *et al*[22]	Chronic liver disease *vs* EHPVO	35 *vs* 18	7 (20%) *vs* 8 (44.4%)	Not reported	Not reported
Aoyama *et al*[23]	Portal hypertension	119	35 (29%)	Not reported	Not reported

PHG: Portal hypertensive gastropathy; EHPVO: Extrahepatic portal vein obstruction; TEE: Transesophageal echocardiogram.

in cirrhotic patients resulted from mechanical venous back-pressure from portal hypertension, rather than a circulating, mucosal, or intraluminal toxic factor. This proposal was supported by successful reversal of erosive gastritis in cirrhotic patients with portal decompression by surgical shunts[1]. In 1984, Sarfeh *et al*[2] recognized a distinct form of gastric mucosal hemorrhage in patients who had portal hypertension, demonstrated by cirrhosis and gastroesophageal varices, which they called "portal hypertensive gastritis". They proposed that gastric mucosa in portal hypertension reacts differently from gastric mucosa without portal hypertension and these patients with portal hypertension may benefit from portal decompressive surgery. One year later, McCormack *et al*[3] reported that the gastritis in patients with portal hypertension differed from that in patients without portal hypertension in mucosal histology, nonresponse to standard therapy for conventional gastritis, and in occasionally having very similar histological changes in other gastrointestinal (GI) organs such as the colon. They called these gastritis-like changes in patients with portal hypertension "congestive gastropathy"[3], and classified it as "mild" or "severe", using criteria described by Taor *et al*[4].

Epidemiology

PHG can present at any age, including pediatric or adult patients. The reported prevalence of PHG varies greatly from 20% to 75% in patients with portal hypertension (Table 1)[3,5-23], and varies greatly from about 35% to 80% in patients with cirrhosis (Table 2)[21,23-68]. For example, in a study of 373 cirrhotic patients, 299 (80.2%) had PHG[34]. In the HALT-C trial, 374 (37%) of 1011 patients with biopsy-proven cirrhosis or bridging fibrosis from hepatitis C had PHG[69]. This wide variability likely reflects variability in classification criteria, interpretation of endoscopic lesions, study populations, and natural history of PHG[10,70,71].

PHG is usually mild as reported by McCormack *et al*[3] or in the NIEC study[32,70]. The prevalence of mild PHG in patients with portal hypertension ranges from 29%-57%, and of severe PHG ranges from 9%-46%[71].

Risk factors for PHG

The main predictors of PHG are portal hypertension and severe liver disease[72].

Portal hypertension: Most studies show that the frequency and severity of PHG is strongly correlated with the severity of portal hypertension, as indicated by multiple parameters, including hepatic venous pressure gradient (HVPG)[36,57], esophageal intravariceal pressure[29], and presence or size of esophageal varices[34,42,57,62,73]. Merkel *et al*[36] reported that the severity of PHG was correlated with the severity of portal hypertension as determined by HVPG, but this correlation was significant only for severe PHG (HVPG = 20.5 ± 4.0 mmHg) *vs* no PHG (HVPG = 17.4 ± 5.2 mmHg, P = 0.0004), and not for mild PHG (HVPG = 16.1 ± 3.2 mmHg) *vs* no PHG [17.4 ± 5.2 mmHg, not significant (NS)]. In a prospective study of 331 cirrhotic patients, Kim *et al*[57] found that patients with severe

Table 2 Rates of portal hypertensive gastropathy in patients with cirrhosis

Ref.	Patients	Total number	PHG	Mild	Severe
Sacchetti *et al*[24]	Cirrhosis	142	38 (27%)	28 (20%)	10 (7%)
D'Amico *et al*[25]	Cirrhosis	212	130 (61%)	110 (52%)	20 (9%)
Calès *et al*[26]	Cirrhosis	100	98 (98%)	57 (57%)	41 (41%)
Rabinovitz *et al*[27]	Cirrhosis	510	(43%)	Not reported	Not reported
Iwao *et al*[28]	Cirrhosis	47	32 (68%)	15 (32%)	17 (36%)
Taranto *et al*[29]	Cirrhosis	394	317 (80.5%)	Not reported	Not reported
Gupta *et al*[30]	Cirrhosis	230	(61%)	(52%)	(9%)
Iwao *et al*[31]	Cirrhosis	476	254 (53%)	208 (43%)	46 (9%)
Carpinelli *et al*[32]	Cirrhosis	566	362 (64%)	192 (34%)	170 (30%)
Zaman *et al*[33]	Cirrhosis	120	74 (62%)	47 (39%)	27 (23%)
Primignani *et al*[34]	Cirrhosis	373	299 (80%)	127 (34%)	172 (46%)
Chaves *et al*[35]	Cirrhosis *vs* schistosomiasis	43	18 (81%) *vs* 7 (33%)	Not reported	Not reported
Merkel *et al*[36]	Cirrhosis	62	49 (79%)	29 (46%)	20 (32%)
Merli *et al*[37]	Cirrhosis, with mild portal hypertension	222	48 (21%)	43 (19%)	5 (2%)
Ito *et al*[38]	Cirrhosis	47	13 (27%)	10 (21%)	3 (6%)
De Palma *et al*[39]	Cirrhosis	37	23 (62%)	Not reported	Not reported
Menchén *et al*[40]	Cirrhosis	549	353 (64%)	275 (50%)	77 (14%)
Yüksel *et al*[41]	Cirrhosis	114 total	76 (66%)	38 (33%)	38 (33%)
Fontana *et al*[42]	Cirrhosis or bridging fibrosis from hepatitis C	1016	374 (37%)	345 (34%)	29 (3%)
Bresci *et al*[43]	Cirrhosis	85	36 (42%)	Not reported	Not reported
Akatsu *et al*[44]	End stage liver disease	29	19 (65.5%)	18 (62.1%)	1 (3.4%)
Zardi *et al*[45]	Cirrhosis	266	84 (31%)	Not reported	Not reported
Barakat *et al*[46]	Cirrhosis with portal hypertensive duodenopathy	105	105 (100%)	17 (16.2%)	88 (83.8%)
Bellis *et al*[47]	Cirrhosis	59	44 (76%)	16 (27%)	28 (47%)
Gravante *et al*[48]	Liver transplant candidates with cirrhosis	80	41 (51.2%)	Not reported	Not reported
Canlas *et al*[49]	Cirrhosis	19	13 (68.4%)	Not reported	Not reported
Kim *et al*[50]	Cirrhosis	83	48 (57.8%)	Not reported	Not reported
Higaki *et al*[51]	Cirrhosis	21	8 (38%)	Not reported	Not reported
Frenette *et al*[52]	Cirrhosis	50	45 (90%)	28 (56%)	17 (34%) moderate
Tarantino *et al*[53]	Cirrhosis	153	88 (57.5%)	Not reported	Not reported
Curvêlo *et al*[54]	Cirrhosis	46	43 (93.4%)	21 (45%)	22 (47%)
Anegawa *et al*[55]	Cirrhosis	70	49 (70%)	32 (46%)	17 (24%)
Kumar *et al*[56]	Cirrhosis	254	140 (55%)	Not reported	Not reported
Kim *et al*[57]	Cirrhosis	331	298 (90%)	Mild 84 (25.4%)	214 (64.7%)
De Lisi *et al*[58]	Cirrhosis	611	448 (73.3%)	37.3%	36%
Abbasi *et al*[59]	Cirrhosis	102	87 (85%)	Not reported	Not reported
Ahmed *et al*[60]	Cirrhosis from hepatitis B or hepatitis C	360	300 (83%)	229 (64%)	71 (20%)
Garcia-Saenz-de-Sicilia *et al*[61]	Cirrhosis	105	72 (68.6%)	Not reported	Not reported
Abbasi *et al*[62]	Cirrhosis	217	172 (79.3%)	56 (25.8%)	116 (53.5%)
Aoyama *et al*[63]	Cirrhosis	60	13 (22%)	Not reported	Not reported
Laleman *et al*[64]	Cirrhosis with refractory chronic hepatic encephalopathy	36	13 (36%)	9 (25%)	4 (11%)
Giannini *et al*[65]	Cirrhosis and undergoing surgery for hepatocellular carcinoma	152	23 (15.1%)	Not reported	Not reported
Abdollahi *et al*[21]	Autoimmune hepatitis	60	27 (45%)	Not reported	Not reported
Aoyama *et al*[23]	Portal hypertension	119	35 (29%)	Not reported	Not reported
Aoyama *et al*[66]	Cirrhosis	134	42 (31%)	Not reported	Not reported
Zardi *et al*[67]	Cirrhosis without gastroesophageal varices	145	75 (51%)	45 (31%)	30 (20%)
Wu *et al*[68]	Cirrhosis	700	449 (64%)	Mild 208 (29.7), moderate 160 (22.9%)	Severe 81 (11.6%)

PHG: Portal hypertensive gastropathy.

PHG had significantly higher HVPG (15.6 ± 4.6 mmHg) than patients with mild PHG (10.7 ± 4.1 mmHg) or no PHG (4.9 ± 1.7 mmHg) ($P < 0.001$). Merkel *et al*[36] similarly reported in a small study that HVPG was significantly higher in patients with severe PHG as compared to mild or no PHG.

Primignani *et al*[34] confirmed the correlation of PHG with severity of portal hypertension, by correlating PHG with presence and size of esophageal varices. The rate of PHG was significantly higher in patients with esophageal varices [80 of 104 patients (76.9%)] than in patients without esophageal varices [51 of 84 (60.7%), $P < 0.007$]. The rate of PHG also significantly increased with increasing variceal size ($\chi^2 = 13.2$; $df = 1$, $P = 0.0003$). Abbasi *et al*[62] reported a significantly positive correlation between esophageal variceal size and rate of PHG ($r = 0.46$; $P < 0.001$). Taranto *et al*[29] reported more severe PHG in cirrhotic patients with more severe portal hypertension, as measured by esophageal intravariceal pressure. Iwao *et al*[28] reported that patients with severe PHG had elevated HVPG, high hepatic sinusoidal resistance, and low hepatic blood

flow, all markers of severe portal hypertension. For example, patients without PHG had hepatic sinusoidal resistance of 1218 ± 528 dyne × s^{-1} × cm^{-5}, patients with mild PHG had resistance of 1968 ± 944 dyne × s^{-1} × cm^{-5} ($P < 0.05$), and patients with severe PHG had resistance of 2082 ± 672 dyne × s^{-1} × cm^{-5} ($P < 0.01$). Presence of PHG was independent of patient age, sex, or cirrhosis etiology[28].

As discussed below, other data supporting an association between PHG and portal hypertension include resolution of PHG after intervention to decrease portal hypertension, including pharmacotherapy[74-78], transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation[74].

Contrariwise, a decided minority of studies showed no significant association between severity of portal hypertension and rate of PHG[8,9,16,26,28,30,31,47,54,67]. Curvêlo *et al*[54] found no significant difference in HVPG in cirrhotic patients with *vs* without PHG. Bellis *et al*[47] demonstrated similar findings. Among patients with portal hypertension from cirrhosis without esophageal varices, Zardi *et al*[67] reported that patients with PHG *vs* patients without PHG had similar mean portal vein diameter, splenic vein diameter, and portal flow volume, all markers of severity of portal hypertension. Erden *et al*[16] showed that the mean diameters of the left gastric, paraesophageal, and azygos veins, which are markers of portal hypertension, were not significantly different between patients with *vs* without PHG. The preponderance of data strongly suggest that the severity of portal hypertension is associated with the severity or frequency of PHG.

Cirrhotic *vs* non-cirrhotic portal hypertension: Primary liver disease usually occurs in PHG, but is not a prerequisite for PHG provided another cause of portal hypertension exists. PHG can occur among patients with non-cirrhotic portal fibrosis (NCPF), extrahepatic portal vein obstruction (EHPVO), hepatic veno-occlusive disease, and schistosomiasis[8,14,35,75,79].

The frequency of PHG appears to be higher in portal hypertension with cirrhosis than in portal hypertension without cirrhosis. Sarin *et al*[8] reported that patients with cirrhosis had a significantly higher frequency of PHG (37.1%) than that in patients with NCPF (16.7%; $P < 0.05$), or non-cirrhotic EHPVO (8.7%; $P < 0.01$) and had a more aggressive course of PHG with progression to more severe PHG with time. These phenomena are attributed to the worse liver function in patients with cirrhosis as compared to patients with NCPF or EHPVO[8]. Chaves *et al*[35] similarly reported a higher incidence of PHG in patients with cirrhosis *vs* patients with portal hypertension from etiologies including schistosomiasis or postsinusoidal hypertension. Chaves *et al*[35] reported that PHG occurred in 18 (81.8%) of 22 patients with cirrhosis *vs* only 7 (33.3%) of 21 patients with portal hypertension from schistosomiasis ($P < 0.05$). Parikh *et al*[9] reported a non-significant trend of more frequent PHG in patients with cirrhosis [64 of 102 patients (63%)] *vs* NCPF [7 of 16 patients (44%)], but the lack of statistical significance may have resulted from the small number of patients with NCPF.

Chaves *et al*[35] reported that the mosaic pattern was significantly more prevalent in patients with cirrhosis [12 of 22 patients (54.5%)] than in patients with schistosomiasis [2 of 21 patients (9.5%); $P < 0.05$]. Sarin *et al*[6] in a study of 50 patients with portal hypertension from various etiologies undergoing endoscopy, reported 6 (16.6%) of 36 patients with underlying cirrhosis had a mosaic pattern of PHG, whereas only 1 (8.5%) of 12 patients with EHPVO had a mosaic pattern of HPG (NS).

Cirrhosis etiology: Several research groups reported that the underlying etiology of cirrhosis did not affect PHG frequency or severity[13,71,80]. For example, Abbasi *et al*[62] reported among 217 patients with cirrhosis that PHG was unassociated with cirrhosis etiology ($r = 0.056$; $P = 0.414$), among 144 patients with hepatitis C, 36 patients with hepatitis B, 21 patients with cryptogenic cirrhosis, 15 patients with hepatitis C and hepatitis B coinfection, and 1 patient with hepatitis B and hepatitis D coinfection. Kim *et al*[57] similarly did not find a correlation between cirrhosis etiology and severity of PHG in a prospective study of 331 patients with cirrhosis, including cirrhosis etiologies of alcohol in 250, hepatitis B in 68, hepatitis C in 15, and cryptogenic cirrhosis in 8. Gupta *et al*[30] in a study of 230 patients with cirrhosis and esophageal varices found no significant difference in the rate of PHG between patients with cirrhosis from alcohol [32 of 52 patients (62%)] *vs* cirrhosis from other causes [110 of 178 patients (62%), P = NS]. Iwao *et al*[31] in an endoscopic study of 47 patients with histologically-proven cirrhosis reported no significant differences in etiology of cirrhosis between patients without PHG *vs* patients with mild or severe PHG.

Iwao *et al*[31] reported no association between etiology of cirrhosis and PHG severity. The etiologies of cirrhosis in this study included 7 from alcoholism *vs* 8 from chronic hepatitis in patients without PHG, 5 from alcoholism *vs* 10 from chronic hepatitis in patients with mild PHG, and 8 from alcoholism *vs* 9 from chronic hepatitis in patients with severe PHG (NS).

Liver disease duration: Generally, duration of liver disease positively correlates with development of PHG[5]. Merli *et al*[37] reported a cumulative incidence of 3% at 1 year, 10% at 2 years, and 24% at 3 years. Most cases were mild, with only 10% of cases reported as severe PHG in cirrhotic patients undergoing esophagogastroduodenoscopy (EGD) to screen for esophageal varices. Primignani *et al*[34] reported that the prevalence of PHG was only 56% in patients with newly diagnosed cirrhosis, rose to 75% in patients with previously diagnosed cirrhosis and no prior variceal bleeding, and rose further to 91% in patients with previously diagnosed cirrhosis and prior variceal bleeding treated with sclerotherapy ($\chi^2 = 34.25$; $df = 1$;

$P < 0.0001$). The frequency of PHG increased by 46% after 5 years of follow-up in patients with cirrhosis[34]. In 30%-60% of cases, preexistent PHG remained stable with time[72], but it can fluctuate in severity with time, with progression in 30%, and regression in 20% of cases[25,34,37]. Child-Pugh stage C cirrhosis was associated with faster progression of PHG[34].

Liver disease severity: Numerous studies reported PHG is correlated with liver disease severity, as measured by Child-Pugh stage[8,9,29,35,37,55,57,67]. The reported strength of this correlation is variable. Some studies showed correlation between all stages of cirrhosis and PHG, whereas other studies showed correlation only for specific stages of cirrhosis. Sarin *et al*[8] reported an 87% prevalence of PHG in patients with Child-Pugh stage C, *vs* only 13% prevalence in patients with Child-Pugh stage A. Another study reported that only Child-Pugh stage C was independently associated with PHG (OR = 2.68; 95%CI: 1.16-6.20, $P = 0.021$)[56]. Merli *et al*[37] reported, in a study of 48 patients with PHG among 222 patients with cirrhosis, that Child-Pugh stage B or C, and presence of esophageal varices were independent risk factors for developing PHG. De Lisi *et al*[58] reported a significantly higher prevalence of PHG in Child-Pugh stages B or C, as compared to stage A. Zardi *et al*[67] reported that cirrhotic patients without esophageal varices with severe PHG had significantly more frequently Child-Pugh stage C than patients with mild PHG. In another study, the MELD (model for end-stage liver disease) score was significantly correlated with PHG severity (mean MELD score in patients without PHG = 7.6 ± 1.7, in patients with mild PHG = 10.2 ± 4.0, and in patients with severe PHG = 11.3 ± 3.5; $P < 0.001$)[57]. In the HALT-C trial, hypoalbuminemia and hyperbilirubinemia, biochemical markers of advanced liver disease, were independent predictors of PHG in a logistic regression model (OR = 0.53, 95%CI: 0.37-0.76 for hypoalbuminemia; OR = 1.77, 95%CI: 1.25-2.51, for hyperbilirubinemia). Markers of portal hypertension (thrombocytopenia) and of insulin resistance (hyperglycemia) were also significant independent predictors of PHG.

Contrariwise, a minority of studies found no correlation between liver disease severity, as determined by Child-Pugh stage, and presence or severity of PHG[34,36,40,47,54,62,70,79]. For example, Primignani *et al*[34] reported the prevalence of severe PHG was lowest in Child-Pugh stage C. In the NIEC study, patients with Child-Pugh stage B had a higher prevalence of PHG than patients with stages A or C. Zardi *et al*[67] reported no significant differences in Child-Pugh stage or in MELD score among cirrhotic patients with *vs* without PHG. The preponderance of the data, however, suggest that severity of cirrhosis, as measured by Child-Pugh score, is correlated with frequency of PHG.

Correlation with varices: Many studies report a correlation between the presence and size of esophageal varices and severity of PHG. For example, among the 188 of 373 patients with cirrhosis not undergoing variceal sclerotherapy in the NIEC study, the prevalence of PHG was significantly higher in patients with esophageal varices [80 of 104 patients (77%)] than in patients without esophageal varices [51 of 84 patients (61%); $P = 0.007$]; and the prevalence of PHG significantly increased with increasing variceal size ($\chi^2 = 13.2$; $P < 0.0003$)[34]. Numerous other studies also demonstrated significant correlation between presence of esophageal varices and PHG, and several studies also demonstrated significant correlations between variceal size and PHG[9,13,29,42,56,57,62]. For example, Abbasi *et al*[62] reported that esophageal variceal size was significantly correlated with PHG frequency among 217 cirrhotic patients ($r = 0.46$; $P < 0.001$).

However, a few studies showed no correlation between presence or size of varices and PHG[26,28,30,47]. All these negative studies but one were relatively small. Gupta *et al*[30] reported no significant association between frequency of PHG and size of esophageal varices among 230 cirrhotic patients. Similarly, in a study of 59 patients with cirrhosis, Bellis *et al*[47] showed a non-significant trend towards more severe PHG in patients with large *vs* small varices. For example, three (50%) of 6 patients without esophageal varices had PHG, 6 of 10 patients (60%) with small varices had PHG, 19 of 25 patients (76%) with medium-sized varices had PHG, and 16 of 18 patients (89%) with large varices had PHG (NS). Iwao *et al*[28] further reported that the frequency of PHG was not correlated with esophageal variceal size. The mean grade of gastroesophageal varices was 1.4 ± 0.9 for no PHG, 2.0 ± 0.9 for mild PHG, and 1.9 ± 1.0 for severe PHG (all NS), and the mean grade of gastric varices was 0.5 ± 0.8 for no PHG, 1.3 ± 1.3 for mild PHG, and 0.9 ± 1.2 for severe PHG (all NS).

Location of varices: Regarding variceal location, Sarin *et al*[8] reported in a study of 107 patients with cirrhosis, NCPF or EHPVO, that PHG was significantly more common in patients with coexistent gastric and esophageal varices as compared to solely esophageal varices. PHG occurred in 15 (42%) of 36 patients with concomitant esophageal and gastric varices, but occurred in only 8 (11%) of 71 patients with solely esophageal varices ($P < 0.01$). Likewise, Gupta *et al*[30] reported a significantly higher prevalence of PHG in patients with esophageal and gastric varices [74 of 107 patients (69%)] compared to solely esophageal varices [68 of 123 patients (55%), $P < 0.05$].

Iwao *et al*[31] reported a significantly higher incidence of PHG in cirrhotic patients with esophageal varices as compared to fundal gastric varices. Merkel *et al*[36] reported that patients with severe PHG localized to the gastric body or fundus had significantly higher HVPG than patients with severe PHG localized to the gastric antrum.

Portal hypertension is usually associated with porto-

Table 3 Effects of variceal ligation on frequency of portal hypertensive gastropathy

Ref.	No. of patients and etiology	Study type	PHG rate before variceal ligation	PHG aggravation after variceal ligation	*P* value of pre *vs* post EVL
Hou *et al*[73]	90 patients with cirrhosis and recent variceal bleeding, 46 patients underwent EVL	Randomized, controlled trial	No PHG-4, mild PHG-33, severe-PHG-9	At eradication: 17/37; 17/37 (45.9%) in EVL; at 3 mo: 17/30 (56.7%); at 6 mo 18/29 (62.1%)	$P > 0.05$
Elnaser *et al*[80]	125 patients with upper GI bleeding undergoing variceal ligation, followed for mean of 31 mo	Retrospective study	22/125 (17.6%)	50/125 (50%)	$P < 0.05$
Yüksel *et al*[41]	114 patients with cirrhosis and portal hypertension undergoing EVL in 85 patients	Retrospective study	27/85 (31.8%) none; 28/85 (32.9%) mild; 30/85 (35.3%) severe	14/85 (16.5%) none; 30/85 (35.3%) mild; 41/85 (48.2%) severe	$P < 0.05$
Lo *et al*[81]	77 patients with bleeding from EV underwent variceal ligation and were randomized to receive propranolol (37/77) or control (40/77); patients with severe PHG prior to treatment excluded from the study	Prospective, randomized, controlled trial	Control group: 7/40 (17%); propranolol group: 8/37 (22%)	At variceal ligation: Control group: 67% (does not state number); Propranolol group: 31% (number not stated); 6 mo after treatment: Control group: 85% (number not stated) propranolol group: 48% (number not stated)	Pre *vs* post ligation, both groups; $P < 0.05$; frequency of PHG significantly higher in control group post ligation when compared to propranolol group; $P = 0.002$
de la Peña *et al*[82]	93 patients with history of variceal hemorrhage and cirrhosis, randomized to receive either EVS (46/88) or EVL (42/88); 5 patients excluded due to diagnosis of hepatoma, non-cirrhotic portal hypertension or portal vein thrombosis	Randomized, prospective study	Not reported	PHG significantly worsened in 23 patients, including 17 patients undergoing EVL	$P < 0.01$

PHG: Portal hypertensive gastropathy; EVL: Endoscopic variceal ligation; EVS: Endoscopic variceal sclerotherapy.

systemic collateral circulation, commonly including esophageal varices, gastric varices, and abdominal or umbilical or hemorrhoidal vein dilatation; and uncommonly including splenorenal, gastric, renal, retroperitoneal, or cardiac angle venous shunts. Wu *et al*[68] reported that the rate of moderate or severe PHG was higher in patients with common collaterals [296 of 439 patients (67.4%)] *vs* uncommon collaterals [70 of 118 patients (59.3%)], but this difference was not statistically significant.

In 2007, Zardi *et al*[45] proposed that PHG is promoted by minimal collateral circulation because a significant collateral circulation would otherwise reduce portal pressure and gastric mucosal congestion. They found that the portal vein diameter in cirrhotic patients was larger in patients with PHG and no esophageal varices (13.0 ± 2.6 mm) than in patients with F1 esophageal varices (12.6 ± 2.3 mm) or F2 esophageal varices (12.9 ± 2.0 mm) (NS). They further supported this concept by finding that patients with portal vein diameter < 12 mm have a significantly higher prevalence of F1 and F2 esophageal varices than patients with a portal diameter between 12-13 mm, and argued that the absence of hepatofugal collateral circulation created by flow inversion, in patients without esophageal varices, left the entire pressure gradient over the portal vein[45].

Esophageal variceal eradication: Numerous studies demonstrated that PHG increased in incidence and that preexistent PHG increased in severity after eradication of esophageal varices by either endoscopic variceal ligation (Table 3)[41,73,80-82] or endoscopic variceal sclerotherapy (Table 4)[8,10,11,25,30,41,73,81-83] in cirrhotic patients with portal hypertension. Both phenomena also occurred after endoscopic variceal eradication in patients with non-cirrhotic portal hypertension, as shown in two studies in pediatric patients with EHPVO. For example, Poddar *et al*[83,84] reported in a prospective study of 274 children undergoing surveillance EGD after endoscopic sclerotherapy for EHPVO that the number of patients with PHG increased from 46 (24.7%) at baseline to 95 (51.6%) after sclerotherapy among 186 patients completing the study ($P < 0.001$). Likewise, Itha *et al*[11] reported that the rate of PHG increased from 12% to 41% after endoscopic sclerotherapy ($P < 0.001$) in a prospective study of 163 children undergoing surveillance EGD at 3 and 6 mo after endoscopic sclerotherapy. In the study by Sarin *et al*[10], 86 (9%) of 967 patients with prior variceal bleeding treated with endoscopic sclerotherapy, had PHG at EGD, of whom 22 (26%) had PHG before variceal eradication and 64 (74%) developed PHG after variceal eradication.

PHG also increases in frequency after angiographic variceal obliteration. Duan *et al*[85] reported *de novo* PHG developed in 13 of 34 patients (38%) after percutaneous transhepatic variceal embolization for massive esophagogastric variceal hemorrhage.

These phenomena are attributed to increased portal pressure and flow after eradication of esophageal varices because of redistribution of residual blood flow that had passed through the previously patent varices[5,41,45,81,86-90]. Itha *et al*[11] concluded that the significant increase in

Table 4 Effects of variceal sclerotherapy on frequency of portal hypertensive gastropathy

Ref.	No. of patients and etiology	Study type	PHG before procedure	PHG aggravation after procedure	*P* value
Hou *et al*[73]	90 cirrhotic patients with recent variceal bleeding; EVS 44, EVL 46	Randomized, controlled trial	Pre EVS group: 6 none/24 mild/14 severe; pre EVL group: 4 none/33 mild/9 severe; total: 10 none/57 mild/23 severe	At eradication: 14/29 (48.3%) in EVS; 17/37 (45.9%) in EVL; at 3 mo: 15/26 (57.7%) in EVS; 17/30 (56.7%) in EVL; at 6 mo 15/25 (60%) in EVS; 18/29 (62.1%) in EVL	Non-significant difference in PHG aggravation between EVS and EVL; $P > 0.05$
Itha *et al*[11]	163 children with extrahepatic portal vein obstruction presenting with variceal bleeding underwent endoscopic injection sclerotherapy	Not reported	12% overall PHG (actual number not stated), 1 patient with severe PHG	41% overall PHG (actual number not stated), 12 patients with severe PHG	$P < 0.001$ for overall PHG; $P < 0.001$ for severe PHG
Poddar *et al*[83]	186 children with extrahepatic portal vein obstruction presenting with variceal bleeding undergoing endoscopic sclerotherapy, and mean follow up of 38 ± 30 mo	Retrospective study	PHG: 46/186 (24.7%), severe PHG: 6/186 (3.2%)	PHG: 96/186 (51.6%), severe PHG: 29/186 (15.6%)	$P < 0.001$ for overall PHG; $P < 0.05$ for severe PHG
Yüksel *et al*[41]	114 patients with cirrhosis and portal hypertension undergoing EVS (29/114) or EVL (85/114)	Retrospective study	Pre EVS group: 11/29 (37.9%) none; 10/29 (24.5%) mild; 8/29 (27.6%) severe; pre EVL group: 27/85 (31.8%) none; 28/85 (32.9%) mild; 30/85 (35.3%) severe	Post EVS group: 4/29 (13.8%) none; 8/29 (27.6%) mild; 17/29 (58.6%) severe; post EVL group: 14/85 (16.5%) none; 30/85 (35.3%) mild; 41/85 (48.2%) severe	Pre EVS *vs* post EVS; $P < 0.05$; pre EVL *vs* post EVL; $P < 0.05$; pre EVS *vs* pre EVL; $P > 0.05$; post EVS *vs* post EVL; $P > 0.05$
Sarin *et al*[10]	967 patients with variceal bleeding underwent endoscopic sclerotherapy; out of whom 88 patients fulfilled the inclusion criteria (including presence of endoscopic lesions consistent with PHG or GAVE, before or within 4 wk after obliteration) were prospectively followed (out of whom 2 had only GAVE)	Prospective study	22 patients had PHG prior to EVS; 2/22 transient (9%); 17/22 persistent (77%); 3/22 progressive (14%)	Additional development in 64 patients post procedure, 28/64 transient (44%), 31/64 persistent (48%), 5/64 progressive (8%)	Only statistically significant difference was the transient PHG that disappeared in 28 (44%) of patients in the group that developed PHG post procedure; $P < 0.05$
Gupta *et al*[30]	230 patients with liver cirrhosis; of which 44 underwent variceal eradication with sclerotherapy	Prospective study	24/44 (54%)	33/44 (75%)	$P < 0.05$
Sarin *et al*[8]	107 patients with portal hypertension presenting with variceal bleeding that underwent sclerotherapy with mean follow-up of 23.2 ± 3.4 mo	Prospective study	4/107 (3.7%)	21 additional patients, 25/107 (23%)	Does not state if this was statistically significant
de la Peña *et al*[82]	93 patients with history of variceal hemorrhage and cirrhosis, randomized to receive either EVS (46/88) or EVL (42/88); 5 patients were excluded due to diagnosis of hematoma, non-cirrhotic portal hypertension or portal vein thrombosis	Prospective study	Not reported	PHG worsened in 23 patients total; statistically significantly more in EVL group than EVS group (17 *vs* 6 patients respectively)	$P < 0.01$
D'Amico *et al*[25]	212 cirrhotic patients of which 75 had an episode of variceal bleeding and were treated with sclerotherapy; 137 without bleeding were not treated with sclerotherapy	Prospective study	No EVS group at admission: 104/137 (75%) none; 28/137 (20%) mild; 5/137 (4%) severe; EVS group at admission: 50/75 (66%) none; 17/75 (22%) mild; 8/75 (11%) severe	No EVS group at end of study 69/137 (50%) none; 61/137 (45%) mild; 7/137 (5%) severe; EVS group at end of study: 13/75 (17%) none; 49/75 (65%) mild; 13/75 (17%) severe	The conclusion was that sclerotherapy is a significant indicator of the risk of PHG in a multivariate analysis ($P = 0.00032$)

PHG: Portal hypertensive gastropathy; EVL: Endoscopic variceal ligation; EVS: Endoscopic variceal sclerotherapy.

frequency and severity of PHG after variceal eradication resulted from decreasing collateral blood flow through esophageal varices causing increasing PHG from gastric mucosal congestion. This mechanism is supported by finding that gastric mucosal blood flow increases after variceal ligation[91]. Another theory is that delayed gastric emptying after sclerotherapy from extravasation of sclerosant, may cause development of PHG[69]. No direct

Table 5 Well-established, important risk factors for portal hypertensive gastropathy

Parameters	Ref.
Portal hypertension	
Non-cirrhotic portal hypertension	[8,14]
Cirrhotic portal hypertension	[8,9,34]
Cirrhosis	
Longer duration of cirrhosis	[34,71]
Greater severity of cirrhosis	[55,67]
Greater size of esophageal varices	[34,62]
Eradication of esophageal varices	
Endoscopic therapies	
Endoscopic variceal ligation	[11,41]
Endoscopic sclerotherapy	[11,83]
Angiographic	
Percutaneous transhepatic variceal embolization	[85]

evidence exists for delayed gastric emptying in PHG[71].

Data on which technique of endoscopic variceal eradication leads to quantitatively more *de novo* PHG is contradictory. Most studies showed no differences in frequency or severity of PHG after variceal ligation *vs* sclerotherapy[19,34,41,73,92,93], but some studies showed worse outcomes after variceal ligation[82,93,94], while some other studies showed worse outcomes after sclerotherapy[95].

De novo PHG after variceal obliteration is often transitory and less severe than PHG that predated the variceal obliteration[10,73]. For example, Sarin *et al*[10] reported in a study of 84 patients followed for a mean of 25 ± 14 mo that PHG resolved in 28 (44%) of 64 patients who developed PHG after sclerotherapy, but resolved in only 2 (9%) of 22 patients who had PHG present before sclerotherapy ($P < 0.05$). Hou *et al*[73] similarly reported that the increased severity of PHG after variceal obliteration was generally transitory and returned to baseline status. The return to baseline severity of PHG was significantly faster after variceal ligation than after sclerotherapy ($P = 0.03$), attributed to ligation achieving subtotal variceal obliteration and permitting faster redistribution of blood flow[10].

Some investigators believe the higher rate of PHG in patients undergoing endoscopic variceal sclerotherapy merely reflects a longer duration of portal hypertension, more advanced liver disease, or more severe portal hypertension in patients selected to undergo variceal sclerotherapy compared to controls rather than the performance of sclerotherapy *per se*[34,78,96]. Primignani *et al*[34,97] demonstrated an almost identical increase in frequency of PHG with time in patients undergoing *vs* not undergoing sclerotherapy, and suggested that PHG evolved identically with time regardless of performance *vs* nonperformance of sclerotherapy.

Additional risk factors: PHG severity is significantly associated with thrombocytopenia or splenomegaly[42,57,58]. In a prospective study of 331 cirrhotic patients performed in South Korea, PHG severity was correlated with splenic diameter: Splenic diameter with severe PHG = 13.1 ± 2.4 cm, diameter with mild PHG = 12.2 ± 2.5 cm, and diameter with no PHG = 10.7 ± 2.9 cm, $P < 0.001$)[57]. In this study, PHG severity was inversely correlated with platelet count: count with no PHG = 174600 ± 109400 platelets/mm^3, count with mild PHG = 132000 ± 100700 platelets/mm^3, count with severe PHG = 102800 ± 68800 platelets/mm^3 ($P < 0.001$). Among 1016 patients with bridging fibrosis or compensated cirrhosis undergoing EGD in the HALT-C trial, including 374 (37%) with PHG, PHG was negatively correlated with platelet count in a logistic regression model (negative estimate: -0.00407, OR = 0.99, 95%CI: 0.99-0.998; $P = 0.0007$)[42].

In one study, PHG in patients with chronic liver disease was correlated with increasing thickness of the lesser omentum, and presence of a splenorenal shunt[22]. This study found that PHG frequency was not associated with severity of hypersplenism[62]. The HALT-C trial showed no association between prevalence or severity of PHG and lifetime alcohol consumption, nonsteroidal anti-inflammatory drugs (NSAIDs) use, COX- (cyclooxygenase-) 2 inhibitor use, or smoking[42]. The lack of association with alcoholism may reflect the need for near abstinence from alcohol to have enrolled in the clinical trial; at study enrollment 86% of patients reported abstinence and 14% reported minimal drinking of alcohol. Table 5[8,9,11,14,34,41,55,62,67,71,83,85] lists well-established risk factors for PHG; Table 6[11,41,44,55,75-77,83,85,98-107] lists therapies that affect the severity of PHG or the risk of bleeding from PHG, and Table 7[8,14,28,30,35,42,84,108-110] lists the factors that do not affect the risk of PGH.

Pathogenesis

Hemodynamic changes: The pathogenesis of PHG is inadequately understood[96]. Hemodynamic changes, especially increased portal pressure, are the suspected underlying cause because PHG develops only with established portal hypertension[72]. However, portal hypertension cannot be the sole factor because many patients with portal hypertension do not develop PHG[36,111]. Hemodynamic changes in patients with portal hypertension lead to hyperdynamic congestion with a change in gastric mucosal blood flow[112], that leads to activation of cytokines, growth factors, and hormones that perpetuate this hyperdynamic gastric circulation[113]. Vascular congestion in PHG alters the gastric microcirculation, but the nature and extent of this alteration is somewhat controversial. The hyperdynamic circulation of portal hypertension is characterized by increased intrahepatic vascular resistance, generalized splanchnic vasodilatation, decreased mean arterial pressure, decreased systemic vascular resistance, increased gastric blood flow, and most likely decreased gastric mucosal flow[110,114,115]. Hashizume *et al*[116] reported that cirrhotic patients have dilated small gastric blood vessels, including arterioles, precapillaries, capillaries, submucosal veins, and subserosal veins, with decreased arteriovenous resistance and straightening of arterioles.

Table 6 Therapies affecting the severity or the risk of bleeding from portal hypertensive gastropathy

Therapies reducing severity of PHG	Ref.
TIPS	[76,77,98]
Transcatheter splenic arterial embolization	[99]
Surgical shunt	
Portocaval shunt	[100]
Central splenorenal shunt	[101]
Laparoscopic splenectomy (in patients with hypersplenism)	[55]
Liver transplantation	[44]
Therapies reducing risk of bleeding from PHG	
TIPS	[75,98,102]
Surgical shunt (portocaval or splenorenal)	[100,101]
Nonselective b β-adrenergic receptor antagonists (*e.g.*, propranolol)	[103 (in rats),104]
Somatostatin family of drugs	
Somatostatin	[105]
Octreotide	[106]
Vasopressin family of drugs	
Vasopressin	[106]
Terlipressin	[107]
Therapies that increase incidence or risk of bleeding from PHG	
Endoscopic therapies for varices	
Variceal ligation	[11,41]
Variceal sclerotherapy	[11,83]
Interventional angiography	
Percutaneous transhepatic variceal embolization	[85]

TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy.

This hyperdynamic circulation impairs gastric mucosal defense mechanisms, causes release of proinflammatory mediators, and inhibits growth factors which render gastric mucosa more susceptible to injury[67,117] and impair mucosal healing[113,114,118,119]. This vulnerable mucosa becomes predisposed to bleeding[117,120]. Decreased gastric mucosal perfusion may explain the increased rate of erosions, ulcers, and bleeding in PHG[118]. Abnormal regulation of the gastric microcirculation in PHG may render gastric mucosa more vulnerable to hypoxia[112,122], and more susceptible to noxious gastric factors, such as aspirin and ethanol[123-125].

Misra *et al*[126] showed that gastric mucosal capillaries, obtained by endoscopic mucosal biopsies, have a much thicker wall in patients with cirrhosis than in healthy volunteers. Ichikawa *et al*[127] reported a narrower diameter in gastric mucosal capillaries and less capillary angiogenesis, measured as percentage of buds in microvessels, after exposure to ethanol in individuals with PHG as compared to healthy controls. Tarnawski *et al*[121] reported prominent cytoplasm in endothelial cells of mucosal microvessels, that narrowed the capillary lumina, in rats with PHG. This finding was confirmed by electron microscopy which showed significantly larger cytoplasmic and pinocytic vesicular areas and increased capillary basement membrane thickness. Additionally, there was arterialization of submucosal veins and thickening of arterioles in the muscularis mucosae and submucosa[121].

Table 7 Factors not affecting risk of portal hypertensive gastropathy

Factors not affecting risk of portal hypertensive gastropathy	Ref.
Etiology of cirrhosis	[8,28,30]
Etiology of non-cirrhotic portal hypertension	[8,14,35,83,108]
Alcoholism	[30,42]
NSAID use	[42]
Use of COX-2 inhibitors	[42]
Smoking tobacco	[42]
Gastric infection with *Helicobacter pylori*	[109,110]

NSAID: Nonsteroidal anti-inflammatory drug; COX-2: Cyclooxygenase-2.

The level of gastric mucosal blood flow in PHG is controversial. Most studies reported decreased mucosal blood flow in patients with PHG[76,128-131], whereas several studies reported increased gastric mucosal blood flow in experimental animals and in humans with PHG[132-136]. Makhija *et al*[118] described in PHG a decrease in gastric mucosal blood flow, an increase in the submucosal and muscular layer blood flow, and a net increase in total gastric blood flow. Mezawa *et al*[76] using a laser Doppler flowmeter to measure gastric mucosal blood flow and near-infrared endoscopy to measure total gastric blood flow, reported decreased mucosal blood flow and increased total blood flow in patients with PHG. These results reversed after undergoing TIPS, with an increase in mucosal blood flow and a decrease in total blood flow. These finding support the hypothesis of decreased mucosal blood flow in patients with PHG. Ohta *et al*[113] reported a decrease in superficial mucosal blood flow rendering mucosa more susceptible to injury, but noted a net increase in total gastric blood flow. Variability in study results arise from study biases including chronic anemia in some patients, variable measurement techniques, different techniques of applying endoscopic probes in laser-Doppler flowmetry, and differences in gastric mucosal angioarchitecture[113]. Laser-Doppler flowmetry, moreover, has limited utility in clinical practice[137,138].

Portal hypertension increases the splenic circulation[139]. Pan *et al*[79] reported that PHG severity was strongly correlated with hypersplenism (P = 0.003). However, Abbasi *et al*[62] did not show this correlation. The difference between these studies may reflect use of different classifications for PHG. Figure 1 describes the hypothesized pathophysiology of PHG. This current mechanism is currently sketchy and likely incomplete.

Patients with secondary polycythemia A have decreased blood flow and oxygen carrying capacity because of sluggish movement of viscous blood; this phenomenon produced endoscopic and histopathologic findings of congestive gastropathy similar to those in PHG that reversed after the patient underwent serial phlebotomies to reverse the polycythemia[140].

Molecular mechanisms: Numerous molecular and cellular mechanisms have been investigated regarding

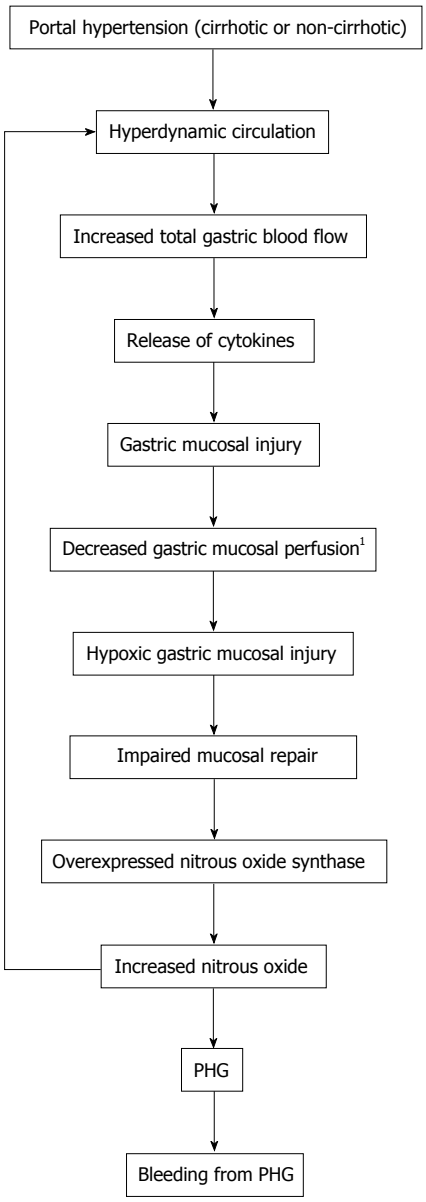

Figure 1 Hypothesized mechanism of portal hypertensive gastropathy. [1]The finding of decreased gastric mucosal perfusion in PHG is somewhat controversial (see text). PHG: Portal hypertensive gastropathy.

the pathogenesis of PHG.

Apoptosis: Wu *et al*[141] showed that rats with PHG had increased gastric mucosal apoptosis and decreased mucosal proliferation. Recently, a p53-upregulated modulator of apoptosis (PUMA) was reported markedly induced in gastric mucosa in patients or mouse models of PHG. PUMA is modulated by endoplasmic reticulum - stress-induced mucosal epithelial apoptosis in PHG[142]. This effect could promote mucosal injury in PHG.

Free radicals and antioxidants: Kaur *et al*[143] showed elevated levels of injurious free radicals and lysosomal enzymes and decreased levels of protective antioxidant enzymes in gastric mucosal homogenates from rats with portal hypertension. Kawanaka *et al*[144] showed impaired endoplasmic reticulum serine/threonine kinase-2 (ERK2) activation after oxidative stress in rat gastric mucosa; ERK2 normally protects against cellular stress by inducing cell proliferation in gastric mucosa. Kinjo *et al*[145] showed that enhanced nitration of ERK by peroxynitrite is involved in impaired MAPK (ERK) signaling in PHG, which impairs mucosal healing and promotes mucosal injury. The levels of lipid peroxide and nitrotyrosine that tend to promote gastric injury increased significantly in rats with PHG as compared to controls.

Mucin: Wang *et al*[146] reported significantly reduced expression of mucin mRNA in rat models of portal hypertension induced by partial portal vein ligation. Decreased mucin production may impair gastric mucosal protection. Rats with portal hypertension had significantly greater injury to gastric mucosa than healthy controls after exposure to gastrotoxic compounds. Tomikawa *et al*[135] reported decreased mucosal gel layer thickness, surface epithelial cell intracellular pH, and oxygenation of gastric mucosal surface in rats with PHG.

Angiogenesis: As aforementioned, the number of angiogenic buds decreased after injury to PHG mucosa. This phenomenon may decrease the reparative capacity of PHG mucosa[127]. However, Tsugawa *et al*[136] reported humans with PHG had increased vascular endothelial growth factor (VEGF), a potent angiogenic factor. Additionally, rats with PHG had a significant decrease in the SaO_2 and PaO_2 of the arterial blood gas, and increased levels of VEGF, proliferating cell nuclear antigen (PCNA) expression, and gastric mucosal blood flow in gastric mucosa. They proposed that gastric mucosal hypoxia in portal hypertension and elevation of VEGF and PCNA levels might accelerate mucosal angiogenesis and increase blood flow[147].

Tumor necrosis factor alpha: Tumor necrosis factor alpha (TNF-α) may directly contribute to the hyperdynamic circulation in PHG. Patients and animal models with portal hypertension had an elevated TNF-α level which stimulated release of nitric oxide (NO) and prostacyclin, important mediators of a hyperdynamic circulation[148]. For example, in one study, 96 healthy rats were injected with either anti-TNF-α polyclonal antibodies or placebo before surgically creating portal vein stenosis (PVS) to induce portal hypertension and 4 d after in the short-term inhibition group and 1, 4, 7 and 10 d after PVS in the long term-inhibition group. Anti-TNF-α treated PVS rats exhibited lower serum levels of TNF-α, which normally stimulates the synthesis of NO and prostacyclin, and exhibited lower serum levels of nitrates and nitrites and of 6-keto-PGF-1-α (6-keto-$PGF_{1\alpha}$), used to monitor NO and prostacyclin release, respectively. The combined nitrate and nitrite level was significantly reduced from 68 ± 9 nmol/mL in controls to 42 ± 8 nmol/mL in the short-term inhibition group ($P < 0.05$), and from 66 ± 6 nmol/mL in controls to 44 ± 4 nmol/mL in the long-term inhibition group (P

< 0.05). Similarly the 6-keto-PGF$_{1\alpha}$ was significantly reduced from 484 ± 92 pg/mL in the controls to 174 ± 12 pg/mL in the short-term inhibition group (P < 0.05), and from 522 ± 98 pg/mL in the controls to 169 ± 18 (SD) pg/mL in the long-term inhibition group (P < 0.05). Kaviani *et al*[149] reported that TNF-α increased by 50% and inducible nitric oxide synthase (iNOS) mRNA levels increased by 300% in gastric strips after ligating the portal vein in rats (P < 0.01 for both). These data are consistent with TNF-α playing a role in the hyperdynamic circulation in PHG *via* NO and prostacyclin.

Baseline constitutional NOS (cNOS) mRNA expression increased by 75% in the PHG group as compared to placebo (P < 0.01)[149]. NOS was significantly reduced after injecting a TNF-α neutralizing antibody during incubation of mucosal strips from portal hypertensive rats; the expression of inducible NOS mRNA levels was incrementally decreased by 40%, 70% and 80% after 1, 2, and 6 h of incubation, respectively (P < 0.05)[149]. Ohta *et al*[150] similarly successfully used TNF-α antibody to normalize gastric mucosal blood flow in rats with PHG and to significantly reverse overexpression of gastric NOS isoform 3. In PHG rats, treatment with TNF-α antibody significantly reduced the elevated NOS isoform 3 mRNA expression by 48% (P < 0.01). Moreover, administration of thalidomide, which enhances TNF-α mRNA degradation, decreased levels of TNF-α and NOS in animals with portal hypertension produced by partial portal vein ligation[114].

Nitric oxide: Patients with portal hypertension and PHG have increased serum levels of NO, a potent vasodilator released by endothelial cells. Ohta *et al*[151] demonstrated gastric cNOS significantly increased, by 67%, in portal hypertensive rats, experimentally produced by portal vein and splenic vein occlusion, as compared to sham-operated rats at 14 d after surgery (P < 0.05). In portal hypertensive rats, cNOS fluorescence intensity was significantly higher in endothelia of submucosal veins [96.2 ± 5.9 (SD) U] as compared to endothelia of mucosal collecting veins (69.5 ± 1.7 (SD) U, P < 0.01), or endothelia of veins of muscularis mucosae (55.7 ± 10.0 U, P < 0.01). The average fluorescence area in submucosal vein endothelia was significantly higher in portal hypertensive rats than in normal controls (1038.5 ± 459.5 (SD) μm^2 *vs* 372.4 ± 180.3 (SD) μm^2, P < 0.01). This finding may provide a molecular mechanism for submucosal vascular dilation in the hyperdynamic circulation in PHG. In another study, gastric mucosal cNOS levels were significantly higher in patients with cirrhosis and severe PHG compared to healthy controls [125.4 ± 4.3 (SD) pmol/mg protein/minute *vs* 88 ± 8.6 (SD) pmol/mg protein/minute, P < 0.002]. Likewise, gastric mucosal iNOS levels were significantly higher in patients with cirrhosis and severe PHG than in healthy controls [259.7 ± 5.5 (SD) pmol/mg protein/min *vs* 130.8 ± 6.6 (SD) pmol/mg protein/min, P < 0.0001][152]. Serum nitrate/nitrite levels were 30.1 ± 3.2 nmol/mL in the first group *vs* 15.5 ± 0.09 (SD) nmol/mL in the second group (P < 0.001)[152]. In another study, iNOS and cNOS levels were also higher in gastric mucosa of patients with PHG than in controls[153], and were significantly higher in patients with severe PHG as compared to patients with mild or no PHG[154]. Nitrous oxide may underlie the gastric vascular dilation[152], and hyperdynamic circulation in PHG[148].

However, Lee *et al*[155] reported administration of aminoguanidine, an iNOS inhibitor, successfully corrected the hyperdynamic circulation without affecting PHG, suggesting that iNOS and NO are important in the hyperdynamic circulation in portal hypertension, but play a limited role in PHG development. They argued that PHG should be treated by reducing portal pressure rather than reversing the hyperdynamic circulation[155,156].

Glucagon: Glucagon levels are elevated in patients with portal hypertension[118]. Curvêlo *et al*[54] found in 43 patients with PHG from portal hypertension with cirrhosis, that the mean serum glucagon level after an overnight fast was significantly higher than the level in healthy controls. Serum glucagon levels were significantly correlated with high systemic vascular resistance index (r = -0.523; P = 0) and HVPG (r = 0.34; P = 0.019). Glucagon significantly increases portal pressure[157-159], and causes splanchnic vasodilation[148]. Geraghty *et al*[158] found a strong correlation between portal pressure and glucagon levels (r = 0.85). Tsui *et al*[160] reported that glucagon significantly increased portal pressure in rats with portal vein ligation, but did not alter portal pressure in sham-operated rats. The effect of glucagon occurred only in rats with preexisting portal hypertension. Exogenous glucagon rendered gastric mucosa more susceptible to injury from toxins, such as ethanol, which was attenuated by somatostatin[160]. For example, the lesion area was significantly higher at > 60% of gastric mucosa after glucagon administration, compared to somatostatin or glucagon and somatostatin administration (P < 0.05, ANOVA)[160].

Prostaglandins: Studies in patients or animal models with portal hypertension failed to show significant differences in prostaglandin E2 (PGE2) levels as compared to healthy controls[125,141,161-163]. Low prostaglandin levels significantly decreased gastric perfusion velocity in cirrhotic rats, whereas misoprostol, a PGE2 analogue, significantly increased gastric perfusion in cirrhotic rats as compared to controls[125]. For example, Beck *et al*[125] found that administration of indomethacin did not affect gastric perfusion velocity in healthy control rats, despite reducing gastric PGE2 synthesis by > 95%, but reduced gastric perfusion velocity by 30% within 10 min in cirrhotic rats achieved by ligating the common bile duct (P < 0.05). The hyperemic response to application of ethanol was significantly reduced in cirrhotic rats compared to healthy rats (56.3% ± 21.7% (SD) *vs* 66.1% ± 17.1% (SD) increase, P < 0.05). Misoprostol applied to gastric mucosa caused

concentration-dependent increase in perfusion velocity, with a significantly greater increase in perfusion velocity in cirrhotic rats with concentrations of misoprostol > 0.8 mcg/mL ($P < 0.05$).

Beck *et al*[164] further reported that administration of misoprostol to cirrhotic rats for 1 mo restored the hyperemia in response to ethanol that sham-operated, non-cirrhotic rats showed, whereas placebo-treated cirrhotic rats failed to increase gastric blood flow in response to ethanol. PGE2-treated cirrhotic rats exhibited significantly less spontaneous gastric mucosal damage [0.2% ± 0.07% (SD)] than placebo-treated cirrhotic rats [3.0% ± 0.8% (SD); $P < 0.05$]. The mean microscopic gastric injury score was significantly less in PGE2-treated cirrhotic rats [0.7 ± 0.3 (SD)] than in placebo-treated cirrhotic rats [2.1 ± 0.4 (SD); $P < 0.05$].

Rats with PHG exhibited suppression of gastric mucosal COX-1 levels, but exhibited normal COX-2 levels compared to healthy controls[141]. Nonselective COX inhibitors, such as aspirin, decrease PGE2 levels resulting in more apoptosis of cells. Payen *et al*[123] reported that gastric mucosal potential difference, an index of mucosal integrity, decreased with increasing severity of PHG, suggesting greater vulnerability of gastric mucosa in patients with PHG. Payen *et al*[123] further reported a significantly greater decline of potential difference after aspirin administration of 11.1 ± 3.6 (SD) mV in 9 patients with severe PHG, *vs* 9.2 ± 3.6 mV in 21 patients with moderate PHG ($P < 0.05$), and *vs* 6.4 ± 1.9 (SD) mV in 10 healthy controls ($P < 0.05$). Also, PGE2 administration suppressed the increased apoptosis which occurred in rats with PHG.

Prostacyclin: Prostacyclin, a vasodilator that inhibits gastric acid secretion, has been proposed as a mediator of the hyperdynamic circulation in PHG from portal hypertension[148,163]. Ohta *et al*[161] found significantly elevated serum levels of 6-keto-$PGF_{1\alpha}$, a metabolite of prostacyclin, in cirrhotic patients with PHG. They also reported that these patients had significantly elevated levels of 6-keto-$PGF_{1\alpha}$ in the mucosa of the gastric fundus.

Other cytokines and growth factors: Several studies have analyzed the roles of endothelin-1, VEGF, and other cytokines in PHG, but further research is required[165]. The gastric concentrations of epidermal growth factor were comparable between patients with and without PHG, and its significance in PHG remains unclear[166]. A high serum level of autotaxin, involved in liver fibrosis, was associated with advanced stage of cirrhosis, presence of esophageal varices, and PHG[167].

Helicobacter pylori: Numerous studies demonstrated that *Helicobacter pylori* (*H. pylori*) infection is not associated with PHG[7,9,25,79,109,110,154,168-172]. Indeed, several studies reported that patients with PHG less frequently have *H. pylori* infection than controls. *H. pylori* does not appear to play a pathogenic role in ulcers associated with PHG[173]. Contrariwise, Sathar *et al*[174] reported an association between *H. pylori* infection and PHG in cirrhotic patients, but this study apparently had limitations, including low specificity and low sensitivity of *H. pylori* serology in cirrhotic patients, potential selection bias, and underreporting of *H. pylori* seroprevalence[174-178].

Diagnosis

Endoscopy: PHG is diagnosed by EGD[72]. The characteristic endoscopic appearance is a mosaic-like pattern or a diffuse, erythematous and reticular cobblestone pattern of gastric mucosa consisting of small polygonal areas, with superimposed red punctate lesions, > 2 mm in diameter and a depressed white border[78,96,177]. The red lesions vary in size and in color depending on PHG severity. The lesions range from pink speckled lesions within a mosaic or snakeskin pattern in mild cases, to localized small areas of intense erythema, resembling a scarlatina rash, in severe cases[70,71,112,139]. These findings occur predominantly in the gastric body and fundus, and rarely in the antrum[71,72,139]. Figure 2 illustrates a patient with classic endoscopic findings of portal hypertensive gastropathy. Toyonaga *et al*[178] reported in a meta-analysis of 6 studies that the mosaic-like pattern had high specificity at 98% (range: 93%-100%), but low sensitivity at 38% (range: 7%-94%) for PHG, with an accuracy of 78% (range: 63%-98%). In severe PHG numerous petechiae and bleeding spots present as a diffuse hemorrhagic gastropathy[112,139].

Endoscopic classification: Endoscopic classification of PHG severity is clinically important because severity is correlated with bleeding risk[31,71,72,179]. PHG can be simply categorized as mild with a mosaic-like pattern without red spots, or as severe, with superimposed red lesions present[78,96]. Multiple formal endoscopic classifications exist (Table 8[3,7,8,70,180-183]), with no consensus as to which classification is the best[5,182-184]. The following classifications are commonly used: Classifications by McCormack *et al*[3], Tanoue *et al*[180], the New Italian Endoscopic Classification (NIEC)[70], and the Baveno scoring system[181].

In 1985, McCormack *et al*[3] classified PHG according to presence of red spots into mild and severe disease. In 1991, McCormick *et al*[7] divided the prior single category of mild PHG into mild and moderate PHG based on absence *vs* presence of erythema, respectively. This moderate category is infrequently used[7]. In 1992 Tanoue *et al*[180] and Parker *et al*[185] also expanded the scoring system by providing a grade between mild and severe. This classification is rendered cumbersome by a lack of sharply defined differences between the added intermediate category and the original categories[71]. This system is, however, simple and can help predict bleeding risk[71,182]. Iwao *et al*[186] found McCormack's classification was accurate for fine pink speckling in 54%, for snakeskin pattern in 76%, and for cherry-red spots in 64%. The NIEC produced a better definition in

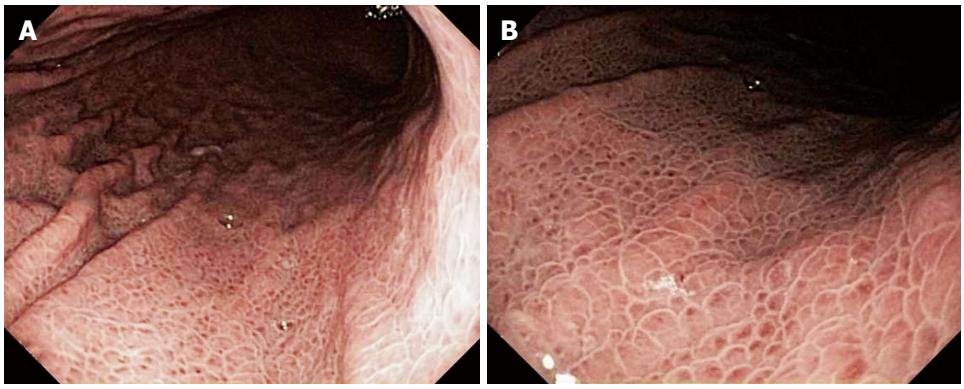

Figure 2 A 60-year-old man presented for routine endoscopic screening for esophageal varices due to a history of Child-Pugh class B cirrhosis, with a model for end-stage liver disease score = 18, from hepatitis C secondary to former intravenous drug use. The patient denied a history of gastrointestinal bleeding. The hematocrit was 40.1%. Esophagogastroduodenoscopy revealed the classic findings of portal hypertensive gastropathy, including a pale white reticular (mosaic) pattern surrounding small polygonal areas of mucosa, with variable erythema, in the entire stomach, but most prominently in the gastric fundus and body. B is a relatively close-up view of the lesions seen in A.

Table 8 Different classification systems for portal hypertensive gastropathy

Ref.	Mild	Moderate	Severe
McCormack *et al*[3]	Fine pink speckling (scarlatina type rash) Superficial reddening, especially on rugal surface (striped appearance) Fine white reticular pattern separating areas of raised edematous mucosa (snake skin)		Discrete red spots (analogous to cherry red spots in esophagus) Diffuse hemorrhagic gastritis
McCormick *et al*[7]	Mosaic or snake skin appearance	Presence of erythema	Presence of erosions or hemorrhagic gastritis
Tanoue *et al*[180]	Mild reddening, congestive mucosa, no mosaic - like pattern	Severe redness and a fine reticular pattern separating the areas of raised edematous mucosa (mosaic-like pattern) or a fine speckling	Grade Ⅲ (severe) Point bleeding + grade Ⅱ (moderate)
Spina *et al*[70] (NIEC)	Mosaic-pattern: Presence of small, polygonal areas surrounded by a whitish-yellow depressed border		Red point lesions (1 mm in diameter, flat) Cherry-red spots (2 mm, slight protrusion) Black-brown spots (irregularly shaped, persistently present after washing)
Sarin *et al*[8]	Discrete cherry red spots, with or without mosaic pattern		Presence of confluent red spots, diffusely distributed in a large portion of the stomach
Sarin *et al*[181] (Baveno Ⅱ Consensus Workshop)[181]	Mild ⩽ 3 points[1]		Severe ⩾ 4 points[1] Gastric antral ectasia Absent (0) Present (2)
Yoo *et al*[182] 2-category classification	Fine pink speckling (scarlatina type rash) Superficial reddening Mosaic pattern		Discrete red spots Diffuse hemorrhagic lesion
Yoo *et al*[182] 3-category classification	Mild reddening Congestive mucosa Diffuse pink areola	Flat red spot in center of a pink areola Severe redness and a fine reticular pattern	Diffusely red areola Pinpoint bleeding Discrete or confluent red mark lesion

[1]Points assigned for Baveno II consensus according to the following: Mild mucosal mosaic pattern = 1 point, severe mucosal mosaic pattern = 2 points; isolated red markings = 1 point, confluent red markings = 2 points; gastric antral ectasia present = 2 points.

1992 of mild and severe HPG[32,34,70]. Elementary lesions of PHG according to the NIEC classification include: (1) mosaic-like pattern defined as small, polygonal areas surrounded by a whitish-yellow, depressed border. This mosaic pattern is mild when the areola is uniformly pink, moderate if the center is red, and severe if the areola is uniformly red; (2) red-point lesions defined as small, flat, 1-mm-wide, punctate, red lesions; (3) cherry-red spots defined as red, 2-mm-wide, round lesions which protrude slightly into the gastric lumen; and (4) black-brown spots defined as irregularly shaped flat black or brown spots from intramucosal hemorrhage that remain after endoscopic irrigation. PHG is defined as mild when only a mosaic-like pattern of any degree was present, and severe when red-point lesions, cherry red spots, or black-brown spots were present. Due to variable data on the classification systems, Hashizume *et al*[184] proposed a simplified classification that divides PHG into three stages by presence of: Non-specific redness, a mosaic pattern, and red spots.

Yoo *et al*[182] demonstrated substantial limitations in intra-observer and inter-observer reproducibility in the most common 2-scoring and 3-scoring systems. Nevertheless, the 2-scoring system by McCormack *et al*[3,7] produced better and more reproducible results than the 3-scoring system by Tanoue *et al*[180]. The mean inter-observer kappa value was 32% higher and mean intra-observer kappa value was 15% higher for the 2-scoring system compared with the 3-scoring system. However, both inter-observer and intra-observer kappa values in both classification systems were below the desirable value of > 0.75[187]. Kappa values represent the degree of agreement as compared with that expected by chance alone, with one being perfect agreement, and zero being no greater agreement than expected by chance alone[182].

The Baveno scoring system uses point calculations to define PHG as mild (⩽ 3 points) *vs* severe (⩾ 4 points)[181]. This system adds gastric antral vascular ectasia (GAVE) into the classification[179]. Stewart *et al*[179] showed that this scoring system was reproducible and accurately reflected the risk of PHG-related bleeding in cirrhotic patients. Kappa values for mucosal mosaic pattern, red marks, and GAVE were > 0.75, indicating good reproducibility. Kappa values for lesion severity were lower, attributed to loss of details in endoscopic photographs.

de Macedo *et al*[187] proposed analyzing binary criteria such as presence *vs* absence of mosaic-like pattern, red punctate lesions, and cherry-red spots, without subdivisions or classification systems. These binary criteria were associated with high inter-observer reliability and accuracy (94%, 81% and 83% respectively). Mosaic-like pattern was associated with high sensitivity (100%). The previously used classifications and subdivisions showed unsatisfactory reliability and low inter-observer agreement.

Current classification systems are suboptimal. The ideal classification system should be simple, clinically useful, accurate, and reproducible with high levels of intra-observer and inter-observer agreement[183]. The 2-scoring system is most commonly used due to relative simplicity and reasonable reproducibility[71].

Capsule endoscopy: Several studies evaluated the diagnostic accuracy of capsule endoscopy. In a study using the PillCam ESO capsule, capsule endoscopy had an overall concordance with EGD of 90.6% for PHG[188]. This study included only 32 patients of whom 19 had PHG, and a large trial is underway to confirm these findings. In another study, PHG was identified by capsule endoscopy in 13 (68.4%) of 19 patients with cirrhosis, portal hypertension, and chronic anemia, but the 19 patients did not undergo EGD to determine capsule endoscopy test sensitivity and specificity[49]. In a study of 50 patients with cirrhosis undergoing both EGD and capsule endoscopy for screening or surveillance of esophageal varices, capsule endoscopy had an accuracy of 57%, sensitivity of 96%, and specificity of 17% compared to EGD. Inter-observer reliability was 0.61. The researchers concluded that more data are required to assess accuracy of capsule endoscopy for diagnosis and staging of PHG[52]. In another study of 50 patients with portal hypertension undergoing EGD and capsule endoscopy, only 24 of 35 patients with PHG diagnosed by EGD had PHG detected by capsule endoscopy (sensitivity = 69%)[23]. Capsule endoscopy was somewhat more sensitive at detecting severe than mild PHG (82% *vs* 63%), but this difference was not significant (P = 0.44). The accuracy was significantly higher in diagnosing PHG in the gastric body (100%) than the fundus (48%) (P = 0.0009).

Dynamic CT: Kim *et al*[50] proposed using dynamic CT to diagnose PHG by demonstrating the transient perfusion defect sign, defined as the presence of transient segmental or subsegmental hypo-attenuating mucosa in the gastric fundus or body during hepatic arterial imaging that returns to normal attenuation on portal venous or equilibrium-phase imaging. This sign had a sensitivity of 75%, specificity of 88.6%, positive predictive value of 90%, and negative predictive value of 72.1% for diagnosing PHG in patients with cirrhosis. Further prospective trials are required to validate this diagnostic modality.

Screening for PHG is currently not recommended in patients with liver disease[189]. To identify predictors of PHG and varices noninvasively in patients with chronic liver disease to increase the cost-benefits of EGD, Min *et al*[190] combined three independent parameters in a multivariate analysis into a "Varices and PHG" (VAP) score. The score = platelets/mm^3 × albumin in g/dL/multidimensional index for spleen volume (M-Index) in cm^3. The M-Index is calculated from spleen length, width, and thickness, as determined by helical computerized tomography, which is designed to reflect splenomegaly as a predictor of esophageal varices and PHG. A VAP cut-off value of 861 had a sensitivity of 85%, positive likelihood ratio of 3.17, and negative predictive value of 86%. This scoring system requires prospective validation[190].

Differentiation from GAVE: Differentiation of PHG from GAVE is important because they have distinct pathologic, clinical, and endoscopic characteristics, and different therapies (Table 9)[34,37,71,72,75,77,103,106,191-213]. Treatments that reduce portal pressure are effective for PHG but ineffective for GAVE[193]. PHG and GAVE also affect different gastric locations. PHG generally affects the proximal stomach, whereas GAVE generally affects the distal stomach[139]. A mosaic-like pattern surrounding polygonal areas of erythema is typical for PHG, but GAVE has erythema most commonly arranged linearly along folds in the antrum, less commonly arranged as diffuse erythema in the antrum, and least commonly arranged as diffuse gastric erythema[75,78,96].

PHG is usually diagnosed by endoscopic criteria. When endoscopic features are uncertain, histologic

Table 9 Differences between portal hypertensive gastropathy and gastric antral vascular ectasia

Parameter	Portal hypertensive gastropathy	Gastric antral vascular ectasia	Ref.
Associated conditions	Conditions associated with portal hypertension: cirrhotic or non-cirrhotic portal hypertension	Cirrhosis, autoimmune disorders, and connective tissue diseases (scleroderma, pernicious anemia, hypothyroidism)	[72]
Association with portal hypertension	Strong association	Only 30% of cases	[191,192]
Sex	Mildly more common in males (alcoholic cirrhosis more common in males than females)	Much more common in females (80%)	[193,194]
Age	Can occur at any age in patients with portal hypertension or cirrhosis	Typically elderly (average age > 70 years old)	
Location	Proximal stomach: Fundus, body	Distal stomach: Antrum	[72,192]
Diagnosis	Endoscopy (endoscopic biopsy sometimes useful). Radiologic imaging usually not helpful	Endoscopy (endoscopic biopsy sometimes useful)	[72,195]
Appearance at endoscopy	Mosaic/snakeskin mucosa with red or brown spots	Tortuous columns of ectatic vessels in "watermelon" or diffuse pattern; erythematous or hemorrhagic	[191]
Histology	Ectatic capillaries, mildly dilated mucosal and submucosal veins; no vascular inflammation, no vascular thrombi	Marked dilation of capillaries and venules in gastric mucosa and submucosa with areas of intimal thickening, fibrin thrombi, fibromuscular hyperplasia and spindle cell proliferation	[72,191,196,197]
Clinical presentation/ complications	Gastrointestinal bleeding: Usually chronic, but sometimes acute	Almost exclusively chronic gastrointestinal bleeding with guaiac positive stools	[37,193]
Primary prophylaxis	Not indicated	Not indicated (unless associated with large varices)	[198]
Medical therapy	Non-selective β-adrenergic receptor antagonists (propranolol), octreotide (for acute bleeding)	No benefit of β-adrenergic receptor antagonists Oral contraceptive pills to temporarily control bleeding Questionable benefit of octreotide	[103,106,198-201]
Endoscopic therapy	Occasionally helpful (for focal bleeding) Argon plasma coagulation Local hemostasis with hemospray	Very helpful at reducing risk of bleeding: Argon plasma coagulation; EBL; Radiofrequency ablation; YAG laser therapy	[202-207]
TIPS	Significantly reduces severity and risk of bleeding by reducing portal hypertension. Option for very severe bleeding from PHG or for moderate PHG in patients with variceal bleeding	Not recommended. Does not affect severity of GAVE or risk of bleeding	[75,77]
Liver transplantation	Resolves. Ultimate therapy mostly reserved for patients with end-stage liver disease	Improves or resolves with liver transplantation	[75,200,208-210]
Other surgery	Usually resolves with shunt surgery that lowers portal pressure. Partial gastrectomy not recommended	Limited surgical resection (partial gastrectomy) recommended for refractory cases. Shunt surgery not recommended	[75,200,211-213]
Prognosis from bleeding	Bleeding rarely severe and very rarely fatal	Bleeding occasionally severe	[34,71,72]

YAG: Yttrium aluminum garnet; TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy; GAVE: Gastric antral vascular ectasia; EBL: Endoscopic band ligation.

analysis of gastric biopsies is useful to differentiate PHG from GAVE[86,183,197,212]. Superficial mucosal biopsies are frequently falsely negative because the lesions of PHG are generally submucosal[214,215]. Endoscopists are reluctant to perform deep biopsies in patients with known portal hypertension or suspected PHG because of increased risks of bleeding because of a coagulopathy from underlying cirrhosis or a bleeding diathesis from underlying portal hypertension[137,183]. However, deep biopsies may be necessary for the histologic diagnosis of PHG.

Characteristic histologic findings of PHG include capillary and venule dilatation, and markedly congested and tortuous submucosal venules[137]. Stromal fibrosis and edema of lamina propria can occurs[137]. Inflammatory cells and fibrin thrombi are generally absent[3,139]. Characteristic histologic features of GAVE include presence of fibrin thrombi in dilated capillaries and fibromuscular proliferation within the lamina propria[96,216].

Differentiating GI bleeding from varices *vs* PHG: PHG may occasionally resemble gastric varices at EGD. PHG can be prominent on gastric rugae in the gastric body and fundus. The intraluminal linear projections of gastric rugae might superficially resemble that of gastric varices. However, gastric varices tend to be more serpiginous than linear and tend to be grayish due to the presence of deoxygenated venous blood within varices, whereas the lesions of PHG on gastric rugae tend to be erythematous and surrounded by a prominent mosaic pattern. It is also important to distinguish between GI bleeding from esophageal varices *vs* PHG in patients having both lesions. Table 10 outlines differences in GI bleeding from PGH *vs* esophageal varices.

Clinical presentation

Acute GI bleeding: GI bleeding is the only known clinically relevant complication of PHG. PHG is responsible for < 1% of upper GI bleeding in the general population, and for about 8% of non-variceal upper GI bleeding in patients with liver disease[217]. The reported frequency of acute upper GI bleeding in patients with

Table 10 Differences in gastrointestinal bleeding from portal hypertensive gastropathy *vs* esophageal varices

Parameter	Portal hypertensive gastropathy	Esophageal varices
Etiology	Portal hypertension: Cirrhotic or non-cirrhotic	Portal hypertension: Cirrhotic or non-cirrhotic
Concurrence	Frequently occur simultaneously with esophageal varices because the two diseases share common risk factors	Frequently occurs simultaneously with PHG because the two diseases have common risk factors
Location	Stomach: Predominantly fundus and body	Distal esophagus: Also can have gastric varices or ectopic varices in other gastrointestinal regions, particularly duodenum
Diagnosis	Esophagogastroduodenoscopy	Esophagogastroduodenoscopy
Endoscopic appearance	Erythematous small polygonal areas of mucosa surrounded by a fine, whitish, reticular or mosaic/snakeskin mucosa with red or brown spots	Serpiginous mucosal greyish luminal projections in distal esophagus
Clinical presentation	Mild acute or chronic bleeding	Acute gastrointestinal bleeding-typically massive
Severity of bleeding	Typically mild and not life-threatening	Typically severe and life-threatening
Histology		Not biopsied at endoscopy
Endoscopic therapy	Limited role	Variceal ligation recommended as initial therapy. Sclerotherapy an alternative therapy
Medical therapy	Octreotide Propranolol Vasopressin or vasopressin analogues-infrequently recommended any more	Octreotide Propranolol Vasopressin or vasopressin analogues-infrequently recommended any more
Blakemore tube	Not recommended	Sometimes used for refractory bleeding especially as a temporizing measure before performing more definitive therapy
Angiographic therapy	TIPS used as a last resort	TIPS recommended if endoscopic therapy fails
Transfusion of packed erythrocytes	Transfuse only to hematocrit of about 28. Over-transfusion may increase portal pressure and induce greater bleeding	Transfuse only to hematocrit of about 28. Over-transfusion may increase portal pressure and induce greater bleeding
Liver transplantation	Improves or resolves with liver transplantation	Improves or resolves with liver transplantation
Prognosis	Rarely fatal	Frequently fatal

TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy.

PHG ranges in incidence from 2%-20% (Table 11[3,8,25,34,37,103,217,218]). Primignani *et al*[34] reported acute GI bleeding in 2.7% of patients with PHG, whereas Stewart *et al*[179] reported a 20% incidence of acute bleeding in patients with PHG. McCormack *et al*[3] reported that 29 (44.6%) of 65 patients with PHG bled from this lesion. In this study, PHG was the second most common cause of GI bleeding, after esophageal varices[3]. The reported variability is partly due to inaccuracies in the endoscopic diagnosis of PHG and in the endoscopic diagnosis of PHG as the cause of bleeding[71]. Diagnosis of PHG as the cause of bleeding can be challenging if a bleeding point is not visualized at EGD[71].

Major risk factors for bleeding from PHG are increasing PHG duration, extent, and severity[72,179]. For example, > 90% of acute bleeding occurs with severe PHG[10,35,71,72], and < 10% of acute bleeding occurs with mild PHG[112]. Other risk factors for bleeding from PHG include advanced cirrhosis, and prior endoscopic eradication of esophageal varies[3,5,10,81,179,180,219]. Unlike bleeding from GAVE, acute bleeding from PHG is rarely severe, very rarely fatal, and typically requires transfusion of only one-to-two units of packed erythrocytes or less[34,71,72,139].

Chronic bleeding: The frequency of chronic bleeding ranges from 3%-26%[25,34,37]. Stewart *et al*[179] reported a 6% incidence of chronic bleeding from PHG, whereas Primignani *et al*[34] reported chronic bleeding in 11% of patients with PHG (Table 11[3,8,25,34,37,103,217,218]).

The incidence of chronic gastrointestinal bleeding from PHG is difficult to determine precisely because of variable definitions of chronic GI bleeding[67,68]. Common definitions include: (1) > 2 g/dL decrease in hemoglobin level during > 6 mo in patients without acute GI bleeding and not receiving NSAID therapy; (2) presence of anemia in patients with cirrhosis; and (3) positive fecal occult blood (Baveno II)[181]. Moreover, chronic GI bleeding can be overestimated if hemoglobin decline is solely used for the diagnosis. Patients with chronic liver disease frequently have anemia without GI bleeding, from causes including alcoholism, chronic kidney disease, hypersplenism, or bone marrow suppression. No studies have objectively quantified chronic blood loss from PHG.

Chronic bleeding from PHG is usually mild to moderate but occasionally severe[37,139]. Patients after endoscopic variceal obliteration have a higher incidence of chronic GI bleeding from PHG[10,25,72]. Chronic GI bleeding from PHG can cause iron deficiency anemia[220,221].

Pharmacotherapy for PHG

Current pharmacologic therapies aim to reduce portal pressure to decrease bleeding from PHG[191,214].

β-adrenergic receptor antagonists: Nonselective β-adrenergic receptor antagonists reduce portal pressure and gastric mucosal blood flow, and thereby reduce bleeding from PHG[103,104,132,191,222-224]. Several studies evaluated the efficacy of propranolol, a nonselective β-adrenergic receptor antagonist in primary and secon-

Table 11 Rates of gastrointestinal bleeding from portal hypertensive gastropathy

Ref.	Year published	Population	Bleeding from PHG	Transfusions required
McCormack *et al*[3]	1985	127 patients with portal hypertension of various etiologies	29 patients out of 65 with PHG, representing 25% of the total number of bleeds from all sources; 9 episodes presenting with bleeding; 71 episodes of subsequent bleeding	2-15 units required for 60 bleeds
D'Amico *et al*[25]	1990	212 patients with cirrhosis; 75 being treated with sclerotherapy		
Sarin *et al*[8]	1992	107 patients with portal hypertension presenting with variceal bleeding, undergoing sclerotherapy	No bleeding before sclerotherapy from PHG (4/107 had PHG); 2/13 post-sclerotherapy patients who developed PHG	Average of 4 units per patient with range of 2-8 units
Pérez-Ayuso *et al*[103]	1991	54 cirrhotic patients with PHG, in a RCT to look for rebleeding; propranolol 26 *vs* control 28	First hemorrhage: Acute/chronic bleeding in propranolol group 12/14; in control 12/16, rebleeding: Acute/chronic; in propranolol 6/6; in control 10/12	
Gostout *et al*[217]	1993	Patients admitted for GI bleeding (1496)	12 patients (0.8%), representing 8% of nonvariceal bleeding in patients with liver disease	
Primignani *et al*[34]	2000	373 patients with cirrhosis; PHG in 299 patients (80.1%)	8 PHG patients with acute bleeding; chronic bleeding in 34 patients	
Merli *et al*[37]	2004	222 cirrhotic patients with portal hypertension; 48 patients with PHG on enrollment	During follow up for 47 ± 28 (SD) mo, acute bleeding 9, chronic bleeding 7 from PHG	
Kimura *et al*[218]	2014	297 patients with living donor liver transplantation; retrospective analysis	2 patients bled from PHG within 3 mo after transplantation	

PHG: Portal hypertensive gastropathy; RCT: Randomized controlled trial; GI: Gastrointestinal.

dary prevention of bleeding from PHG[104,225]. Pérez-Ayuso *et al*[103] reported in a multi-center, randomized, controlled trial of 57 patients with acute or chronic bleeding from severe PHG with cirrhosis that the 26 patients administered propranolol at 20-160 mg twice daily rebled significantly less frequently than the 31 controls receiving only iron therapy as needed at 12 mo (38% *vs* 65%; $P < 0.05$), and at 30 mo follow-up (7% *vs* 52%, $P < 0.05$). Patients receiving propranolol were transfused less units of packed erythrocytes than the controls, but this difference was not statistically significant [0.10 ± 0.06 (SD) units/mo *vs* 0.60 ± 0.20 (SD) units/mo, $P = 0.08$].

Propranolol also reduced the risk of developing PHG after esophageal variceal eradication[81]. Lo *et al*[81] reported in a randomized, controlled trial that 40 patients receiving placebo had a significant increase in PHG severity after variceal ligation ($P < 0.01$, ANOVA), but the 37 patients receiving propranolol [mean dose = 96 ± 20 (SD) mg/d] had no significant increase in PHG severity. The frequency of PHG 6 mo after variceal ligation was significantly less in patients receiving propranolol than in the controls (48% *vs* 85%, $P = 0.002$). This difference gradually decreased over time and became not significant at 12 mo. Also, the mean PHG severity score was lower in patients receiving propranolol than in the controls at 6 mo after variceal ligation ($P < 0.05$).

Propranolol at 240-480 mg/d has been used to arrest acute bleeding from PHG. Bleeding stopped within 3 d in 13 (93%) of 14 patients with portal hypertension administered propranolol in one study[101]. None of these patients rebled while receiving propranolol during a median of 23 mo of follow-up, but 4 out of 7 patients rebled after electively discontinuing propranolol therapy[104]. Nonresponse to β-adrenergic receptor antagonists, defined as continued bleeding despite this therapy and transfusion-dependency despite iron replacement therapy, should prompt consideration of interventional therapies[214].

Nonspecific β-adrenergic receptor antagonists are a first line therapy for secondary prophylaxis of PHG bleeding[191,208]. Nadolol alone was as effective as nadolol with isosorbide mononitrate in preventing the first episode of PHG bleeding[226]. No studies have analyzed the efficacy of carvedilol, another nonspecific β-adrenergic receptor antagonist, in controlling bleeding from PHG[227].

Somatostatin and octreotide: Somatostatin and octreotide, a synthetic somatostatin analogue, cause splanchnic vasoconstriction, reduce portal pressure, reduce portal blood flow, and decrease gastric perfusion in animal models and in patients with PHG[105,106,160,228-231]. For example, Chan *et al*[228] found octreotide infusion, compared to placebo, significantly increased systemic vascular resistance [3.4 ± 0.2 (SD) mmHg/mL per minute per 100 g *vs* 2.7 ± 0.2 (SD) mmHg/mL per minute per 100 g, $P < 0.05$], and significantly decreased portal pressure [9.9 ± 0.5 (SD) mmHg *vs* 12.5 ± 1.2 (SD) mmHg, $P < 0.05$] in cirrhotic rats. Another study found that somatostatin only modestly reduced portal pressure in PHG[232]. Octreotide treatment also significantly reduced mean cross-sectional area of gastric mucosal vessels compared to placebo [1810 ± 101 (SD) microns *vs* 2290 ± 145 (SD) microns, $P < 0.05$], and significantly inhibited release of several vasoactive gastrointestinal polypeptides, gastric acid, and pepsinogen[106,233]. In the stomach, somatostatin activates K^+-ATP channels (adenosine triphosphate-dependent potassium channels) which normally protect against gastric mucosal injury in the presence of portal hypertension, and antagonizes

the portal hypertensive and injury-promoting effects of glucagon[160].

Octreotide is a first-line treatment for acute bleeding from PHG. In a randomized controlled trial, octreotide, at 100 mcg bolus followed by infusion of 25 mcg/min for the first 24 h and then 20 mcg/min for the second 24 h, controlled bleeding from PHG in 20 (83%) of 24 patients at 24 h and in 24 (100%) of 24 patients at 48 h[106]. Octreotide significantly more frequently controlled the bleeding than vasopressin (64%, $P < 0.005$), or omeprazole (59%, $P < 0.005$), and tended to be more effective than both vasopressin and omeprazole (88%, NS)[106]. Octreotide also controlled the bleeding significantly faster and required significantly less transfusions of packed erythrocytes than vasopressin or omeprazole[106]. Octreotide even successfully stopped bleeding within 48 h in the patients with bleeding refractory to vasopressin and omeprazole therapy.

Kouroumalis *et al*[105] reported that somatostatin or octreotide infusion for 3 d stopped severe bleeding from PHG in all 26 study patients. Only 3 patients experienced recurrent bleeding which stopped after retreatment with somatostatin, and only one patient required gastrectomy for refractory bleeding.

Somatostatin and octreotide only temporarily reduce portal pressure. Escorsell *et al*[232] reported rapid desensitization to the effects of octreotide with prolonged administration in cirrhotic patients with portal hypertension. Therefore somatostatin and octreotide are useful for acute bleeding but not for preventing chronic bleeding from PHG. Octreotide did not significantly change the severity of PHG at endoscopy.

Vasopressin and terlipressin: Vasopressin, a systemic vasoconstrictor, reduces splanchnic blood flow, lowers portal pressure, and decreases gastric mucosal blood flow[106]. In a randomized, controlled trial, vasopressin, administered intravenously (IV) at a rate of 1 unit/min for the first 10 min, followed by continuous infusion at 0.1 unit/min for 48 h, arrested bleeding from PHG in 14 (64%) of 22 patients[106]. However, as aforementioned, this result was inferior to that achieved by octreotide, possibly because vasopressin does not inhibit release of peptides, including glucagon and vasoactive intestinal polypeptide, and does not inhibit gastric acid secretion[106]. Concomitant omeprazole therapy may modestly increase vasopressin efficacy[106]. Vasopressin is considered an alternative therapy to octreotide.

Vasopressin causes significantly more frequent side effects (41%) than octreotide, especially abdominal pain[106]. Vasopressin reduces oxygen saturation of gastric mucosa, but this reduction can be partly reversed by administering supplemental oxygen[234,235]. Two analogues of vasopressin have been studied. Glypressin showed similar reduction in gastric mucosal perfusion as vasopressin by laser-Doppler flowmetry, but less impairment in gastric mucosal oxygenation[235]. Terlipressin may be useful in controlling acute bleeding from PHG, especially when used at a dose of 1 mg IV every 4 h for 5 d[103,107,192].

Antioxidants: Antioxidants help in free radical scavenging and in reversing impairment of oxidative stress-induced ERK2 activation. They may decrease susceptibility of PHG gastric mucosa to alcoholic injury, as demonstrated by administration of vitamin E, an antioxidant[144]. Vitamin E reduced oxidative state, normalized MKP-1 expression, and reversed impairment of oxidative stress-induced ERK2 activation[144]. Vitamin E helped reduce gastric injury from alcohol exposure in rats with PHG[71].

Vitamin E administration decreased mucosal lipid peroxidation, decreased lysosomal enzymes, and increased levels of antioxidants. Kaur *et al*[143] administered vitamin E 240 mg subcutaneously to rats with common bile duct ligation *vs* sham surgery. Seven days after ligation or sham surgery, the level of thiobarbituric acid reactive substances in gastric mucosa was significantly higher in ligated rats not receiving vitamin E [0.78 ± 0.22 (SD) nmol of malondialdehyde formed/mg protein] as compared to sham surgery rats administered vitamin E [0.56 ± 0.07 (SD) nmol of malondialdehyde formed/mg protein, $P < 0.01$]. These data suggest that vitamin E decreased mucosal lipid peroxidation. In the ligation group vitamin E administered preoperatively significantly reduced the levels of β-glucuronidase as compared to untreated or post-operatively-treated groups ($P < 0.01$). Preoperative vitamin E therapy significantly lowered levels of acid phosphatase as compared to untreated or postoperatively treated groups ($P < 0.01$). Preoperative administration of vitamin E in the ligation group led to significantly increased levels of the three major antioxidant enzymes, including superoxide dismutase ($P < 0.005$), glutathione peroxidase ($P < 0.01$), and catalase ($P < 0.05$) when compared to the levels of these antioxidant enzymes in untreated groups or in groups treated postoperatively with vitamin E. These data provide a theoretical basis that vitamin E administration may potentially improve PHG.

Kawanaka *et al*[144] administered vitamin E or saline for 13 d in rats with PHG *vs* sham-operated rats used as a control. Rats with PHG had a 2.3-fold increased area of gastric mucosal necrosis after gastric exposure to ethanol than sham-operated rats ($P < 0.05$), but vitamin E treatment in rats with PHG almost completely reversed this increased necrosis compared to controls ($P < 0.05$). Vitamin E treatment did not significantly change portal pressure or gastric mucosal blood flow in PHG gastric mucosa.

Rebamipide: Rebamipide, an antiulcer medication, protects against oxygen-derived production of free radicals by scavenging free radicals. Intragastric administration ameliorates oxidative stress, reduces nitration of tyrosine residues of ERK, and reverses delayed mucosal healing occurring in PHG. It reversed the increased susceptibility to ethanol-induced injury and

reversed the delayed healing after gastric injury in rats with PHG[145]. Kinjo *et al*[145] reported that administration of rebamipide in rats with PHG, significantly decreased lipid peroxide and nitrotyrosine and nitration of ERK by peroxynitrite in PHG mucosa, therefore normalizing ERK activation and restoring normal gastric mucosal healing after ethanol injury. Rebamipide requires further study as a therapy for PHG[119].

Estrogen and progesterone: Estrogen and progesterone therapy reduced gastric mucosal blood flow, portal pressure, and porto-collateral resistance in rats with surgically-induced portal hypertension[236]. Panés *et al*[236] reported that treatment with estradiol, dihydroxyprogesterone, or low dose combination estradiol-dihydroxyprogesterone significantly decreased gastric mucosal blood flow in rats that underwent portal vein ligation as compared to placebo [56 ± 3.5 (SD) mL/min per 100 g for placebo; 43 ± 3.4 (SD) mL/min per 100 g for estrogen; 32 ± 2.6 mL/min per 100 g for dihydroxyprogesterone, and 42 ± 6.1 (SD) mL/min per 100 g for low dose estrogen/dihydroxyprogesterone, $P < 0.05$]. Estrogen and progesterone have not been studied in patients with PHG.

Thalidomide: Thalidomide blunts development of a hyperdynamic circulation and decreases portal pressure by reducing NO production[114]. Thalidomide, at a low dose of 100 mg daily, was successful as a last resort therapy in one case report of bleeding from PHG caused by neoplastic invasion of the portal vein[237]. Before thalidomide therapy, the patient had required transfusion of 30 units of packed erythrocytes during 35 d while treated with propranolol and terlipressin.

Corticosteroids: There is one case report of cessation of PHG bleeding with corticosteroid therapy, using prednisolone 20 mg/d, after being admitted for five times during 5 mo with severe iron deficiency anemia from chronic GI bleeding from PHG that was refractory to propranolol therapy. At 2 mo follow-up the hemoglobin was rising and at 4 mo follow-up repeat EGD showed an improved endoscopic appearance of PHG[238]. The patient was stable during 3-years of follow-up using 15 mg prednisolone every other day, with no recurrence of the anemia.

Losartan: Hepatic stellate cells help modulate sinusoidal resistance and the sinusoidal microcirculation. These cells are influenced by vasoconstrictors such as endothelin and angiotensin Ⅱ. The angiotensin Ⅱ receptor antagonist, losartan, lowers portal pressure by inhibiting stellate cell contraction and by reducing sinusoidal resistance[239]. Administration of losartan at 25 or 50 mg/d resulted in improvement of PHG in 9 (56.3%) of 16 patients during 4 wk of follow-up. The higher dose had greater efficacy. There was also evidence of decreased portal pressure. Further studies are needed to evaluate the effect of losartan on PHG[239].

Sucralfate and acid-suppressing medications: Proton pump inhibitors, sucralfate[74], and histamine-2 receptor antagonists are not very effective at reducing bleeding from PHG because most patients with PHG already have hypochlorhydria[79,106,240-242]. However, proton pump inhibitors may indirectly stop bleeding from the stomach by raising intraluminal gastric pH and thereby stabilizing blood clots[243,244]. Zhou *et al*[106] reported that omeprazole at 40 mg IV bolus every 12 h for 48 h successfully stopped bleeding in 59% of patients with PHG bleeding. Additionally, patients whose bleeding was refractory to vasopressin, benefited from omeprazole co-administration and vice versa.

Teprenone: In a controlled clinical trial, teprenone (geranylgeranyl acetone) administered to 15 patients with PHG decreased VEGF and hexosamine content in the gastric antrum, and thereby significantly decreased the severity of PHG[136]. Among these 15 treated patients, one patient decreased from severe to moderate PHG and another patient decreased from moderate to mild PHG[180]. Contrariwise, all 15 patients receiving placebo experienced no change in PHG severity.

Endoscopic therapies: Endoscopic therapies play a minor role in PHG bleeding because the bleeding is typically diffuse and obscure. Little data exist on efficacy of endoscopic therapy for PHG bleeding[71,245]. No single predominant site of bleeding is identified that can be locally treated at endoscopy. The role of endoscopic therapy is limited to the rare circumstances in which a single active bleeding site identified that is amenable to point therapy such as cauterization or sclerotherapy.

Argon plasma coagulation (APC) or hemospray, a rapid hemostatic agent, are experimental endoscopic therapies for PHG. These therapies can treat a larger bleeding surface area than cauterization or sclerotherapy. Nine (81%) of 11 patients undergoing APC for PHG bleeding achieved hemostasis, with a significant rise in hematocrit from baseline values after a mean of 2.2 ± 2.0 (SD) endoscopic therapy sessions. The other two treated patients required fewer blood transfusions after APC therapy[202].

Hemospray has recently shown promise in halting active PHG bleeding while long-term therapy is being initiated[203,246]. Ibrahim *et al*[246] reported complete cessation of diffuse bleeding from severe PHG after spraying hemospray TC-325 (a nanopowder hemostatic agent[247]) in a 41-year-old woman who presented with a hemoglobin of 8.8 g/dL. No active bleeding was seen on follow-up endoscopy performed 24 h later. In another study, however, one of four patients treated with hemospray for bleeding from PHG expired from GI perforation[203].

Endoscopic cryotherapy has been used for PHG bleeding after all other modalities failed. In one patient salvage cryotherapy was successful after failed TIPS and APC, with normal hemoglobin levels maintained during 4 wk of follow-up[248].

TIPS: TIPS increases gastric mucosal blood flow while decreasing total gastric blood flow due to decreasing portal hypertension[76]. TIPS reduces the frequency and severity of PHG because it lowers portal pressure[76]. PHG can sometimes resolve completely after TIPS[75-77,249-253]. Urata *et al*[77] reported in a prospective study of 12 Japanese patients undergoing TIPS for portal hypertension that portal pressure declined from 25.1 ± 8.8 (SD) mmHg before TIPS to 17.1 ± 6.2 (SD) mmHg after TIPS ($P < 0.005$). This decline in portal pressure was correlated with a significant decrease in PHG severity after TIPS ($P < 0.01$), and a significant decrease in number of patients with PHG (10 before *vs* 4 after TIPS, $P < 0.01$). In particular, PHG disappeared in 2 of 5 patients who had severe PHG before TIPS. Mezawa *et al*[76], likewise, reported that mean portal pressure declined from 23.4 to 14.0 mmHg in 16 cirrhotic patients after TIPS ($P < 0.01$). All four patients with severe PHG before TIPS, had significant improvement in PHG severity after lowering portal pressure with TIPS, and five of 12 patients with mild PHG had resolution of PHG after TIPS. In contrast, GAVE does not resolve after lowering portal pressure with TIPS, and GAVE is, therefore, likely related to hepatic dysfunction rather than portal hypertension[78].

TIPS also decreased the risk of PHG bleeding[75-77,100,249-253]. For example, Kamath *et al*[75] reported TIPS led to improvement or resolution of PHG findings and decreased transfusion requirements from 2.9 ± 2.0 (SD) units/mo of packed erythrocytes before TIPS to 0.6 ± 0.8 units/mo after TIPS performed for severe PHG ($P = 0.04$). Ashraf *et al*[98] reported one patient with chronic liver disease from hepatitis C who presented with chronic bleeding from PHG that required transfusions of 28 units of packed erythrocytes during the prior 6 mo. The bleeding ceased after TIPS with marked improvement in the severity of PHG. Contrariwise, GAVE does not respond to TIPS or other measures that lower portal pressure.

Shunt surgery: Shunt surgery decreases portal hypertension, decreases PHG severity, decreases risk of PHG bleeding, and may sometimes completely resolve the endoscopic features of PHG[100]. Shunt surgery is rarely used today to control bleeding because TIPS is preferred because of less invasiveness[100,101,238,254].

TIPS and shunt surgery are therapies of last resort for patients who fail other therapies for PHG because they entail more morbidity and mortality than pharmacologic therapy[71]. TIPS, however, is very useful for refractory bleeding from esophageal varices from portal hypertension[255], and is a reasonable option in patients having recurrent severe bleeding from PHG despite administration of β-adrenergic receptor antagonists[102].

Other invasive therapies: Liver transplantation is the ultimate therapy for PHG[118]. In a study of 29 patients undergoing living donor liver transplantation for end stage liver disease, PHG resolved in all 19 patients who had PHG before transplantation[44].

Kimura *et al*[218] retrospectively examined the 19 patients experiencing gross GI bleeding, defined as gross melena or hematemesis, within 3 mo after liver transplantation among 297 patients undergoing living donor liver transplantation. The etiologies included PHG in 2 patients, varices in 1, anastomotic ulcer in 13, and other in 3.

Splenic embolization, by transcatheter splenic arterial embolization, significantly improves PHG in patients with hypersplenism as compared to controls[99,255]. Ohmagari *et al*[99] evaluated 30 patients with hypersplenism who underwent transcatheter splenic arterial embolization in 17 *vs* no interventional therapy in 13 patients. Splenic embolization significantly reduced the frequency of PHG (reduction of 71% *vs* 8%, $P < 0.05$). Partial splenic embolization also successfully controlled PHG bleeding in one case report[256].

Laparoscopic splenectomy, for various indications, was reported to decrease PHG severity[55]. Anegawa *et al*[55] prospectively analyzed the effect of laparoscopic splenectomy on preexistent PHG in 70 patients with liver cirrhosis from various etiologies. All patients underwent EGD before and 1 mo after splenectomy. Splenectomy was performed for indications of bleeding diathesis, interferon induction, hepatocellular cancer treatment, and sclerotherapy-resistant varices. Before splenectomy, 49 of 70 patients had PHG, including mild PHG in 32 and severe PHG in 17 patients. After splenectomy, PHG resolved completely in 7 patients with prior severe PHG, resolved completely in 12 patients with mild PHG, and was reduced from severe to mild PHG in 9 patients ($P < 0.0001$).

Summary of clinical treatment

Acute bleeding: Variceal bleeding must be excluded by performing EGD before initiating treatment for PHG[257,258]. General measures for patients presenting with acute bleeding from PHG include volume resuscitation and cautious transfusion of packed erythrocytes, as necessary, to maintain the hemoglobin level at 8 g/dL[192,259,260]. Over-transfusion to a higher hemoglobin level could promote bleeding from PHG by raising portal pressure, as reported for bleeding from esophageal varices[261,262]. However, patients with cardiopulmonary disease or severe other comorbidities may require a hemoglobin level of 9-10 g/dL[263]. Antibiotic prophylaxis is generally recommended for bleeding from PHG[214], just as it is recommended for esophageal variceal bleeding in cirrhotic patients[189,264-266] because of an increased risk of systemic infections, particularly spontaneous bacterial peritonitis, in cirrhotic patients with GI bleeding[267].

Bleeding from PHG may be exacerbated by a coagulopathy with an elevated international normalized ratio from advanced liver disease. This coagulopathy may require transfusion of fresh frozen plasma. Severe thrombocytopenia may occur from bone marrow suppression in alcoholic cirrhosis and from hypersplenism with portal hypertension in any cirrhotic patient.

Table 12 Treatment of acute or chronic gastrointestinal bleeding from portal hypertensive gastropathy

Acute bleeding
Patient stabilization
Treat severe coagulopathy with highly elevated INR associated with cirrhosis with fresh frozen plasma
Treat severe thrombocytopenia associated with hypersplenism and bone marrow suppression from alcoholism with platelet transfusions
Transfuse packed erythrocytes to main hemoglobin level at about 8 g/dL
Consider antibiotic prophylaxis in patient with cirrhosis
Endoscopic therapy from bleeding-rarely used
Consider argon plasma coagulation
Hemospray - an experimental therapy
Pharmacotherapy
Octreotide - first line therapy
Vasopressin or terlipressin - second line therapy
Proton pump inhibitor therapy - adjunct therapy
Propranolol - can be instituted after bleeding controlled and patient stabilized
Interventional therapy
TIPS - for uncontrolled hemorrhage or for bleeding from PHG associated with variceal bleeding
Liver transplantation - for advanced end stage liver disease
Chronic bleeding
Treatment of anemia
Transfusions of packed erythrocytes as necessary
Iron replacement therapy
Pharmacotherapy
Consider propranolol

TIPS: Transjugular intrahepatic portosystemic shunt; PHG: Portal hypertensive gastropathy; INR: International normalized ratio.

Platelet transfusion may be necessary for severe thrombocytopenia in the setting of active bleeding from PGH.

Somatostatin or octreotide are first line therapies. Vasopressin or terlipressin are second-line therapies for acute bleeding[106]. Once the acute bleeding is controlled and the patient is hemodynamically stable, a nonselective β-adrenergic receptor antagonist is instituted for secondary prevention of PHG bleeding[103,258,268]. Propranolol is the recommended drug in this class because it has been the most studied. Propranolol should be started at a dose of 20 mg twice daily and gradually escalated to 160 mg twice daily or the maximum tolerated dose, maintaining it as long as the portal hypertension is present[214]. The dose is titrated to slow the pulse to 60 beats/min. This class of drugs is not used in the acute setting because it can blunt the physiologic tachycardia to restore end-organ perfusion in response to hypovolemia and requires gradual dose titration to achieve an adequate response[214]. This class of drugs also prevents bleeding from concomitant esophageal varices.

Treatment of chronic bleeding: Scant data exist regarding management of chronic bleeding from PHG[72]. In patients with suspected chronic bleeding from PHG, after excluding other etiologies, iron replacement therapy should be initiated to avoid depleting iron reserves[260]. Propranolol is the primary therapy to reduce portal pressure and prevent chronic bleeding[72,214,260]. However, propranolol was not superior to placebo in one study, as determined by percentage of patients free from chronic GI bleeding during long term follow-up[103].

Liver transplantation is an option in patients with decompensated cirrhosis and PHG bleeding. Table 12 summarizes the recommendations for the treatment of acute and chronic bleeding from PHG.

Prevention

The risk of bleeding from mild PHG is low. Primary prophylaxis is, therefore, not recommended for patients with mild PHG[72,191,269]. Propranolol can be used for primary prophylaxis for severe PHG, and can significantly reduce the risk of bleeding. However, scant evidence exists that this reduction will affect the risk of a primary bleeding episode in PHG patients[72,103,104,269,270]. Propranolol is recommended regardless of the severity or presence of PHG in patients with esophageal varices because it treats both entities by reducing portal pressure[105-107,198,271,272].

Prophylaxis of bleeding from PHG is not recommended[260]. Current guidelines do not recommend endoscopic surveillance in patients with cirrhosis who have asymptomatic PHG, without evident esophageal varices, other than the standard surveillance for development of esophageal varices in these patients[189].

Mortality: Limited data exist on mortality from bleeding from PHG, but this bleeding is rarely fatal[72]. It contributes little to overall morbidity and mortality from portal hypertension, especially in comparison to variceal bleeding[118]. It represents a minor cause (< 1%) of mortality in cirrhotic patients because the bleeding is typically mild[25,34,37,71]. Only one patient expired from PHG in one series of 38 deaths among 373 study patients with cirrhosis[34]. Bleeding-related mortality was much lower for PHG [1 of 8 patients (12.5%)] than that for esophageal varices [9 of 20 patients (45%)][34].

Lesions resembling PHG in other gastrointestinal regions: PHG-like lesions can occur in other parts of

the GI tract and are named according to the involved segment as portal hypertensive duodenopathy[40], portal hypertensive biliopathy, small intestinal vasculopathy[139], and portal hypertensive colopathy[96,139]. These uncommon extragastric lesions occur particularly in patients with extrahepatic portal hypertension[71]. Portal hypertensive duodenopathy has been defined as the endoscopic appearance of patchy or diffuse congestion of duodenal mucosa associated with portal hypertension[40], but a consensus definition is not established[273]. Histologically, vascular changes predominate, including capillary angiogenesis, dilatation and congestion, as well as fibrous proliferation and apoptosis[46]. This duodenopathy is significantly more severe in patients having severe than mild PHG (56.8% *vs* 23.5%, $P < 0.05$)[46]. Portal congestive jejunopathy is defined histologically by the presence of ectatic capillaries and venules in the villi, with an increase in the number of vessels to > 6/villus[274]. Portal hypertensive ileopathy[275], and portal hypertensive colopathy[38,276] are also associated with portal hypertension. The colopathy histologically appears as dilatation of mucosal blood vessels and is classified into four different types by Ito *et al*[38], including solitary vascular ectasias, diffuse vascular ectasias, erythema, and blue vein.

DISCUSSION

The pathophysiology of PHG is not well understood. Portal hypertension plays a central role in the pathogenesis, and liver disease a subsidiary role in the disease, but a hyperdynamic circulation likely also plays an important role. However, the precise nature and pathophysiology of the hyperdynamic circulation must be further elucidated. The pathophysiology of more severe gastric mucosal injury and blunted reparative response after exposure to toxic substances in PHG must be clarified in terms of molecular mediators and histopathology. In particular, the pathophysiologic basis of decreased superficial mucosal perfusion in PHG must be better characterized in terms of its molecular mechanisms.

The current pharmacotherapy for bleeding from PHG focuses on decreasing portal pressure because portal hypertension is a prerequisite for developing PHG. Understanding the molecular mechanisms of this disease may permit development of better targeted and more effective pharmacotherapies.

COMMENTS

Background

Portal hypertensive gastropathy (PHG) is characterized at endoscopy by characteristic lesions present in the proximal stomach; characterized pathophysiologically by a hyperdynamic circulation induced by portal hypertension by inadequately understood mechanisms; and characterized clinically by mild-to-moderate acute or chronic gastrointestinal bleeding from the endoscopically identified lesions. However, much about the pathophysiology and clinical therapy of PHG is inadequately understood. This work systematically reviews the literature on the pathophysiology, natural history and therapy of PHG to report what is known and what is not known or controversial about PHG.

Research frontiers

This work systematically reviews gaps or controversies in the current understanding of PHG. First, this work exposes gaps in the current understanding of the pathophysiology. Portal hypertension is necessary but insufficient to develop PHG because many patients have portal hypertension without PHG. The pathogenesis is related to a hyperdynamic circulation, induced by portal hypertension, characterized by increased intrahepatic resistance to flow, increased splanchnic flow, increased total gastric flow, and most likely decreased gastric mucosal flow. However, this review shows that the cellular and molecular mechanisms for this hyperdynamic circulation are inadequately characterized. Nitrous oxide, free radicals, tumor necrosis factor-alpha, and glucagon may be important mediators of PHG. Second, this work reports the inadequacies of the current recommended therapies for PHG and for bleeding from PHG based on the currently inadequate understanding of the pathophysiology. This work should be useful to clinicians, clinical researchers, and basic researchers by describing what is known, controversial, or unknown about the pathophysiology, natural history, and therapy of PHG. It is hoped that this work stimulates further research in this field by exposing gaps in the current understanding of PHG.

Innovations and breakthroughs

This systematic review extensively reviews what is known and what is not known or controversial about PHG. This work is particularly helpful to clinicians in reporting the current recommended therapy for PHG, the clinical trials supporting the current recommendations, and the limitations of the current therapies. This is also helpful to clinical and basic researchers in systematically reviewing the current state of knowledge about its pathophysiology, including gaps, uncertainties, and controversies in the current understanding of the pathophysiology.

Applications

This systematic review extensively reviews what is known and what is not known or controversial about PHG. First, this work exposes gaps in the understanding of the pathophysiology. Portal hypertension is necessary but insufficient to develop PHG because many patients have portal hypertension without PHG. The pathogenesis is related to a hyperdynamic circulation, induced by portal hypertension, characterized by increased intrahepatic resistance to flow, increased splanchnic flow, increased total gastric flow, and most likely decreased gastric mucosal flow. However, this review shows that the cellular and molecular mechanisms for this hyperdynamic circulation are inadequately characterized. Nitrous oxide, free radicals, tumor necrosis factor-alpha, and glucagon may be important mediators of PHG development. Second, this work describes the natural history of PHG. PHG increases in frequency with more severe portal hypertension, advanced liver disease, longer liver disease duration, presence of esophageal varices, and endoscopic variceal obliteration. Acute and chronic gastrointestinal bleeding are the only clinical complications. Bleeding is typically mild-to-moderate. Third, this work reports the current therapies for PHG and for bleeding from PHG and characterizes their inadequacies based on the currently inadequate understanding of the pathophysiology. In particular, this work reviews clinical trials of the therapeutic efficacy of octreotide; proton pump inhibitors; nonselective β-adrenergic receptor antagonists, particularly propranolol; and vasopressin or terlipressin. This work should be useful to clinicians, clinical researchers, and basic researchers by describing what is known, controversial, and uncertain about the pathophysiology, natural history, and therapy of PHG.

Terminology

This work systematically reviews portal hypertensive gastropathy, characterized at endoscopy by characteristic lesions present in the proximal stomach; characterized pathophysiologically by a hyperdynamic circulation induced by portal hypertension by inadequately understood mechanisms, and characterized clinically by mild-to-moderate acute or chronic gastrointestinal bleeding from the endoscopically identified lesions.

Peer-review

This review by Mihajlo Gjeorgjievski on portal hypertensive gastropathy is well

written and helpful to understand its pathophysiology, clinical presentation, natural history and therapy. This review is informative and helpful to readers who are interested in the topic or subtopics.

REFERENCES

1 **Palmer ED**. Erosive gastritis in cirrhosis; influence of portal hypertension on the gastric mucosa. *Am J Dig Dis* 1957; **2**: 31-36 [PMID: 13394564 DOI: 10.1007/BF02232594]
2 **Sarfeh IJ**, Tarnawski A. Portal hypertensive gastritis. *Gastroenterology* 1984; **86**: 592 [PMID: 6607188]
3 **McCormack TT**, Sims J, Eyre-Brook I, Kennedy H, Goepel J, Johnson AG, Triger DR. Gastric lesions in portal hypertension: inflammatory gastritis or congestive gastropathy? *Gut* 1985; **26**: 1226-1232 [PMID: 3877665 DOI: 10.1136/gut.26.11.1226]
4 **Taor RE**, Fox B, Ware J, Johnson AG. Gastritis: gastroscopic and microscopic. *Endoscopy* 1975; **7**: 209-215 [DOI: 10.1055/s-0028-1098575]
5 **Sarin SK**, Misra SP, Singal A, Thorat V, Broor SL. Evaluation of the incidence and significance of the "mosaic pattern" in patients with cirrhosis, noncirrhotic portal fibrosis, and extrahepatic obstruction. *Am J Gastroenterol* 1988; **83**: 1235-1239 [PMID: 3263791]
6 **DeWeert TM**, Gostout CJ, Wiesner RH. Congestive gastropathy and other upper endoscopic findings in 81 consecutive patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 1990; **85**: 573-576 [PMID: 2186617]
7 **McCormick PA**, Sankey EA, Cardin F, Dhillon AP, McIntyre N, Burroughs AK. Congestive gastropathy and Helicobacter pylori: an endoscopic and morphometric study. *Gut* 1991; **32**: 351-354 [PMID: 2026332 DOI: 10.1136/gut.32.4.351]
8 **Sarin SK**, Sreenivas DV, Lahoti D, Saraya A. Factors influencing development of portal hypertensive gastropathy in patients with portal hypertension. *Gastroenterology* 1992; **102**: 994-999 [PMID: 1537536]
9 **Parikh SS**, Desai SB, Prabhu SR, Trivedi MH, Shankaran K, Bhukhanwala FA, Kalro RH, Desai HG. Congestive gastropathy: factors influencing development, endoscopic features, Helicobacter pylori infection, and microvessel changes. *Am J Gastroenterol* 1994; **89**: 1036-1042 [PMID: 8017362]
10 **Sarin SK**, Shahi HM, Jain M, Jain AK, Issar SK, Murthy NS. The natural history of portal hypertensive gastropathy: influence of variceal eradication. *Am J Gastroenterol* 2000; **95**: 2888-2893 [PMID: 11051364 DOI: 10.1111/j.1572-0241.2000.03200.x]
11 **Itha S**, Yachha SK. Endoscopic outcome beyond esophageal variceal eradication in children with extrahepatic portal venous obstruction. *J Pediatr Gastroenterol Nutr* 2006; **42**: 196-200 [PMID: 16456415 DOI: 10.1097/01.mpg.0000189351.55666.45]
12 **Rana SS**, Bhasin DK, Jahagirdar S, Raja K, Nada R, Kochhar R, Joshi K. Is there ileopathy in portal hypertension? *J Gastroenterol Hepatol* 2006; **21**: 392-397 [PMID: 16509864 DOI: 10.1111/j.1440-1746.2005.04037.x]
13 **El-Rifai N**, Mention K, Guimber D, Michaud L, Boman F, Turck D, Gottrand F. Gastropathy and gastritis in children with portal hypertension. *J Pediatr Gastroenterol Nutr* 2007; **45**: 137-140 [PMID: 17592382 DOI: 10.1097/MPG.0b013e318049cbe2]
14 **Sogaard KK**, Astrup LB, Vilstrup H, Gronbaek H. Portal vein thrombosis; risk factors, clinical presentation and treatment. *BMC Gastroenterol* 2007; **7**: 34 [PMID: 17697371 DOI: 10.1186/1471-230X-7-34]
15 **Figueiredo P**, Almeida N, Lérias C, Lopes S, Gouveia H, Leitão MC, Freitas D. Effect of portal hypertension in the small bowel: an endoscopic approach. *Dig Dis Sci* 2008; **53**: 2144-2150 [PMID: 18026837 DOI: 10.1007/s10620-007-0111-z]
16 **Erden A**, Idilman R, Erden I, Ozden A. Veins around the esophagus and the stomach: do their calibrations provide a diagnostic clue for portal hypertensive gastropathy? *Clin Imaging* 2009; **33**: 22-24 [PMID: 19135925 DOI: 10.1016/j.clinimag.2008.06.023]
17 **Duché M**, Ducot B, Tournay E, Fabre M, Cohen J, Jacquemin E, Bernard O. Prognostic value of endoscopy in children with biliary atresia at risk for early development of varices and bleeding. *Gastroenterology* 2010; **139**: 1952-1960 [PMID: 20637201 DOI: 10.1053/j.gastro.2010.07.004]
18 **Aydoğan A**, Güllüoğlu M, Onder SY, Gökçe S, Celtik C, Durmaz O. Portal gastropathy and duodenopathy in children with extrahepatic and intrahepatic portal hypertension: endoscopic diagnosis and histologic scoring. *J Pediatr Gastroenterol Nutr* 2011; **52**: 612-616 [PMID: 21464749 DOI: 10.1097/MPG.0b013e3182125e7c]
19 **dos Santos JM**, Ferreira AR, Fagundes ED, Ferreira AP, Ferreira LS, Magalhães MC, Bittencourt PF, Carvalho SD, Figueiredo Filho PP, Penna FJ. Endoscopic and pharmacological secondary prophylaxis in children and adolescents with esophageal varices. *J Pediatr Gastroenterol Nutr* 2013; **56**: 93-98 [PMID: 22785415 DOI: 10.1097/MPG.0b013e318267c334]
20 **Pantham G**, Waghray N, Einstadter D, Finkelhor RS, Mullen KD. Bleeding risk in patients with esophageal varices undergoing transesophageal echocardiography. *Echocardiography* 2013; **30**: 1152-1155 [PMID: 23742625 DOI: 10.1111/echo.12274]
21 **Abdollahi MR**, Somi MH, Faraji E. Role of international criteria in the diagnosis of autoimmune hepatitis. *World J Gastroenterol* 2013; **19**: 3629-3633 [PMID: 23801865 DOI: 10.3748/wjg.v19.i23.3629]
22 **de Alcantara RV**, Yamada RM, Cardoso SR, de Fátima M, Servidoni CP, Hessel G. Ultrasonographic predictors of esophageal varices. *J Pediatr Gastroenterol Nutr* 2013; **57**: 700-703 [PMID: 23941999 DOI: 10.1097/MPG.0b013e3182a7bc2e]
23 **Aoyama T**, Oka S, Aikata H, Nakano M, Watari I, Naeshiro N, Yoshida S, Tanaka S, Chayama K. Is small-bowel capsule endoscopy effective for diagnosis of esophagogastric lesions related to portal hypertension? *J Gastroenterol Hepatol* 2014; **29**: 511-516 [PMID: 23981241 DOI: 10.1111/jgh.12372]
24 **Sacchetti C**, Capello M, Rebecchi P, Roncucci L, Zanghieri G, Tripodi A, Ponz de Leon M. Frequency of upper gastrointestinal lesions in patients with liver cirrhosis. *Dig Dis Sci* 1988; **33**: 1218-1222 [PMID: 3168693 DOI: 10.1007/BF01536669]
25 **D'Amico G**, Montalbano L, Traina M, Pisa R, Menozzi M, Spanò C, Pagliaro L. Natural history of congestive gastropathy in cirrhosis. The Liver Study Group of V. Cervello Hospital. *Gastroenterology* 1990; **99**: 1558-1564 [PMID: 2227271]
26 **Calès P**, Zabotto B, Meskens C, Caucanas JP, Vinel JP, Desmorat H, Fermanian J, Pascal JP. Gastroesophageal endoscopic features in cirrhosis. Observer variability, interassociations, and relationship to hepatic dysfunction. *Gastroenterology* 1990; **98**: 156-162 [PMID: 2293575]
27 **Rabinovitz M**, Yoo YK, Schade RR, Dindzans VJ, Van Thiel DH, Gavaler JS. Prevalence of endoscopic findings in 510 consecutive individuals with cirrhosis evaluated prospectively. *Dig Dis Sci* 1990; **35**: 705-710 [PMID: 2344804 DOI: 10.1007/BF01540171]
28 **Iwao T**, Toyonaga A, Sumino M, Takagi K, Oho K, Nishizono M, Ohkubo K, Inoue R, Sasaki E, Tanikawa K. Portal hypertensive gastropathy in patients with cirrhosis. *Gastroenterology* 1992; **102**: 2060-2065 [PMID: 1587424]
29 **Taranto D**, Suozzo R, Romano M, di Sapio M, Caporaso N, Del Vecchio Blanco C, Coltorti M. Gastric endoscopic features in patients with liver cirrhosis: correlation with esophageal varices, intra-variceal pressure, and liver dysfunction. *Digestion* 1994; **55**: 115-120 [PMID: 8187974 DOI: 10.1159/000201135]
30 **Gupta R**, Saraswat VA, Kumar M, Naik SR, Pandey R. Frequency and factors influencing portal hypertensive gastropathy and duodenopathy in cirrhotic portal hypertension. *J Gastroenterol Hepatol* 1996; **11**: 728-733 [PMID: 8872769 DOI: 10.1111/j.1440-1746.1996.tb00322.x]
31 **Iwao T**, Toyonaga A, Oho K, Sakai T, Tayama C, Masumoto H, Sato M, Nakahara K, Tanikawa K. Portal-hypertensive gastropathy develops less in patients with cirrhosis and fundal varices. *J Hepatol* 1997; **26**: 1235-1241 [PMID: 9210609 DOI: 10.1016/S0168-8278(97)80457-6]
32 **Carpinelli L**, Primignani M, Preatoni P, Angeli P, Battaglia G, Beretta L, Bortoli A, Capria A, Cestari R, Cosentino F, Crotta S, Gerunda G, Lorenzini I, Maiolo P, Merighi A, Rossi A, Sangiovanni A, de Franchis R. Portal hypertensive gastropathy: reproducibility of a classification, prevalence of elementary lesions, sensitivity and specificity in the diagnosis of cirrhosis of the liver.

A NIEC multicentre study. New Italian Endoscopic Club. *Ital J Gastroenterol Hepatol* 1997; **29**: 533-540 [PMID: 9513828]

33 **Zaman A**, Hapke R, Flora K, Rosen H, Benner K. Prevalence of upper and lower gastrointestinal tract findings in liver transplant candidates undergoing screening endoscopic evaluation. *Am J Gastroenterol* 1999; **94**: 895-899 [PMID: 10201453 DOI: 10.1111/j.1572-0241.1999.984_g.x]

34 **Primignani M**, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A, Cestari R, Angeli P, Gatta A, Rossi A, Spinzi G, De Franchis R. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). *Gastroenterology* 2000; **119**: 181-187 [PMID: 10889167 DOI: 10.1053/gast.2000.8555]

35 **Chaves DM**, Sakai P, Mucenic M, Iriya K, Iriya Y, Ishioka S. Comparative study of portal hypertensive gastropathy in schistosomiasis and hepatic cirrhosis. *Endoscopy* 2002; **34**: 199-202 [PMID: 11870569]

36 **Merkel C**, Schipilliti M, Bighin R, Bellini B, Angeli P, Bolognesi M, Vescovi F, Gatta A. Portal hypertension and portal hypertensive gastropathy in patients with liver cirrhosis: a haemodynamic study. *Dig Liver Dis* 2003; **35**: 269-274 [PMID: 12801039 DOI: 10.1016/S1590-8658(03)00064-1]

37 **Merli M**, Nicolini G, Angeloni S, Gentili F, Attili AF, Riggio O. The natural history of portal hypertensive gastropathy in patients with liver cirrhosis and mild portal hypertension. *Am J Gastroenterol* 2004; **99**: 1959-1965 [PMID: 15447756 DOI: 10.1111/j.1572-0241.2004.40246.x]

38 **Ito K**, Shiraki K, Sakai T, Yoshimura H, Nakano T. Portal hypertensive colopathy in patients with liver cirrhosis. *World J Gastroenterol* 2005; **11**: 3127-3130 [PMID: 15918202 DOI: 10.3748/wjg.v11.i20.3127]

39 **De Palma GD**, Rega M, Masone S, Persico F, Siciliano S, Patrone F, Matantuono L, Persico G. Mucosal abnormalities of the small bowel in patients with cirrhosis and portal hypertension: a capsule endoscopy study. *Gastrointest Endosc* 2005; **62**: 529-534 [PMID: 16185966 DOI: 10.1016/S0016-5107(05)01588-9]

40 **Menchén L**, Ripoll C, Marín-Jiménez I, Colón A, Gómez-Camarero J, González-Asanza C, Menchén P, Cos E, Bañares R. Prevalence of portal hypertensive duodenopathy in cirrhosis: clinical and haemodynamic features. *Eur J Gastroenterol Hepatol* 2006; **18**: 649-653 [PMID: 16702855 DOI: 10.1097/00042737-200606000-00012]

41 **Yüksel O**, Köklü S, Arhan M, Yolcu OF, Ertuğrul I, Odemiş B, Altiparmak E, Sahin B. Effects of esophageal varice eradication on portal hypertensive gastropathy and fundal varices: a retrospective and comparative study. *Dig Dis Sci* 2006; **51**: 27-30 [PMID: 16416205 DOI: 10.1007/s10620-006-3078-2]

42 **Fontana RJ**, Sanyal AJ, Mehta S, Doherty MC, Neuschwander-Tetri BA, Everson GT, Kahn JA, Malet PF, Sheikh MY, Chung RT, Ghany MG, Gretch DR. Portal hypertensive gastropathy in chronic hepatitis C patients with bridging fibrosis and compensated cirrhosis: results from the HALT-C trial. *Am J Gastroenterol* 2006; **101**: 983-992 [PMID: 16573786 DOI: 10.1111/j.1572-0241.2006.00461.x]

43 **Bresci G**, Parisi G, Capria A. Clinical relevance of colonic lesions in cirrhotic patients with portal hypertension. *Endoscopy* 2006; **38**: 830-835 [PMID: 17001574 DOI: 10.1055/s-2006-944629]

44 **Akatsu T**, Yoshida M, Kawachi S, Tanabe M, Shimazu M, Kumai K, Kitajima M. Consequences of living-donor liver transplantation for upper gastrointestinal lesions: high incidence of reflux esophagitis. *Dig Dis Sci* 2006; **51**: 2018-2022 [PMID: 17024572 DOI: 10.1007/s10620-006-9362-3]

45 **Zardi EM**, Uwechie V, Gentilucci UV, Dobrina A, Petitti T, Laghi V, Picardi A, Afeltra A. Portal diameter in the diagnosis of esophageal varices in 266 cirrhotic patients: which role? *Ultrasound Med Biol* 2007; **33**: 506-511 [PMID: 17337112 DOI: 10.1016/j.ultrasmedbio.2006.10.002]

46 **Barakat M**, Mostafa M, Mahran Z, Soliman AG. Portal hypertensive duodenopathy: clinical, endoscopic, and histopathologic profiles. *Am J Gastroenterol* 2007; **102**: 2793-2802 [PMID: 17900330 DOI: 10.1111/j.1572-0241.2007.01536.x]

47 **Bellis L**, Nicodemo S, Galossi A, Guarisco R, Spilabotti L, Durola L, Dell'Unto O, Puoti C. Hepatic venous pressure gradient does not correlate with the presence and the severity of portal hypertensive gastropathy in patients with liver cirrhosis. *J Gastrointestin Liver Dis* 2007; **16**: 273-277 [PMID: 17925921]

48 **Gravante G**, Delogu D, Venditti D. Upper and lower gastrointestinal diseases in liver transplant candidates. *Int J Colorectal Dis* 2008; **23**: 201-206 [PMID: 17932680 DOI: 10.1007/s00384-007-0386-8]

49 **Canlas KR**, Dobozi BM, Lin S, Smith AD, Rockey DC, Muir AJ, Agrawal NM, Poleski MH, Patel K, McHutchison JG. Using capsule endoscopy to identify GI tract lesions in cirrhotic patients with portal hypertension and chronic anemia. *J Clin Gastroenterol* 2008; **42**: 844-848 [PMID: 18277884 DOI: 10.1097/MCG.0b013e318038d312]

50 **Kim TU**, Kim S, Woo SK, Lee JW, Lee TH, Jeong YJ, Heo J. Dynamic CT of portal hypertensive gastropathy: significance of transient gastric perfusion defect sign. *Clin Radiol* 2008; **63**: 783-790 [PMID: 18555036 DOI: 10.1016/j.crad.2008.02.003]

51 **Higaki N**, Matsui H, Imaoka H, Ikeda Y, Murakami H, Hiasa Y, Matsuura B, Onji M. Characteristic endoscopic features of portal hypertensive enteropathy. *J Gastroenterol* 2008; **43**: 327-331 [PMID: 18592149 DOI: 10.1007/s00535-008-2166-9]

52 **Frenette CT**, Kuldau JG, Hillebrand DJ, Lane J, Pockros PJ. Comparison of esophageal capsule endoscopy and esophagogastroduodenoscopy for diagnosis of esophageal varices. *World J Gastroenterol* 2008; **14**: 4480-4485 [PMID: 18680226 DOI: 10.3748/wjg.14.4480]

53 **Tarantino G**, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, Tripodi FS, Cirillo M, Lobello R. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. *BMC Gastroenterol* 2009; **9**: 21 [PMID: 19292923 DOI: 10.1186/1471-230X-9-21]

54 **Curvêlo LA**, Brabosa W, Rhor R, Lanzoni V, Parise ER, Ferrari AP, Kondo M. Underlying mechanism of portal hypertensive gastropathy in cirrhosis: a hemodynamic and morphological approach. *J Gastroenterol Hepatol* 2009; **24**: 1541-1546 [PMID: 19743998 DOI: 10.1111/j.1440-1746.2009.05871.x]

55 **Anegawa G**, Kawanaka H, Uehara H, Akahoshi T, Konishi K, Yoshida D, Kinjo N, Hashimoto N, Tomikawa M, Hashizume M, Maehara Y. Effect of laparoscopic splenectomy on portal hypertensive gastropathy in cirrhotic patients with portal hypertension. *J Gastroenterol Hepatol* 2009; **24**: 1554-1558 [PMID: 19743999 DOI: 10.1111/j.1440-1746.2009.05906.x]

56 **Kumar A**, Mishra SR, Sharma P, Sharma BC, Sarin SK. Clinical, laboratory, and hemodynamic parameters in portal hypertensive gastropathy: a study of 254 cirrhotics. *J Clin Gastroenterol* 2010; **44**: 294-300 [PMID: 19730114 DOI: 10.1097/MCG.0b013e3181b37ea1]

57 **Kim MY**, Choi H, Baik SK, Yea CJ, Won CS, Byun JW, Park SY, Kwon YH, Kim JW, Kim HS, Kwon SO, Kim YJ, Cha SH, Chang SJ. Portal hypertensive gastropathy: correlation with portal hypertension and prognosis in cirrhosis. *Dig Dis Sci* 2010; **55**: 3561-3567 [PMID: 20407828 DOI: 10.1007/s10620-010-1221-6]

58 **De Lisi S**, Peralta S, Arini A, Simone F, Craxì A. Oesophagogastroduodenoscopy in patients with cirrhosis: Extending the range of detection beyond portal hypertension. *Dig Liver Dis* 2011; **43**: 48-53 [PMID: 20471338 DOI: 10.1016/j.dld.2010.04.004]

59 **Abbasi A**, Butt N, Bhutto AR, Munir SM. Correlation of thrombocytopenia with grading of esophageal varices in chronic liver disease patients. *J Coll Physicians Surg Pak* 2010; **20**: 369-372 [PMID: 20642964]

60 **Ahmed S**, Mumtaz K, Ahmed US, Shah HA, Abid S, Hamid S, Jafri W. Frequency and characteristic features of portal hypertensive gastropathy in patients with viral cirrhosis. *J Coll Physicians Surg Pak* 2010; **20**: 714-718 [PMID: 21078242]

61 **Garcia-Saenz-de-Sicilia M**, Sanchez-Avila F, Chavez-Tapia NC, Lopez-Arce G, Garcia-Osogobio S, Ruiz-Cordero R, Tellez-

Avila FI. PPIs are not associated with a lower incidence of portal-hypertension-related bleeding in cirrhosis. *World J Gastroenterol* 2010; **16**: 5869-5873 [PMID: 21155009 DOI: 10.3748/wjg.v16.i46.5869]

62 **Abbasi A**, Bhutto AR, Butt N, Munir SM, Dhillo AK. Frequency of portal hypertensive gastropathy and its relationship with biochemical, haematological and endoscopic features in cirrhosis. *J Coll Physicians Surg Pak* 2011; **21**: 723-726 [PMID: 22166690]

63 **Aoyama T**, Oka S, Aikata H, Nakano M, Watari I, Naeshiro N, Yoshida S, Tanaka S, Chayama K. Small bowel abnormalities in patients with compensated liver cirrhosis. *Dig Dis Sci* 2013; **58**: 1390-1396 [PMID: 23247799 DOI: 10.1007/s10620-012-2502-z]

64 **Laleman W**, Simon-Talero M, Maleux G, Perez M, Ameloot K, Soriano G, Villalba J, Garcia-Pagan JC, Barrufet M, Jalan R, Brookes J, Thalassinos E, Burroughs AK, Cordoba J, Nevens F. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. *Hepatology* 2013; **57**: 2448-2457 [PMID: 23401201 DOI: 10.1002/hep.26314]

65 **Giannini EG**, Savarino V, Farinati F, Ciccarese F, Rapaccini G, Marco MD, Benvegnù L, Zoli M, Borzio F, Caturelli E, Chiaramonte M, Trevisani F. Influence of clinically significant portal hypertension on survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. *Liver Int* 2013; **33**: 1594-1600 [PMID: 23654354 DOI: 10.1111/liv.12199]

66 **Aoyama T**, Oka S, Aikata H, Igawa A, Nakano M, Naeshiro N, Yoshida S, Tanaka S, Chayama K. Major predictors of portal hypertensive enteropathy in patients with liver cirrhosis. *J Gastroenterol Hepatol* 2015; **30**: 124-130 [PMID: 24988903 DOI: 10.1111/jgh.12658]

67 **Zardi EM**, Ghittoni G, Margiotta D, Viera FT, Di Matteo F, Rossi S. Portal hypertensive gastropathy in cirrhotics without varices: a case-control study. *Eur J Gastroenterol Hepatol* 2015; **27**: 91-96 [PMID: 25386762 DOI: 10.1097/MEG.0000000000000234]

68 **Wu Q**, Shen L, Chu J, Ma X, Jin B, Meng F, Chen J, Wang Y, Wu L, Han J, Zhang W, Ma W, Wang H, Li H. Characterization of uncommon portosystemic collateral circulations in patients with hepatic cirrhosis. *Oncol Lett* 2015; **9**: 347-350 [PMID: 25435990]

69 **Fontana RJ**, Sanyal AJ, Ghany MG, Bonkovsky HL, Morgan TR, Litman HJ, Reid AE, Lee WM, Naishadham D. Development and progression of portal hypertensive gastropathy in patients with chronic hepatitis C. *Am J Gastroenterol* 2011; **106**: 884-893 [PMID: 21139575 DOI: 10.1038/ajg.2010.456]

70 **Spina GP**, Arcidiacono R, Bosch J, Pagliaro L, Burroughs AK, Santambrogio R, Rossi A. Gastric endoscopic features in portal hypertension: final report of a consensus conference, Milan, Italy, September 19, 1992. *J Hepatol* 1994; **21**: 461-467 [PMID: 7836719 DOI: 10.1016/S0168-8278(05)80329-0]

71 **Thuluvath PJ**, Yoo HY. Portal Hypertensive gastropathy. *Am J Gastroenterol* 2002; **97**: 2973-2978 [PMID: 12492178 DOI: 10.1111/j.1572-0241.2002.07094.x]

72 **Cubillas R**, Rockey DC. Portal hypertensive gastropathy: a review. *Liver Int* 2010; **30**: 1094-1102 [PMID: 20536720 DOI: 10.1111/j.1478-3231.2010.02286.x]

73 **Hou MC**, Lin HC, Chen CH, Kuo BI, Perng CL, Lee FY, Lee SD. Changes in portal hypertensive gastropathy after endoscopic variceal sclerotherapy or ligation: an endoscopic observation. *Gastrointest Endosc* 1995; **42**: 139-144 [PMID: 7590049 DOI: 10.1016/S0016-5107(95)70070-6]

74 **Trevino HH**, Brady CE, Schenker S. Portal hypertensive gastropathy. *Dig Dis* 1996; **14**: 258-270 [PMID: 8843981 DOI: 10.1159/000171557]

75 **Kamath PS**, Lacerda M, Ahlquist DA, McKusick MA, Andrews JC, Nagorney DA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. *Gastroenterology* 2000; **118**: 905-911 [PMID: 10784589 DOI: 10.1016/S0016-5085(00)70176-4]

76 **Mezawa S**, Homma H, Ohta H, Masuko E, Doi T, Miyanishi K, Takada K, Kukitsu T, Sato T, Niitsu Y. Effect of transjugular intrahepatic portosystemic shunt formation on portal hypertensive gastropathy and gastric circulation. *Am J Gastroenterol* 2001; **96**: 1155-1159 [PMID: 11316163 DOI: 10.1111/j.1572-0241.2001.03694.x]

77 **Urata J**, Yamashita Y, Tsuchigame T, Hatanaka Y, Matsukawa T, Sumi S, Matsuno Y, Takahashi M. The effects of transjugular intrahepatic portosystemic shunt on portal hypertensive gastropathy. *J Gastroenterol Hepatol* 1998; **13**: 1061-1067 [PMID: 9835325 DOI: 10.1111/j.1440-1746.1998.tb00571.x]

78 **Kamath PS**, Shah VH. Portal hypertension and bleeding esophageal varices. In: Boyer TD, Manns MP, Sanyal AJ, editors. In: Zakim and Boyer's Hepatology: A textbook of liver disease. 6th ed. Philadelphia: Elsevier Saunders, 2012: 296-326

79 **Pan WD**, Xun RY, Chen YM. Correlations of portal hypertensive gastropathy of hepatitis B cirrhosis with other factors. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 527-531 [PMID: 14607680]

80 **Elnaser MS**, Elebiary S, Bastawi MB, El Shafei A, Elmagd IM, Hamza MM. The prevalence of portal hypertensive gastropathy and duodenopathy in some Egyptian cirrhotic patients. *J Egypt Soc Parasitol* 2004; **34**: 915-923 [PMID: 15587317]

81 **Lo GH**, Lai KH, Cheng JS, Hsu PI, Chen TA, Wang EM, Lin CK, Chiang HT. The effects of endoscopic variceal ligation and propranolol on portal hypertensive gastropathy: a prospective, controlled trial. *Gastrointest Endosc* 2001; **53**: 579-584 [PMID: 11323582 DOI: 10.1067/mge.2001.114062]

82 **de la Peña J**, Rivero M, Sanchez E, Fábrega E, Crespo J, Pons-Romero F. Variceal ligation compared with endoscopic sclerotherapy for variceal hemorrhage: prospective randomized trial. *Gastrointest Endosc* 1999; **49**: 417-423 [PMID: 10202052 DOI: 10.1016/S0016-5107(99)70036-2]

83 **Poddar U**, Bhatnagar S, Yachha SK. Endoscopic band ligation followed by sclerotherapy: Is it superior to sclerotherapy in children with extrahepatic portal venous obstruction? *J Gastroenterol Hepatol* 2011; **26**: 255-259 [PMID: 21261713 DOI: 10.1111/j.1440-1746.2010.06397.x]

84 **Poddar U**, Thapa BR, Singh K. Frequency of gastropathy and gastric varices in children with extrahepatic portal venous obstruction treated with sclerotherapy. *J Gastroenterol Hepatol* 2004; **19**: 1253-1256 [PMID: 15482531 DOI: 10.1111/j.1440-1746.2004.03470.x]

85 **Duan X**, Zhang K, Han X, Ren J, Xu M, Huang G, Zhang M. Comparison of percutaneous transhepatic variceal embolization (PTVE) followed by partial splenic embolization versus PTVE alone for the treatment of acute esophagogastric variceal massive hemorrhage. *J Vasc Interv Radiol* 2014; **25**: 1858-1865 [PMID: 25311969 DOI: 10.1016/j.jvir.2014.08.019]

86 **Lo GH**, Liang HL, Lai KH, Chang CF, Hwu JH, Chen SM, Lin CK, Chiang HT. The impact of endoscopic variceal ligation on the pressure of the portal venous system. *J Hepatol* 1996; **24**: 74-80 [PMID: 8834028 DOI: 10.1016/S0168-8278(96)80189-9]

87 **Korula J**, Ralls P. The effects of chronic endoscopic variceal sclerotherapy on portal pressure in cirrhotics. *Gastroenterology* 1991; **101**: 800-805 [PMID: 1860642]

88 **Kimura K**, Ohto M, Matsutani S, Furuse J, Hoshino K, Okuda K. Relative frequencies of portosystemic pathways and renal shunt formation through the "posterior" gastric vein: portographic study in 460 patients. *Hepatology* 1990; **12**: 725-728 [PMID: 2210674 DOI: 10.1002/hep.1840120417]

89 **Smith-Laing G**, Camilo ME, Dick R, Sherlock S. Percutaneous transhepatic portography in the assessment of portal hypertension. Clinical correlations and comparison of radiographic techniques. *Gastroenterology* 1980; **78**: 197-205 [PMID: 6965281]

90 **Watanabe K**, Kimura K, Matsutani S, Ohto M, Okuda K. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988; **95**: 434-440 [PMID: 3391371]

91 **Yoshikawa I**, Murata I, Nakano S, Otsuki M. Effects of endoscopic variceal ligation on portal hypertensive gastropathy and gastric mucosal blood flow. *Am J Gastroenterol* 1998; **93**: 71-74 [PMID: 9448178 DOI: 10.1111/j.1572-0241.1998.071_c.x]

92 **Balan KK**, Grime JS, Sutton R, Critchley M, Jenkins SA. Do alterations in the rate of gastric emptying after injection sclerotherapy for oesophageal varices play any role in the development of portal hypertensive gastropathy? *HPB Surg* 1999; **11**: 141-148; discussion 148-150 [PMID: 10371058]

93 **Sarwar S**, Khan AA, Alam A, Butt AK, Shafqat F, Malik K, Ahmad I, Niazi AK. Effect of band ligation on portal hypertensive gastropathy and development of fundal varices. *J Ayub Med Coll Abbottabad* 2006; **18**: 32-35 [PMID: 16773966]

94 **Lo GH**, Lai KH, Cheng JS, Hwu JH, Chang CF, Chen SM, Chiang HT. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology* 1995; **22**: 466-471 [PMID: 7635414 DOI: 10.1002/hep.1840220215]

95 **Sarin SK**, Govil A, Jain AK, Guptan RC, Issar SK, Jain M, Murthy NS. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J Hepatol* 1997; **26**: 826-832 [PMID: 9126795 DOI: 10.1016/S0168-8278(97)80248-6]

96 **Feldman M**, Lee EL. Gastritis. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 10th ed. Philadelphia: Elsevier Saunders, 2010: 868-883

97 **Primignani M**, Materia M, Preatoni P, Carta A, Morbin T. Does endoscopic treatment of esophageal varices with sclerotherapy (ES) or ligation (EL) influence the evolution of portal hypertensive gastropathy (PHG) in cirrhotic patients? *Gastroenterology* 1998; **114**; A1324 [DOI: 10.1016/S0016-5085(98)85375-4]

98 **Ashraf P**, Shah GM, Shaikh H, Manan A, Kumar M. Transjugular intrahepatic portosystemic stenting in portal hypertensive gastropathy. *J Coll Physicians Surg Pak* 2009; **19**: 584-585 [PMID: 19728947]

99 **Ohmagari K**, Toyonaga A, Tanikawa K. Effects of transcatheter splenic arterial embolization on portal hypertensive gastric mucosa. *Am J Gastroenterol* 1993; **88**: 1837-1841 [PMID: 8237929]

100 **Orloff MJ**, Orloff MS, Orloff SL, Haynes KS. Treatment of bleeding from portal hypertensive gastropathy by portacaval shunt. *Hepatology* 1995; **21**: 1011-1017 [PMID: 7705773 DOI: 10.1016/0270-9139(95)90248-1]

101 **Soin AS**, Acharya SK, Mathur M, Sahni P, Nundy S. Portal hypertensive gastropathy in noncirrhotic patients. The effect of lienorenal shunts. *J Clin Gastroenterol* 1998; **26**: 64-67; discussion 68 [PMID: 9492868 DOI: 10.1097/00004836-199801000-00017]

102 **Boyer TD**, Haskal ZJ. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Hepatology* 2005; **41**: 386-400 [PMID: 15660434 DOI: 10.1002/hep.20559]

103 **Pérez-Ayuso RM**, Piqué JM, Bosch J, Panés J, González A, Pérez R, Rigau J, Quintero E, Valderrama R, Viver J. Propranolol in prevention of recurrent bleeding from severe portal hypertensive gastropathy in cirrhosis. *Lancet* 1991; **337**: 1431-1434 [PMID: 1675316 DOI: 10.1016/0140-6736(91)93125-S]

104 **Hosking SW**, Kennedy HJ, Seddon I, Triger DR. The role of propranolol in congestive gastropathy of portal hypertension. *Hepatology* 1997; **7**: 437-441 [PMID: 3552921 DOI: 10.1002/hep.1840070304]

105 **Kouroumalis EA**, Koutroubakis IE, Manousos ON. Somatostatin for acute severe bleeding from portal hypertensive gastropathy. *Eur J Gastroenterol Hepatol* 1998; **10**: 509-512 [PMID: 9855068 DOI: 10.1097/00042737-199806000-00013]

106 **Zhou Y**, Qiao L, Wu J, Hu H, Xu C. Comparison of the efficacy of octreotide, vasopressin, and omeprazole in the control of acute bleeding in patients with portal hypertensive gastropathy: a controlled study. *J Gastroenterol Hepatol* 2002; **17**: 973-979 [PMID: 12167118 DOI: 10.1046/j.1440-1746.2002.02775.x]

107 **Bruha R**, Marecek Z, Spicak J, Hulek P, Lata J, Petrtyl J, Urbanek P, Taimr P, Volfova M, Dite P. Double-blind randomized, comparative multicenter study of the effect of terlipressin in the treatment of acute esophageal variceal and/or hypertensive gastropathy bleeding. *Hepatogastroenterology* 2002; **49**: 1161-1166 [PMID: 12143227]

108 **Mori T**, Aisa Y, Yajima T, Shimizu T, Kato J, Nakazato T, Hibi T, Ikeda Y, Okamoto S. Esophageal varices and portal hypertensive gastropathy associated with hepatic veno-occlusive disease after allogeneic hematopoietic stem cell transplantation. *Int J Hematol* 2008; **87**: 231-232 [PMID: 18256788 DOI: 10.1007/s12185-008-0023-5]

109 **Urso G**, Interlandi D, Puglisi M, Abate G, Bertino G, Raciti C, Sciacca C, Bruno M, Panarello A, Di Prima P, La Rosa G. Role of Helicobacter pylori in patients with portal hypertensive gastropathy by liver cirrhosis hepatitis C virus-related. *Minerva Gastroenterol Dietol* 2006; **52**: 303-308 [PMID: 16971874]

110 **Al Mofleh IA**. Does Helicobacter pylori affect portal hypertensive gastropathy? *Saudi J Gastroenterol* 2007; **13**: 95-97 [PMID: 19858622 DOI: 10.4103/1319-3767.32186]

111 **Bayraktar Y**, Balkanci F, Uzunalimoglu B, Gokoz A, Koseoglu T, Batman F, Gurakar A, Van Thiel DH, Kayhan B. Is portal hypertension due to liver cirrhosis a major factor in the development of portal hypertensive gastropathy? *Am J Gastroenterol* 1996; **91**: 554-558 [PMID: 8633508]

112 **Thuluvath PJ**. Management of upper gastrointestinal hemorrhage related to portal hypertension. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW, editors. Textbook of Gastroenterology. 5th ed. Wiley-Blackwell, 2009: 2897-3017 [DOI: 10.1002/9781444303414.ch89]

113 **Ohta M**, Yamaguchi S, Gotoh N, Tomikawa M. Pathogenesis of portal hypertensive gastropathy: a clinical and experimental review. *Surgery* 2002; **131**: S165-S170 [PMID: 11821805 DOI: 10.1067/msy.2002.119499]

114 **Lopez-Talavera JC**, Cadelina G, Olchowski J, Merrill W, Groszmann RJ. Thalidomide inhibits tumor necrosis factor alpha, decreases nitric oxide synthesis, and ameliorates the hyperdynamic circulatory syndrome in portal-hypertensive rats. *Hepatology* 1996; **23**: 1616-1621 [PMID: 8675185 DOI: 10.1053/jhep.1996.v23.pm0008675185]

115 **Blendis L**, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther* 2001; **89**: 221-231 [PMID: 11516477 DOI: 10.1016/S0163-7258(01)00124-3]

116 **Hashizume M**, Tanaka K, Inokuchi K. Morphology of gastric microcirculation in cirrhosis. *Hepatology* 1993; **3**: 1008-1012 [PMID: 6629315 DOI: 10.1002/hep.1840030619]

117 **Perini RF**, Camara PR, Ferraz JG. Pathogenesis of portal hypertensive gastropathy: translating basic research into clinical practice. *Nat Clin Pract Gastroenterol Hepatol* 2009; **6**: 150-158 [PMID: 19190600 DOI: 10.1038/ncpgasthep1356]

118 **Makhija S**, Burak K, Beck PL. Portal hypertensive gastropathy and gastric antral vascular ectasia. In: Helmy A, editor. Portal hypertension: pathogenesis and management. New York: Nova Science Publishers Inc, 2006: 137-166

119 **Nayeb-Hashemi H**, Kaunitz JD. Gastroduodenal mucosal defense. *Curr Opin Gastroenterol* 2009; **25**: 537-543 [PMID: 19654540 DOI: 10.1097/MOG.0b013e328330da7b]

120 **Ferraz JG**, Wallace JL. Underlying mechanisms of portal hypertensive gastropathy. *J Clin Gastroenterol* 1997; **25** Suppl 1: S73-S78 [PMID: 9479629 DOI: 10.1097/00004836-199700001-00012]

121 **Tarnawski AS**, Sarfeh IJ, Stachura J, Hajduczek A, Bui HX, Dabros W, Gergely H. Microvascular abnormalities of the portal hypertensive gastric mucosa. *Hepatology* 1988; **8**: 1488-1494 [PMID: 3192161 DOI: 10.1002/hep.1840080604]

122 **Albillos A**, Colombato LA, Enriquez R, Ng OC, Sikuler E, Groszmann RJ. Sequence of morphological and hemodynamic changes of gastric microvessels in portal hypertension. *Gastroenterology* 1992; **102**: 2066-2070 [PMID: 1587425]

123 **Payen JL**, Cales P, Pienkowski P, Sozzani P, Kervran A, Frexinos J, Pascal JP. Weakness of mucosal barrier in portal hypertensive gastropathy of alcoholic cirrhosis. Effects of propranolol and enprostil. *J Hepatol* 1995; **23**: 689-696 [PMID: 8750168 DOI: 10.1016/0168-8278(95)80035-2]

124 **Beck PL**, Lee SS, McKnight GW, Wallace JL. Characterization of spontaneous and ethanol-induced gastric damage in cirrhotic rats. *Gastroenterology* 1992; **103**: 1048-1055 [PMID: 1499905]

125 **Beck PL**, McKnight W, Lee SS, Wallace JL. Prostaglandin modulation of the gastric vasculature and mucosal integrity in cirrhotic rats. *Am J Physiol* 1993; **265**: G453-G458 [PMID: 8214067]

126 **Misra V**, Misra SP, Dwivedi M. Thickened gastric mucosal capillary wall: a histological marker for portal hypertension. *Pathology* 1998; **30**: 10-13 [PMID: 9534201 DOI: 10.1080/00313029800169595]

127 **Ichikawa Y**, Tarnawski A, Sarfeh IJ, Ishikawa T, Shimada H. Distorted microangioarchitecture and impaired angiogenesis in gastric mucosa of portal hypertensive rats. *Gastroenterology* 1994; **106**: 702-708 [PMID: 7509763]

128 **Gupta R**, Sawant P, Parameshwar RV, Lele VR, Kulhalli PM, Mahajani SS. Gastric mucosal blood flow and hepatic perfusion index in patients with portal hypertensive gastropathy. *J Gastroenterol Hepatol* 1998; **13**: 921-926 [PMID: 9794191 DOI: 10.1111/j.1440-1746.1998.tb00762.x]

129 **Iwao T**, Toyonaga A, Ikegami M, Oho K, Sumino M, Harada H, Sakaki M, Shigemori H, Aoki T, Tanikawa K. Reduced gastric mucosal blood flow in patients with portal-hypertensive gastropathy. *Hepatology* 1993; **18**: 36-40 [PMID: 8325619 DOI: 10.1002/hep.1840180107]

130 **Kotzampassi K**, Eleftheriadis E, Aletras H. Gastric mucosal blood flow in portal hypertension patients--a laser Doppler flowmetry study. *Hepatogastroenterology* 1992; **39**: 39-42 [PMID: 1533200]

131 **Vyas K**, Gala B, Sawant P, Das HS, Kulhalli PM, Mahajan SS. Assessment of portal hemodynamics by ultrasound color Doppler and laser Doppler velocimetry in liver cirrhosis. *Indian J Gastroenterol* 2002; **21**: 176-178 [PMID: 12416745]

132 **Shigemori H**, Iwao T, Ikegami M, Toyonaga A, Tanikawa K. Effects of propranolol on gastric mucosal perfusion and serum gastrin level in cirrhotic patients with portal hypertensive gastropathy. *Dig Dis Sci* 1994; **39**: 2433-2438 [PMID: 7956612 DOI: 10.1007/BF02087662]

133 **Ohta M**, Hashizume M, Higashi H, Ueno K, Tomikawa M, Kishihara F, Kawanaka H, Tanoue K, Sugimachi K. Portal and gastric mucosal hemodynamics in cirrhotic patients with portal-hypertensive gastropathy. *Hepatology* 1994; **20**: 1432-1436 [PMID: 7982641 DOI: 10.1002/hep.1840200609]

134 **Chung RS**, Bruch D, Dearlove J. Endoscopic measurement of gastric mucosal blood flow by laser Doppler velocimetry: effect of chronic esophageal variceal sclerosis. *Am Surg* 1988; **54**: 116-120 [PMID: 2963569]

135 **Tomikawa M**, Akiba Y, Kaunitz JD, Kawanaka H, Sugimachi K, Sarfeh IJ, Tarnawski AS. New insights into impairment of mucosal defense in portal hypertensive gastric mucosa. *J Gastrointest Surg* 2000; **4**: 458-463 [PMID: 11077319 DOI: 10.1016/S1091-255X(00)80086-4]

136 **Tsugawa K**, Hashizume M, Migou S, Kishihara F, Kawanaka H, Tomikawa M, Sugimachi K. Role of vascular endothelial growth factor in portal hypertensive gastropathy. *Digestion* 2000; **61**: 98-106 [PMID: 10705173 DOI: 10.1159/000007741]

137 **De BK**, Das TK. Color Doppler and laser velocimetry studies in the assessment of portal hemodynamics and severity of chronic liver disease. *Indian J Gastroenterol* 2002; **21**: 173-175 [PMID: 12416744]

138 **Casadevall M**, Panés J, Piqué JM, Bosch J, Terés J, Rodés J. Limitations of laser-Doppler velocimetry and reflectance spectrophotometry in estimating gastric mucosal blood flow. *Am J Physiol* 1992; **263**: G810-G815 [PMID: 1443154]

139 **Bhattacharya B**. Non-neoplastic disorders of the stomach. In: Iacobuzio-Donahue CA. Montgomery E, Goldblum JR, editors. Gastrointestinal and liver pathology. 2nd ed. Philadelphia: Elsevier Saunders, 2012: 65-141 [DOI: 10.1016/b978-1-4377-0925-4.00012-2]

140 **Misra SP**, Dwivedi M, Misra V, Barthwal R. Portal-hypertensive-gastropathy-like changes in a patient with secondary polycythemia: reversal of endoscopic and histopathologic changes with phlebotomy. *Gastrointest Endosc* 2004; **59**: 916-919 [PMID: 15173815 DOI: 10.1016/S0016-5107(04)00338-4]

141 **Wu B**, Zeng L, Lin Y, Wen Z, Chen G, Iwakiri R, Fujimoto K. Downregulation of cyclooxygenase-1 is involved in gastric mucosal apoptosis via death signaling in portal hypertensive rats. *Cell Res* 2009; **19**: 1269-1278 [PMID: 19668263 DOI: 10.1038/cr.2009.97]

142 **Tan S**, Wei X, Song M, Tao J, Yang Y, Khatoon S, Liu H, Jiang J, Wu B. PUMA mediates ER stress-induced apoptosis in portal hypertensive gastropathy. *Cell Death Dis* 2014; **5**: e1128 [PMID: 24625987 DOI: 10.1038/cddis.2014.95]

143 **Kaur S**, Kaur U, Tandon C, Dhawan V, Ganguly NK, Majumdar S. Gastropathy and defense mechanisms in common bile duct ligated portal hypertensive rats. *Mol Cell Biochem* 2000; **203**: 79-85 [PMID: 10724335 DOI: 10.1023/A:1007090205886]

144 **Kawanaka H**, Tomikawa M, Jones MK, Szabo IL, Pai R, Baatar D, Tsugawa K, Sugimachi K, Sarfeh IJ, Tarnawski AS. Defective mitogen-activated protein kinase (ERK2) signaling in gastric mucosa of portal hypertensive rats: potential therapeutic implications. *Hepatology* 2001; **34**: 990-999 [PMID: 11679970 DOI: 10.1053/jhep.2001.28507]

145 **Kinjo N**, Kawanaka H, Akahoshi T, Yamaguchi S, Yoshida D, Anegawa G, Konishi K, Tomikawa M, Tanoue K, Tarnawski A, Hashizume M, Maehara Y. Significance of ERK nitration in portal hypertensive gastropathy and its therapeutic implications. *Am J Physiol Gastrointest Liver Physiol* 2008; **295**: G1016-G1024 [PMID: 18787063 DOI: 10.1152/ajpgi.90329.2008]

146 **Wang JY**, Hsieh JS, Lin SR, Huang TJ. The effect of portal hypertension on expression of gastric mucin mRNA in rats. *Hepatogastroenterology* 2001; **48**: 667-671 [PMID: 11462898]

147 **Tsugawa K**, Hashizume M, Tomikawa M, Migou S, Kawanaka H, Shiraishi S, Sueishi K, Sugimachi K. Immunohistochemical localization of vascular endothelial growth factor in the rat portal hypertensive gastropathy. *J Gastroenterol Hepatol* 2001; **16**: 429-437 [PMID: 11354282 DOI: 10.1046/j.1440-1746.2001.02452.x]

148 **Muñoz J**, Albillos A, Pérez-Páramo M, Rossi I, Alvarez-Mon M. Factors mediating the hemodynamic effects of tumor necrosis factor-alpha in portal hypertensive rats. *Am J Physiol* 1999; **276**: G687-G693 [PMID: 10070045]

149 **Kaviani A**, Ohta M, Itani R, Sander F, Tarnawski AS, Sarfeh IJ. Tumor necrosis factor-alpha regulates inducible nitric oxide synthase gene expression in the portal hypertensive gastric mucosa of the rat. *J Gastrointest Surg* 1997; **1**: 371-376 [PMID: 9834372 DOI: 10.1016/S1091-255X(97)80059-5]

150 **Ohta M**, Tarnawski AS, Itani R, Pai R, Tomikawa M, Sugimachi K, Sarfeh IJ. Tumor necrosis factor alpha regulates nitric oxide synthase expression in portal hypertensive gastric mucosa of rats. *Hepatology* 1998; **27**: 906-913 [PMID: 9537427 DOI: 10.1002/hep.510270403]

151 **Ohta M**, Tanoue K, Tarnawski AS, Pai R, Itani RM, Sander FC, Sugimachi K, Sarfeh IJ. Overexpressed nitric oxide synthase in portal-hypertensive stomach of rat: a key to increased susceptibility to damage? *Gastroenterology* 1997; **112**: 1920-1930 [PMID: 9178684 DOI: 10.1053/gast.1997.v112.pm9178684]

152 **El-Newihi HM**, Kanji VK, Mihas AA. Activity of gastric mucosal nitric oxide synthase in portal hypertensive gastropathy. *Am J Gastroenterol* 1996; **91**: 535-538 [PMID: 8633504]

153 **Hartleb M**, Michielsen PP, Dziurkowska-Marek A. The role of nitric oxide in portal hypertensive systemic and portal vascular pathology. *Acta Gastroenterol Belg* 1997; **60**: 222-232 [PMID: 9396180]

154 **Arafa UA**, Fujiwara Y, Higuchi K, Shiba M, Uchida T, Watanabe T, Tominaga K, Oshitani N, Matsumoto T, Arakawa T. No additive effect between Helicobacter pylori infection and portal hypertensive gastropathy on inducible nitric oxide synthase expression in gastric mucosa of cirrhotic patients. *Dig Dis Sci* 2003; **48**: 162-168 [PMID: 12645804 DOI: 10.1023/A:1021707103590]

155 **Lee FY**, Wang SS, Tsai YT, Lin HJ, Lin HC, Chu CJ, Wu SL, Tai CC, Lee SD. Aminoguanidine corrects hyperdynamic

circulation without ameliorating portal hypertension and portal hypertensive gastropathy in anesthetized portal hypertensive rats. *J Hepatol* 1997; **26**: 687-693 [PMID: 9075678 DOI: 10.1016/S0168-8278(97)80436-9]

156 **Chu CJ**, Lee FY, Wang SS, Chang FY, Lin HC, Hou MC, Wu SL, Tai CC, Chan CC, Lee SD. Aminoguanidine ameliorates splanchnic hyposensitivity to glypressin in a haemorrhage-transfused rat model of portal hypertension. *Clin Sci* (Lond) 1998; **95**: 629-636 [PMID: 9791050 DOI: 10.1042/cs0950629]

157 **Silva G**, Navasa M, Bosch J, Chesta J, Pilar Pizcueta M, Casamitjana R, Rivera F, Rodés J. Hemodynamic effects of glucagon in portal hypertension. *Hepatology* 1990; **11**: 668-673 [PMID: 2328958 DOI: 10.1002/hep.1840110421]

158 **Geraghty JG**, Angerson WJ, Carter DC. Splanchnic haemodynamics and vasoactive agents in experimental cirrhosis. *HPB Surg* 1994; **8**: 83-87; discussion 87-88 [PMID: 7880777 DOI: 10.1155/1994/52975]

159 **Benoit JN**, Zimmerman B, Premen AJ, Go VL, Granger DN. Role of glucagon in splanchnic hyperemia of chronic portal hypertension. *Am J Physiol* 1986; **251**: G674-G677 [PMID: 3777172]

160 **Tsui CP**, Sung JJ, Leung FW. Role of acute elevation of portal venous pressure by exogenous glucagon on gastric mucosal injury in rats with portal hypertension. *Life Sci* 2003; **73**: 1115-1129 [PMID: 12818720 DOI: 10.1016/S0024-3205(03)00413-2]

161 **Ohta M**, Kishihara F, Hashizume M, Kawanaka H, Tomikawa M, Higashi H, Tanoue K, Sugimachi K. Increased prostacyclin content in gastric mucosa of cirrhotic patients with portal hypertensive gastropathy. *Prostaglandins Leukot Essent Fatty Acids* 1995; **53**: 41-45 [PMID: 7675821 DOI: 10.1016/0952-3278(95)90081-0]

162 **Weiler H**, Weiler C, Gerok W. Gastric mucosal prostaglandin E2 levels in cirrhosis and portal hypertension. *J Hepatol* 1990; **11**: 58-64 [PMID: 2398267 DOI: 10.1016/0168-8278(90)90272-S]

163 **Arakawa T**, Satoh H, Fukuda T, Nakamura H, Kobayashi K. Endogenous prostaglandin E2 in gastric mucosa of patients with alcoholic cirrhosis and portal hypertension. *Gastroenterology* 1987; **93**: 135-140 [PMID: 3472989]

164 **Beck PL**, McKnight GW, Kelly JK, Wallace JL, Lee SS. Hepatic and gastric cytoprotective effects of long-term prostaglandin E1 administration in cirrhotic rats. *Gastroenterology* 1993; **105**: 1483-1489 [PMID: 8224652 DOI: 10.1016/0016-5085(93)90155-6]

165 **Migoh S**, Hashizume M, Tsugawa K, Tanoue K, Sugimachi K. Role of endothelin-1 in congestive gastropathy in portal hypertensive rats. *J Gastroenterol Hepatol* 2000; **15**: 142-147 [PMID: 10735537 DOI: 10.1046/j.1440-1746.2000.02061.x]

166 **Romano M**, Meise KS, Suozzo R, Sessa G, Persico M, Coffey RJ. Regional distribution of transforming growth factor-alpha and epidermal growth factor in normal and portal hypertensive gastric mucosa in humans. *Dig Dis Sci* 1995; **40**: 263-267 [PMID: 7851187 DOI: 10.1007/BF02065407]

167 **Pleli T**, Martin D, Kronenberger B, Brunner F, Köberle V, Grammatikos G, Farnik H, Martinez Y, Finkelmeier F, Labocha S, Ferreirós N, Zeuzem S, Piiper A, Waidmann O. Serum autotaxin is a parameter for the severity of liver cirrhosis and overall survival in patients with liver cirrhosis--a prospective cohort study. *PLoS One* 2014; **9**: e103532 [PMID: 25062038 DOI: 10.1371/journal.pone.0103532]

168 **Misra SP**, Dwivedi M, Misra V, Agarwal SK, Gupta R, Gupta SC, Mital VP. Endoscopic and histologic appearance of the gastric mucosa in patients with portal hypertension. *Gastrointest Endosc* 1990; **36**: 575-579 [PMID: 2279646 DOI: 10.1016/S0016-5107(90)71167-4]

169 **Dong L**, Zhang ZN, Fang P, Ma SY. Portal hypertensive gastropathy and its interrelated factors. *Hepatobiliary Pancreat Dis Int* 2003; **2**: 226-229 [PMID: 14599974]

170 **Giofré MR**, Meduri G, Pallio S, Calandra S, Magnano A, Niceforo D, Cinquegrani M, di Leo V, Mazzon E, Sturniolo GC, Longo G, Fries W. Gastric permeability to sucrose is increased in portal hypertensive gastropathy. *Eur J Gastroenterol Hepatol* 2000; **12**: 529-533 [PMID: 10833096 DOI: 10.1097/00042737-200012050-00009]

171 **Bahnacy A**, Kupcsulik P, Elés ZS, Jàray B, Flautner L. Helicobacter pylori and congestive gastropathy. *Z Gastroenterol* 1997; **35**: 109-112 [PMID: 9066100]

172 **Balan KK**, Jones AT, Roberts NB, Pearson JP, Critchley M, Jenkins SA. The effects of Helicobacter pylori colonization on gastric function and the incidence of portal hypertensive gastropathy in patients with cirrhosis of the liver. *Am J Gastroenterol* 1996; **91**: 1400-1406 [PMID: 8678003]

173 **Auroux J**, Lamarque D, Roudot-Thoraval F, Deforges L, Chaumette MT, Richardet JP, Delchier JC. Gastroduodenal ulcer and erosions are related to portal hypertensive gastropathy and recent alcohol intake in cirrhotic patients. *Dig Dis Sci* 2003; **48**: 1118-1123 [PMID: 12822873 DOI: 10.1023/A:1023772930681]

174 **Sathar SA**, Kunnathuparambil SG, Sreesh S, Narayanan P, Vinayakumar KR. Helicobacter pylori infection in patients with liver cirrhosis: prevalence and association with portal hypertensive gastropathy. *Ann Gastroenterol* 2014; **27**: 48-52 [PMID: 24714519]

175 **Zullo A**, Hassan C, Ridola L, Francesco VD. Helicobacter pylori and portal hypertensive gastropathy: any new information? *Ann Gastroenterol* 2014; **27**: 91 [PMID: 24714507]

176 **Abbas Z**, Yakoob J, Usman MW, Shakir T, Hamid S, Jafri W. Effect of Helicobacter pylori and its virulence factors on portal hypertensive gastropathy and interleukin (IL)-8, IL-10, and tumor necrosis factor-alpha levels. *Saudi J Gastroenterol* 2014; **20**: 120-127 [PMID: 24705150 DOI: 10.4103/1319-3767.129477]

177 **Vigneri S**, Termini R, Piraino A, Scialabba A, Pisciotta G, Fontana N. The stomach in liver cirrhosis. Endoscopic, morphological, and clinical correlations. *Gastroenterology* 1991; **101**: 472-478 [PMID: 2065923]

178 **Toyonaga A**, Iwao T. Portal-hypertensive gastropathy. *J Gastroenterol Hepatol* 1998; **13**: 865-877 [PMID: 9794183 DOI: 10.1111/j.1440-1746.1998.tb00754.x]

179 **Stewart CA**, Sanyal AJ. Grading portal gastropathy: validation of a gastropathy scoring system. *Am J Gastroenterol* 2003; **98**: 1758-1765 [PMID: 12907330 DOI: 10.1111/j.1572-0241.2003.07595.x]

180 **Tanoue K**, Hashizume M, Wada H, Ohta M, Kitano S, Sugimachi K. Effects of endoscopic injection sclerotherapy on portal hypertensive gastropathy: a prospective study. *Gastrointest Endosc* 1992; **38**: 582-585 [PMID: 1397916 DOI: 10.1016/S0016-5107(92)70522-7]

181 **Sarin, SK**. Diagnostic issues: Portal hypertensive gastropathy and gastric varices. In: DeFranchis R, editor. Portal hypertension II. Proceedings of the second Baveno international consensus workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science, 1996: 30-55

182 **Yoo HY**, Eustace JA, Verma S, Zhang L, Harris M, Kantsevoy S, Lee LA, Kalloo AN, Ravich WJ, Thuluvath PJ. Accuracy and reliability of the endoscopic classification of portal hypertensive gastropathy. *Gastrointest Endosc* 2002; **56**: 675-680 [PMID: 12397275 DOI: 10.1016/S0016-5107(02)70116-8]

183 **Burak KW**, Beck PL. Diagnosis of portal hypertensive gastropathy. *Curr Opin Gastroenterol* 2003; **19**: 477-482 [PMID: 15703593 DOI: 10.1097/00001574-200309000-00008]

184 **Hashizume M**, Sugimachi K. Classification of gastric lesions associated with portal hypertension. *J Gastroenterol Hepatol* 1995; **10**: 339-343 [PMID: 7548815 DOI: 10.1111/j.1440-1746.1995.tb01105.x]

185 **Parker DM**, Wilsoncroft WE, Olshansky T. The relationship between life change and relative autonomic balance. *J Clin Psychol* 1976; **32**: 149-153 [PMID: 1249217]

186 **Iwao T**, Toyonaga A, Ikegami M, Shigemori H, Oho K, Sumino M, Sakaki M, Nakayama M, Nishiyama T, Minetoma T. McCormack's endoscopic signs for diagnosing portal hypertension: comparison with gastroesophageal varices. *Gastrointest Endosc* 1994; **40**: 470-473 [PMID: 7926538 DOI: 10.1016/S0016-5107(94)70212-8]

187 **de Macedo GF**, Ferreira FG, Ribeiro MA, Szutan LA, Assef MS, Rossini LG. Reliability in endoscopic diagnosis of portal hypertensive gastropathy. *World J Gastrointest Endosc* 2013; **5**: 323-331 [PMID: 23858376 DOI: 10.4253/wjge.v5.i7.323]

188 **Eisen GM**, Eliakim R, Zaman A, Schwartz J, Faigel D, Rondonotti

E, Villa F, Weizman E, Yassin K, deFranchis R. The accuracy of PillCam ESO capsule endoscopy versus conventional upper endoscopy for the diagnosis of esophageal varices: a prospective three-center pilot study. *Endoscopy* 2006; **38**: 31-35 [PMID: 16429352 DOI: 10.1055/s-2005-921189]

189 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938 [PMID: 17879356 DOI: 10.1002/hep.21907]

190 **Min YW**, Bae SY, Gwak GY, Paik YH, Choi MS, Lee JH, Paik SW, Yoo BC, Koh KC. A clinical predictor of varices and portal hypertensive gastropathy in patients with chronic liver disease. *Clin Mol Hepatol* 2012; **18**: 178-184 [PMID: 22893868 DOI: 10.3350/cmh.2012.18.2.178]

191 **Patwardhan VR**, Cardenas A. Review article: the management of portal hypertensive gastropathy and gastric antral vascular ectasia in cirrhosis. *Aliment Pharmacol Ther* 2014; **40**: 354-362 [PMID: 24889902 DOI: 10.1111/apt.12824]

192 **Ripoll C**, Garcia-Tsao G. Treatment of gastropathy and gastric antral vascular ectasia in patients with portal hypertension. *Curr Treat Options Gastroenterol* 2007; **10**: 483-494 [PMID: 18221609]

193 **Burak KW**, Lee SS, Beck PL. Portal hypertensive gastropathy and gastric antral vascular ectasia (GAVE) syndrome. *Gut* 2001; **49**: 866-872 [PMID: 11709525]

194 **Dulai GS**, Jensen DM, Kovacs TO, Gralnek IM, Jutabha R. Endoscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. *Endoscopy* 2004; **36**: 68-72 [PMID: 14722858]

195 **Urrunaga NH**, Rockey DC. Portal hypertensive gastropathy and colopathy. *Clin Liver Dis* 2014; **18**: 389-406 [PMID: 24679502 DOI: 10.1016/j.cld.2014.01.008]

196 **Naidu H**, Huang Q, Mashimo H. Gastric antral vascular ectasia: the evolution of therapeutic modalities. *Endosc Int Open* 2014; **2**: E67-E73 [PMID: 26135263 DOI: 10.1055/s-0034-1365525]

197 **Payen JL**, Calès P, Voigt JJ, Barbe S, Pilette C, Dubuisson L, Desmorat H, Vinel JP, Kervran A, Chayvialle JA. Severe portal hypertensive gastropathy and antral vascular ectasia are distinct entities in patients with cirrhosis. *Gastroenterology* 1995; **108**: 138-144 [PMID: 7806035]

198 **Siramolpiwat S**. Transjugular intrahepatic portosystemic shunts and portal hypertension-related complications. *World J Gastroenterol* 2014; **20**: 16996-17010 [PMID: 25493012 DOI: 10.3748/wjg.v20.i45.16996]

199 **Tran A**, Villeneuve JP, Bilodeau M, Willems B, Marleau D, Fenyves D, Parent R, Pomier-Layrargues G. Treatment of chronic bleeding from gastric antral vascular ectasia (GAVE) with estrogen-progesterone in cirrhotic patients: an open pilot study. *Am J Gastroenterol* 1999; **94**: 2909-2911 [PMID: 10520843]

200 **Spahr L**, Villeneuve JP, Dufresne MP, Tassé D, Bui B, Willems B, Fenyves D, Pomier-Layrargues G. Gastric antral vascular ectasia in cirrhotic patients: absence of relation with portal hypertension. *Gut* 1999; **44**: 739-742 [PMID: 10205216]

201 **Barbara G**, De Giorgio R, Salvioli B, Stanghellini V, Corinaldesi R. Unsuccessful octreotide treatment of the watermelon stomach. *J Clin Gastroenterol* 1998; **26**: 345-346 [PMID: 9649027]

202 **Herrera S**, Bordas JM, Llach J, Ginès A, Pellisé M, Fernández-Esparrach G, Mondelo F, Mata A, Cárdenas A, Castells A. The beneficial effects of argon plasma coagulation in the management of different types of gastric vascular ectasia lesions in patients admitted for GI hemorrhage. *Gastrointest Endosc* 2008; **68**: 440-446 [PMID: 18423466 DOI: 10.1016/j.gie.2008.02.009]

203 **Smith LA**, Morris AJ, Stanley AJ. The use of hemospray in portal hypertensive bleeding; a case series. *J Hepatol* 2014; **60**: 457-460 [PMID: 24140803 DOI: 10.1016/j.jhep.2013.10.008]

204 **Probst A**, Scheubel R, Wienbeck M. Treatment of watermelon stomach (GAVE syndrome) by means of endoscopic argon plasma coagulation (APC): long-term outcome. *Z Gastroenterol* 2001; **39**: 447-452 [PMID: 11474999]

205 **Ng I**, Lai KC, Ng M. Clinical and histological features of gastric antral vascular ectasia: successful treatment with endoscopic laser therapy. *J Gastroenterol Hepatol* 1996; **11**: 270-274 [PMID: 8742925]

206 **Wells CD**, Harrison ME, Gurudu SR, Crowell MD, Byrne TJ, Depetris G, Sharma VK. Treatment of gastric antral vascular ectasia (watermelon stomach) with endoscopic band ligation. *Gastrointest Endosc* 2008; **68**: 231-236 [PMID: 18533150 DOI: 10.1016/j.gie.2008.02.021]

207 **McGorisk T**, Krishnan K, Keefer L, Komanduri S. Radiofrequency ablation for refractory gastric antral vascular ectasia (with video). *Gastrointest Endosc* 2013; **78**: 584-588 [PMID: 23660565 DOI: 10.1016/j.gie.2013.04.173]

208 **Turon F**, Casu S, Hernández-Gea V, Garcia-Pagán JC. Variceal and other portal hypertension related bleeding. *Best Pract Res Clin Gastroenterol* 2013; **27**: 649-664 [PMID: 24160925 DOI: 10.1016/j.bpg.2013.08.004]

209 **Vincent C**, Pomier-Layrargues G, Dagenais M, Lapointe R, Létourneau R, Roy A, Paré P, Huet PM. Cure of gastric antral vascular ectasia by liver transplantation despite persistent portal hypertension: a clue for pathogenesis. *Liver Transpl* 2002; **8**: 717-720 [PMID: 12149766]

210 **Novitsky YW**, Kercher KW, Czerniach DR, Litwin DE. Watermelon stomach: pathophysiology, diagnosis, and management. *J Gastrointest Surg* 2003; **7**: 652-661 [PMID: 12850679]

211 **Jin T**, Fei BY, Zheng WH, Wang YX. Successful treatment of refractory gastric antral vascular ectasia by distal gastrectomy: a case report. *World J Gastroenterol* 2014; **20**: 14073-14075 [PMID: 25320549 DOI: 10.3748/wjg.v20.i38.14073]

212 **Fuccio L**, Mussetto A, Laterza L, Eusebi LH, Bazzoli F. Diagnosis and management of gastric antral vascular ectasia. *World J Gastrointest Endosc* 2013; **5**: 6-13 [PMID: 23330048 DOI: 10.4253/wjge.v5.i1.6]

213 **Calès P**, Voigt JJ, Payen JL, Bloom E, Berg P, Vinel JP, Pradère B, Broussy P, Pascal JP. Diffuse vascular ectasia of the antrum, duodenum, and jejunum in a patient with nodular regenerative hyperplasia. Lack of response to portosystemic shunt or gastrectomy. *Gut* 1993; **34**: 558-561 [PMID: 8491407]

214 **Ripoll C**, Garcia-Tsao G. Management of gastropathy and gastric vascular ectasia in portal hypertension. *Clin Liver Dis* 2010; **14**: 281-295 [PMID: 20682235 DOI: 10.1016/j.cld.2010.03.013]

215 **Suit PF**, Petras RE, Bauer TW, Petrini JL. Gastric antral vascular ectasia. A histologic and morphometric study of «the watermelon stomach». *Am J Surg Pathol* 1987; **11**: 750-757 [PMID: 3499091]

216 **Kar P**, Mitra S, Resnick JM, Torbey CF. Gastric antral vascular ectasia: case report and review of the literature. *Clin Med Res* 2013; **11**: 80-85 [PMID: 23262190 DOI: 10.3121/cmr.2012.1036]

217 **Gostout CJ**, Viggiano TR, Balm RK. Acute gastrointestinal bleeding from portal hypertensive gastropathy: prevalence and clinical features. *Am J Gastroenterol* 1993; **88**: 2030-2033 [PMID: 8249969]

218 **Kimura K**, Ikegami T, Bekki Y, Ninomiya M, Yamashita Y, Yoshizumi T, Yoshiya S, Soejima Y, Harada N, Shirabe K, Maehara Y. Clinical significance of gastrointestinal bleeding after living donor liver transplantation. *Transpl Int* 2014; **27**: 705-711 [PMID: 24673842 DOI: 10.1111/tri.12325]

219 **Kotzampassi K**, Eleftheriadis E, Aletras H. The 'mosaic-like' pattern of portal hypertensive gastric mucosa after variceal eradication by sclerotherapy. *J Gastroenterol Hepatol* 1990; **5**: 659-663 [PMID: 2129836]

220 **Qamar AA**, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, Ripoll C, Maurer R, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Makuch R, Rendon G. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clin Gastroenterol Hepatol* 2009; **7**: 689-695 [PMID: 19281860 DOI: 10.1016/j.cgh.2009.02.021]

221 **Mathurin SA**, Agüero AP, Dascani NA, Prestera JA, Gianserra C, Londero E, Chiorra C. [Anemia in hospitalized patients with cirrhosis: prevalence, clinical relevance and predictive factors]. *Acta Gastroenterol Latinoam* 2009; **39**: 103-111 [PMID: 19663083]

222 **Pagliaro L**. Lebrec D, Poynard T, Hillon P, Benhamou J-P. Propranolol for prevention of recurrent gastrointestinal bleeding

in patients with cirrhosis. A controlled study [N Engl J Med 1981; 305: 1371-1374]. *J Hepatol* 2002; **36**: 148-150 [PMID: 11830324]
223 **Panés J**, Bordas JM, Piqué JM, García-Pagán JC, Feu F, Terés J, Bosch J, Rodés J. Effects of propranolol on gastric mucosal perfusion in cirrhotic patients with portal hypertensive gastropathy. *Hepatology* 1993; **17**: 213-218 [PMID: 8428718]
224 **Triantos C**, Kalafateli M. Primary prevention of bleeding from esophageal varices in patients with liver cirrhosis. *World J Hepatol* 2014; **6**: 363-369 [PMID: 25018847 DOI: 10.4254/wjh.v6.i6.363]
225 **Lebrec D**, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a controlled study. *N Engl J Med* 1981; **305**: 1371-1374 [PMID: 7029276]
226 **Merkel C**, Marin R, Sacerdoti D, Donada C, Cavallarin G, Torboli P, Amodio P, Sebastianelli G, Bolognesi M, Felder M, Mazzaro C, Gatta A. Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000; **31**: 324-329 [PMID: 10655253]
227 **Abid S**, Ali S, Baig MA, Waheed AA. Is it time to replace propranolol with carvedilol for portal hypertension? *World J Gastrointest Endosc* 2015; **7**: 532-539 [PMID: 25992192 DOI: 10.4253/wjge.v7.i5.532]
228 **Chan CC**, Lee FY, Wang SS, Chang FY, Lin HC, Lin HJ, Chu CJ, Wu SL, Tai CC, Lee SD. Chronic administration of octreotide ameliorates portal hypertension and portal hypertensive gastropathy in rats with cirrhosis. *Clin Sci* (Lond) 1998; **94**: 367-371 [PMID: 9640342]
229 **Li MK**, Sung JJ, Woo KS, Sanderson J, Leung NW, Yu LM, Tsui CP, Chung SC, Leung FW. Somatostatin reduces gastric mucosal blood flow in patients with portal hypertensive gastropathy: a randomized, double-blind crossover study. *Dig Dis Sci* 1996; **41**: 2440-2446 [PMID: 9011455]
230 **Sung JJ**, Tsui CP, Li MK, Leung FW. Somatostatin attenuates the hyperdynamic circulatory state in the gastric mucosa of rats with portal hypertension. *Scand J Gastroenterol* 1995; **30**: 921-926 [PMID: 8578194]
231 **Panés J**, Piqué JM, Bordas JM, Casadevall M, Terés J, Bosch J, Rodés J. Effect of bolus injection and continuous infusion of somatostatin on gastric perfusion in cirrhotic patients with portal-hypertensive gastropathy. *Hepatology* 1994; **20**: 336-341 [PMID: 7913906]
232 **Escorsell A**, Bandi JC, Andreu V, Moitinho E, García-Pagán JC, Bosch J, Rodés J. Desensitization to the effects of intravenous octreotide in cirrhotic patients with portal hypertension. *Gastroenterology* 2001; **120**: 161-169 [PMID: 11208725]
233 **Law AW**, Gales MA. Octreotide or vasopressin for bleeding esophageal varices. *Ann Pharmacother* 1997; **31**: 237-238 [PMID: 9034426]
234 **Iwao T**, Toyonaga A, Shigemori H, Oho K, Sumino M, Sato M, Tanikawa K. Vasopressin plus oxygen vs vasopressin alone in cirrhotic patients with portal-hypertensive gastropathy: effects on gastric mucosal haemodynamics and oxygenation. *J Gastroenterol Hepatol* 1996; **11**: 216-222 [PMID: 8742916]
235 **Panés J**, Piqué JM, Bordas JM, Llach J, Bosch J, Terés J, Rodés J. Reduction of gastric hyperemia by glypressin and vasopressin administration in cirrhotic patients with portal hypertensive gastropathy. *Hepatology* 1994; **19**: 55-60 [PMID: 8276367]
236 **Panés J**, Casadevall M, Fernández M, Piqué JM, Bosch J, Casamitjana R, Cirera I, Bombí JA, Terés J, Rodés J. Gastric microcirculatory changes of portal-hypertensive rats can be attenuated by long-term estrogen-progestagen treatment. *Hepatology* 1994; **20**: 1261-1270 [PMID: 7927261]
237 **Karajeh MA**, Hurlstone DP, Stephenson TJ, Ray-Chaudhuri D, Gleeson DC. Refractory bleeding from portal hypertensive gastropathy: a further novel role for thalidomide therapy? *Eur J Gastroenterol Hepatol* 2006; **18**: 545-548 [PMID: 16607153]
238 **Cremers MI**, Oliveira AP, Alves AL, Freitas J. Portal hypertensive gastropathy: treatment with corticosteroids. *Endoscopy* 2002; **34**: 177 [PMID: 11822018]
239 **Wagatsuma Y**, Naritaka Y, Shimakawa T, Kanako H, Keiichiro I, Shunichi S, Konno S, Katsube T, Ogawa K. Clinical usefulness of the angiotensin II receptor antagonist losartan in patients with portal hypertensive gastropathy. *Hepatogastroenterology* 2006; **53**: 171-174 [PMID: 16608017]
240 **Smart HL**, Triger DR. Clinical features, pathophysiology and relevance of portal hypertensive gastropathy. *Endoscopy* 1991; **23**: 224-228 [PMID: 1915140]
241 **Pique JM**, Leung FW, Kitahora T, Sarfeh IJ, Tarnawski A, Guth PH. Gastric mucosal blood flow and acid secretion in portal hypertensive rats. *Gastroenterology* 1988; **95**: 727-733 [PMID: 3165076]
242 **Benoit JN**, Barrowman JA, Harper SL, Kvietys PR, Granger DN. Role of humoral factors in the intestinal hyperemia associated with chronic portal hypertension. *Am J Physiol* 1984; **247**: G486-G493 [PMID: 6496739]
243 **Yen HH**, Yang CW, Su WW, Soon MS, Wu SS, Lin HJ. Oral versus intravenous proton pump inhibitors in preventing re-bleeding for patients with peptic ulcer bleeding after successful endoscopic therapy. *BMC Gastroenterol* 2012; **12**: 66 [PMID: 22681960 DOI: 10.1186/1471-230X-12-66]
244 **Pang SH**, Graham DY. A clinical guide to using intravenous proton-pump inhibitors in reflux and peptic ulcers. *Therap Adv Gastroenterol* 2010; **3**: 11-22 [PMID: 21180586 DOI: 10.1177/1756283X09352095]
245 **Gostout CJ**, Ahlquist DA, Radford CM, Viggiano TR, Bowyer BA, Balm RK. Endoscopic laser therapy for watermelon stomach. *Gastroenterology* 1989; **96**: 1462-1465 [PMID: 2785467]
246 **Ibrahim M**, Degré D, Devière J. Active bleeding caused by portal hypertensive gastropathy. *Gastrointest Endosc* 2014; **80**: 724 [PMID: 24576479 DOI: 10.1016/j.gie.2014.01.020]
247 **Giday SA**. Preliminary data on the nanopowder hemostatic agent TC-325 to control gastrointestinal bleeding. *Gastroenterol Hepatol* (N Y) 2011; **7**: 620-622 [PMID: 22299002]
248 **Patel J**, Parra V, Kedia P, Sharaiha RZ, Kahaleh M. Salvage cryotherapy in portal hypertensive gastropathy. *Gastrointest Endosc* 2015; **81**: 1003 [PMID: 25028270 DOI: 10.1016/j.gie.2014.05.326]
249 **Sezai S**, Ito M, Sakurai Y, Kamisaka K, Abe T, Ikegami F, Yamamoto Y, Hirano M. Effects on gastric circulation of treatment for portal hypertension in cirrhosis. *Dig Dis Sci* 1998; **43**: 1302-1306 [PMID: 9635622 DOI: 10.1023/A:1018872227652]
250 **Hassoun Z**, Pomier-Layrargues G. The transjugular intrahepatic portosystemic shunt in the treatment of portal hypertension. *Eur J Gastroenterol Hepatol* 2004; **16**: 1-4 [PMID: 15095845 DOI: 10.1097/00042737-200401000-00001]
251 **Bosch J**, Abraldes JG. Management of gastrointestinal bleeding in patients with cirrhosis of the liver. *Semin Hematol* 2004; **41**: 8-12 [PMID: 14872414 DOI: 10.1053/j.seminhematol.2003.11.003]
252 **Rosado B**, Kamath PS. Transjugular intrahepatic portosystemic shunts: an update. *Liver Transpl* 2003; **9**: 207-217 [PMID: 12619016 DOI: 10.1053/jlts.2003.50045]
253 **McCashland TM**. Current use of transjugular intrahepatic portosystemic shunts. *Curr Gastroenterol Rep* 2003; **5**: 31-38 [PMID: 12530946 DOI: 10.1007/s11894-003-0007-9]
254 **Babb RR**, Mitchell RL. Persistent hemorrhagic gastritis in a patient with portal hypertension and esophagogastric varices: the role of portal decompressive surgery. *Am J Gastroenterol* 1988; **83**: 777-779 [PMID: 3260069]
255 **Biecker E**. Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. *World J Gastroenterol* 2013; **19**: 5035-5050 [PMID: 23964137 DOI: 10.3748/wjg.v19.i31.5035]
256 **Yoshida H**, Mamada Y, Taniai N, Tajiri T. Partial splenic embolization. *Hepatol Res* 2008; **38**: 225-233 [PMID: 18034810]
257 **Shimizu T**, Onda M, Tajiri T, Yoshida H, Mamada Y, Taniai N, Aramaki T, Kumazaki T. Bleeding portal-hypertensive gastropathy managed successfully by partial splenic embolization. *Hepatogastroenterology* 2002; **49**: 947-949 [PMID: 12143250]
258 **Hosking SW**. Congestive gastropathy in portal hypertension: variations in prevalence. *Hepatology* 1989; **10**: 257-258 [PMID:

2663698]
259 **Garcia-Tsao G**, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med* 2010; **362**: 823-832 [PMID: 20200386]
260 **Ripoll C**, Garcia-Tsao G. The management of portal hypertensive gastropathy and gastric antral vascular ectasia. *Dig Liver Dis* 2011; **43**: 345-351 [PMID: 21095166 DOI: 10.1016/j.dld.2010.10.006]
261 **Kravetz D**, Sikuler E, Groszmann RJ. Splanchnic and systemic hemodynamics in portal hypertensive rats during hemorrhage and blood volume restitution. *Gastroenterology* 1986; **90**: 1232-1240 [PMID: 3956942]
262 **Toubia N**, Sanyal AJ. Portal hypertension and variceal hemorrhage. *Med Clin North Am* 2008; **92**: 551-574, viii [PMID: 18387376 DOI: 10.1016/j.mcna.2007.12.003]
263 **Hogue CW Jr**, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. *Transfusion* 1998; **38**: 924-931 [PMID: 9767742 DOI: 10.1046/j.1537-2995.1998.381098440856.x]
264 **Hwang JH**, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Foley KQ, Fonkalsrud L, Jue T, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD. The role of endoscopy in the management of variceal hemorrhage. *Gastrointest Endosc* 2014; **80**: 221-227 [PMID: 25034836 DOI: 10.1016/j.gie.2013.07.023]
265 **Soares-Weiser K**, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev* 2002; (**2**): CD002907 [PMID: 12076458 DOI: 10.1002/14651858.cd002907]
266 **Soares-Weiser K**, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2003; **38**: 193-200 [PMID: 12678337 DOI: 10.1080/00365520310000690]
267 **Chavez-Tapia NC**, Soares-Weiser K, Brezis M, Leibovici L. Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. *Cochrane Database Syst Rev* 2009; (**1**): CD002232 [PMID: 19160207 DOI: 10.1002/14651858.CD002232.pub2]
268 **de Franchis R**. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005; **43**: 167-176 [PMID: 15925423]
269 **Cremers I**, Ribeiro S. Management of variceal and nonvariceal upper gastrointestinal bleeding in patients with cirrhosis. *Therap Adv Gastroenterol* 2014; **7**: 206-216 [PMID: 25177367 DOI: 10.1177/1756283X14538688]
270 **Snyder P**, Ali R, Poles M, Gross SA. Portal hypertensive gastropathy with a focus on management. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1207-1216 [PMID: 26293979 DOI: 10.1586/17474124.2015.1059275]
271 **Cirera I**, Feu F, Luca A, García-Pagán JC, Fernández M, Escorsell A, Bosch J, Rodés J. Effects of bolus injections and continuous infusions of somatostatin and placebo in patients with cirrhosis: a double-blind hemodynamic investigation. *Hepatology* 1995; **22**: 106-111 [PMID: 7601400 DOI: 10.1016/0270-9139(95)90360-7]
272 **Villanueva C**, Planella M, Aracil C, López-Balaguer JM, González B, Miñana J, Balanzó J. Hemodynamic effects of terlipressin and high somatostatin dose during acute variceal bleeding in nonresponders to the usual somatostatin dose. *Am J Gastroenterol* 2005; **100**: 624-630 [PMID: 15743361 DOI: 10.1111/j.1572-0241.2004.40665.x]
273 **Oluyemi A**, Amole A. Portal hypertensive duodenopathy manifesting as "kissing" duodenal ulcers in a nigerian with alcoholic cirrhosis: a case report and brief review of the literature. *Case Rep Med* 2012; **2012**: 618729 [PMID: 23118766 DOI: 10.1155/2012/618729]
274 **Nagral AS**, Joshi AS, Bhatia SJ, Abraham P, Mistry FP, Vora IM. Congestive jejunopathy in portal hypertension. *Gut* 1993; **34**: 694-697 [PMID: 8504973 DOI: 10.1136/gut.34.5.694]
275 **Misra SP**, Dwivedi M, Misra V, Gupta M. Ileal varices and portal hypertensive ileopathy in patients with cirrhosis and portal hypertension. *Gastrointest Endosc* 2004; **60**: 778-783 [PMID: 15557954 DOI: 10.1016/S0016-5107(04)02049-8]
276 **Kozarek RA**, Botoman VA, Bredfeldt JE, Roach JM, Patterson DJ, Ball TJ. Portal colopathy: prospective study of colonoscopy in patients with portal hypertension. *Gastroenterology* 1991; **101**: 1192-1197 [PMID: 1936789]

P- Reviewer: Dang SS, He JY, Mihaila RG, Pan JJ, Umit A
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i4.263

World J Hepatol 2016 February 8; 8(4): 263-264
ISSN 1948-5182 (online)

Non-invasive evaluation of liver fibrosis by acoustic radiation force impulse and aminotransferase:platelet ratio index in chronic hepatitis C

Ergenekon Karagoz, Coskun Ozturker, Ali Kemal Sivrioglu

Ergenekon Karagoz, Department of Infectious Diseases, Van Military Hospital, 65040 Van, Turkey

Coskun Ozturker, Department of Radiology, Canakkale Military Hospital, 17100 Canakkale, Turkey

Ali Kemal Sivrioglu, Department of Radiology, Kasimpasa Military Hospital, 34440 Beyoglu Istanbul, Turkey

Author contributions: Karagoz E and Ozturker C designed the research and wrote the letter; Sivrioglu AK revised the letter.

Conflict-of-interest statement: The author(s) indicate no potential conflicts of interest.

Correspondence to: Dr. Coskun Ozturker, MD, Department of Radiology, Canakkale Military Hospital, Zubeyde Hanim Sk., Cevatpasa Mh., 17100 Canakkale, Turkey. drozturker@gmail.com
Telephone: +90-534-5414979

Received: November 26, 2015
Peer-review started: November 26, 2015
First decision: December 22, 2015
Revised: December 28, 2015
Accepted: January 16, 2016
Article in press: January 19, 2016
Published online: February 8, 2016

Abstract

In a previous issue of the *World Journal of Gastroenterology*, we have read the article by Li *et al* with great interest. We would like to thank the authors for their comprehensive contribution. However, it is our wish to make minor criticism over the present study from the perspective of methodology.

Key words: Cirrhosis; Intercostal approach; Subcostal approach; Acoustic radiation force impulse; Liver fibrosis

Core tip: Hepatitis B virus infection is still one of the leading causes of cirrhosis and hepatocellular carcinoma. Liver biopsy is the gold standard method to assess the severity of liver fibrosis. However, there are several limitations of liver biopsy, including its invasive nature, small tissue sample size, and subjective grading system. Nowadays, noninvasive parameters have been utilized to evaluate liver histology. Additionally, ultrasound-based techniques, such as acoustic radiation force impulse have gained popularity in assessing liver fibrosis. Herein, we aimed to make a minor criticism regarding this study.

Karagoz E, Ozturker C, Sivrioglu AK. Non-invasive evaluation of liver fibrosis by acoustic radiation force impulse and aminotransferase:platelet ratio index in chronic hepatitis C. *World J Hepatol* 2016; 8(4): 263-264 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i4/263.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i4.263

TO THE EDITOR

In a previous issue of the *World Journal of Gastroenterology*, we have read the article by Li *et al*[1] with great interest. We would like to thank the authors for their

comprehensive contribution. However, it is our wish to make minor criticism over the present study from the perspective of methodology.

First, the measurements of Acoustic Radiation Force Impulse Imaging were performed in the right liver lobe through the intercostal space in present study[1]. Uslu *et al*[2] demonstrated that subcostal approach to the liver parenchyma was significantly superior to intercostal approach for the evaluation of liver stiffness in their study. As the pressure was transmitted better to liver parenchyma and the anterior abdominal wall, we are of the opinion that subcostal approach would give better results than intercostal approach in terms of determining the elasticity of the liver.

Second, it would have been better, if the authors had stated the length of the biopsy material and the number of the pieces of the portal tracts. Fibrosis is heterogeneously distributed throughout the liver, whereas a biopsy evaluates only 1/50000 of the total volume of the liver[3]. Additionally, if the biopsy material is not long enough, appropriate evaluation cannot be done. A length of at least 25 mm is required to assess the fibrosis score accurately[3]. It would have been better, if the authors had mentioned these conditions as limitations.

Further studies are needed to indicate the role of acoustic radiation force impulse imaging method in the management of liver fibrosis and cirrhosis in patients with chronic hepatitis C.

REFERENCES

1 **Li SM**, Li GX, Fu DM, Wang Y, Dang LQ. Liver fibrosis evaluation by ARFI and APRI in chronic hepatitis C. *World J Gastroenterol* 2014; **20**: 9528-9533 [PMID: 25071348 DOI: 10.3748/wjg.v20.i28.9528]

2 **Uslu A**, Batur A, Biyik M, Acikgozoglu S. Non-Invasive Evaluation of Liver Fibrosis Using Real-Time Elastography and Comparison of Intercostal and Subcostal Approaches. *Eur J Gen Med* 2015; **12**: 109-113 [DOI: 10.15197/sabad.1.12.23]

3 **Frulio N**, Trillaud H, Perez P, Asselineau J, Vandenhende M, Hessamfar M, Bonnet F, Maire F, Delaune J, De Ledinghen V, Morlat P. Acoustic Radiation Force Impulse (ARFI) and Transient Elastography (TE) for evaluation of liver fibrosis in HIV-HCV co-infected patients. *BMC Infect Dis* 2014; **14**: 405 [PMID: 25041708 DOI: 10.1186/1471-2334-14-405]

P- Reviewer: Grassi A, Wang K **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com