CORRESPONDENCE

"Nonalcoholic Fatty Liver Disease" in a Developing Country: A Different Perspective

To the Editor:

I read with great interest the article by Das et al.[1] Although presence of nonalcoholic fatty liver (NAFL) in nonobese individuals is a fairly common observation in India, this is the first such scientific documentation for the same. However, I would like to make a few points in this regard.

First, NAFL constitutes a wide spectrum of liver disease with varied natural history extending from simple steatosis to more sinister variants, i.e., nonalcoholic steatohepatitis (NASH) and fibrosis/cirrhosis. Only a proportion of NAFL actually progresses to the more sinister end of this spectrum. Therefore, instead of a blanket focus on NAFL, it would be more appropriate to identify the subset of patients with NAFL who are more likely to progress to NASH. In this regard, the authors have defined "potentially significant NAFL" as "subjects with definite NAFL who had persistently elevated ALT (>40 IU/L)". However, even in this study only one-third of these subjects with "potentially significant NAFL" were found to have NASH on liver biopsy, which means elevated ALT alone is not a good enough marker of "potentially significant" NAFL. A full panel of noninvasive markers of liver fibrosis would be more appropriate to define this subset and save costly and/or potentially harmful procedures like liver biopsy or computed tomography scans for them.

Second, although the authors have claimed to have excluded people with alcohol consumption from this study, this population in context comes largely from a tribal background who indulges in many nonconventional forms of ethanol consumption, e.g., mahua flower (*Madhuca longifolia*). It would be interesting to know if the authors have ruled out those possibilities as well.

Third, risk of NAFL is undoubtedly associated with obesity and metabolic syndrome and has been traditionally associated with more affluent living standards. In the current study too, even nonobese subjects with NAFL had worse metabolic parameters and higher income than their age-matched and sex-matched counterparts who did not have NAFL. Nevertheless, coexistence of intrauterine and neonatal malnutrition and the development of obesity, type 2 diabetes, and related comorbidities have been confirmed in a number of studies in humans and animal models.[2] Moreover, it has been shown that, in humans, the intrahepatic lipid content increase following starvation also may be due to reduced apolipoprotein B-100 production and hepatic lipid export, and/or impaired mitochondrial function; this could have implications for exacerbations of steatohepatitis that is sometimes seen with rapid weight loss, anorexia nervosa, and parenteral nutrition.[3] Therefore, in contrast to the popular view, malnutrition rather than obesity at different stages of life may well be an explanation for pathogenesis of NAFL in this predominantly poor population.

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References

1. Das K, Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology 2010; 51:1593-1602.
2. Kalhan SC. Metabolism of methionine in vivo: impact of pregnancy, protein restriction and fatty liver disease. Nestle Nutr Workshop Ser Pediatr Program 2009;63:121-131; discussion, 131-133, 259-268.
3. Gan SK, Watts GF. Is adipose tissue lipolysis always an adaptive response to starvation?: implications for non-alcoholic fatty liver disease. Clin Sci (Lond) 2008;114:543-545.

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Reply:

We read with great interest the comments by Dr. Maitra regarding our article[1] published in Hepatology. We thank the author for his kind interest in our work and welcome the opportunity to clarify the points raised by him.

First, there is a difference between a field study and a clinic-based study. Despite its fallacies, the measurement of alanine aminotransferase remains the most cost-effective screening tool for significant underlying liver disease, even nonalcoholic fatty liver (NAFL) disease.[2] Moreover, an elevated alanine aminotransferase level is one of the components of the various noninvasive scoring systems used for identifying NAFL subjects with advanced liver disease.[3] Unfortunately, despite attempts to develop multiple noninvasive (but not necessarily cheap) scoring systems or tests for identifying subjects with nonalcoholic steatohepatitis, liver biopsy remains the ultimate gold standard for diagnosing nonalcoholic steatohepatitis.[3]

Second, despite the concerns regarding the unconventional forms of ethanol consumption by tribals in India, there were only 35 tribals (1.8%) among the 1911 subjects, and we rigorously excluded alcohol consumption in our study population (see the supporting information for our article[1]).

Finally, we also speculated about the role of malnutrition in the genesis of NAFL in our population.[1] However, in a case-control substudy of subsets of subjects with a body mass index < 18.5 kg/m^2, we found that those with NAFL had higher indices of adiposity and a higher prevalence of markers of metabolic syndrome versus those without NAFL (see the supporting tables for our article[1]). We agree with Maitra that the thrifty phenotype hypothesis,[4] introduced approximately 20 years ago to explain the associations between poor fetal and infant growth and the increased risk of developing impaired glucose tolerance and metabolic syndrome in adult life, can play a pathophysiological role in the development of the third-world NAFL phenotype, as highlighted by us.[1]

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References

1. Das K, Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology 2010; 51:1593-1602.
2. Clark JM, Diehl AM. Defining nonalcoholic fatty liver disease: implications for epidemiologic studies. Gastroenterology 2003;124: 248-250.

3. Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008;134:1682-1698.
4. Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992;35:595-601.

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Antituberculosis Therapy Drug-Induced Liver Injury and Acute Liver Failure

To the Editor:

We read with great interest the study by Kumar et al.,[1] who reported antituberculosis therapy (ATT) as the only cause of drug-induced acute liver failure (ALF) in northern India, in contrast to antimicrobials, anticonvulsants, and paracetamol in the West[2-6] and in southern India.[7]

Our experience with drug-induced liver injury (DILI), including injury due to ATT, from 1997 to 2008 at the Department of Gastroenterology of St. John's Medical College Hospital (Bangalore, India) offers something in support of their findings and something at odds.[7] Table 1 outlines the clinical and biochemical characteristics of all patients with DILI due to ATT. Kumar et al.[1] found a mortality rate of 67% among 70 patients (mean age = 32 years) with ATT-caused ALF; most (63%) were treated empirically for tuberculosis. In support of their findings, we observed that our patients were young (mean age = 40 years) and that the mortality rate was 67% among 49 patients with ALF due to ATT and 42% among patients who were inappropriately treated for tuberculosis. Our model, using a combination of the bilirubin level [odds ratio (OR) = 1.17, confidence interval (CI) = 1.06-1.35], prothrombin time (OR = 1.13, CI = 1.06-1.24), and creatinine level (OR = 9.77, CI = 2.58-57.63), yielded a concordance of 97% for mortality.

We were intrigued to find ATT as the sole cause of drug-induced ALF in their series over 22 years. In our series, ATT was a contributing factor in 58% of all cases of DILI (n = 313) and in 76.6% of patients with drug-induced ALF. Others who presented with ALF included users of phenytoin (n = 5), dapsone (n = 3), paracetamol (n = 1), complementary medicine (n = 1), amoxicillin-clavulanate (n = 1), hormones (n = 1), atorvastatin (n = 1), and chemotherapeutics (n = 2). How can the differences be explained? Were patients with only select types of ALF admitted while others sought admission elsewhere? Moreover, is it possible to determine the proportion of patients with ALF among all ATT-caused DILI patients because such patients are reported by the institute?[8] Despite the increasing prevalence of tuberculosis and acquired immune deficiency syndrome in the last decade, we were surprised to read about the decreasing incidence of ALF due to ATT and the absence of human immunodeficiency virus infection; this is contrary to our experience.

In summary, ATT-induced ALF is a major cause of drug-induced ALF in India, but it is not the only cause; phenytoin, dapsone, and others also contribute. Inappropriate medications contribute to a large number of ATT-caused cases of DILI and ALF, which are

Table 1. Summary of Demographic, Clinical, and Laboratory Variables for Survivors and Nonsurvivors of ATT-Caused DILI with Univariate Logistic Regressions

Variable	Survivors (n = 142)	Nonsurvivors (n = 39)	OR (95% CI)*	*P* Value*	Concordance (%)
Age (years)	42.9	40.2	1.00 (0.96-1.01)	0.351	52
Male	101 (55.8%)	80 (44.2%)	0.79 (0.38-1.62)	0.522	53
Jaundice	96 (67.6%)	39 (100%)	37.0 (9.2-658.5)	<0.001	70
Skin rashes	15 (10.6%)	09 (23.7%)	2.6 (1.0-6.5)	0.05	56
Encephalopathy	16 (11.3%)	33 (84.6%)	43.3 (16.7-130.2)	<0.001	87
Ascites	25 (17.7%)	25 (64.1%)	8.3 (3.8-18.6)	<0.001	73
Treatment duration (months)	1.8	2.2	1.0 (0.99-1.0)	0.34	60
Total proteins (g/dL)	6.3	5.6	0.6 (0.4-0.8)	0.003	66
Albumin (g/dL)	3.0	2.4	0.3 (0.2-0.5)	<0.001	70
Total bilirubin (mg/dL)	6.5	20.4	1.2 (1.1-1.3)	<0.001	88
Direct bilirubin (mg/dL)	4.4	11.2	1.2 (1.1-1.3)	<0.001	88
AST (u/L)	381.4	733.2	1.00 (1.00-1.00)†	0.006	63
ALT (u/L)	340.1	590.7	1.00 (1.00-1.0)†	0.062	53
ALP (u/L)	227	331	1.00 (1.00-1.00)†	0.03	69
PT (seconds)	23.9	60.2	1.09 (1.06-1.13)	<0.001	90
INR	1.7	5.0	2.7 (1.9-4.1)	<0.001	90
Serum creatinine (mg/dL)	0.9	1.9	5.7 (2.1-27.2)	<0.001	74
WBC (μL)	9784	13907	1.00 (1.00-1.00)‡	0.002	64
Eosinophils (%)	2.3	1.1	0.8 (0.6-1.00)	0.05	62
Platelets ($10^5/\mu$L)	2.2	2.0	0.8 (0.6-1.2)	0.39	64
MELD	15.1	36.8	1.3 (1.2-1.9)	<0.001	97

Data are presented as means or n (%).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PT, prothrombin time; WBC, white blood count.

*From a univariate logistic regression model predicting death (yes versus no).

†OR for a 100-U increase.

‡OR for a 1000-U increase.

potentially preventable. A high Model for End-Stage Liver Disease score or a combination of the bilirubin level, prothrombin time, and creatinine level is associated with mortality, and patients may be selected for early referral for transplantation.

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References

1. Kumar R, Shalimar Bhatia V, Sreenivas V, Gupto SD, Panda SK, et al. Antitubercular therapy-induced acute liver failure: magnitude, profile, prognosis and predictors of outcome. HEPATOLOGY 2010;51: 1665-1674.
2. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al., for the Drug-Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135:1924-1934.
3. Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. HEPATOLOGY 2005;42:481-489.
4. Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, et al., for the Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512-521.
5. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl 2004;10:1018-1023.
6. O'Grady JG, Graeme GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-445.
7. Devarbhavi H, Dierkhsing R, Kremers W, Sandeep MS, Karanth D, Adarsh CK. Single center experience with drug induced liver injury from India: causes, outcome, prognosis, and predictors of molarity. Am J Gastroenterol 2010. In press.
8. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med 2002;166:916-919.

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Reply:

The data reported by Devarbhavi et al. in their letter on antituberculosis therapy (ATT)–induced acute liver failure (ALF) are indeed similar to the figures reported by us.[1] These patients had a high mortality rate (67% in both reports) and were young (mean ages of 32 and 40 years), and most of the patients in both reports underwent, without definite evidence of tuberculosis, antitubercular treatment that could have been avoided (63% and 42%).

Devarbhavi et al. suggested that there are other causes of drug-induced liver injury (DILI) and DILI-ALF in India. To support this statement, they provided their data on DILI: approximately 60% of all DILI cases and approximately 77% (three-fourths) of DILI-ALF cases were due to ATT. Therefore, in India, ATT is the most important drug implicated in DILI. The collated data on consecutive patients with ALF reported from Kashmere,[2] central India,[3] and north India[4,5] by other Indian authors also show that ATT-induced ALF was the sole cause of DILI-ALF in their series. The All India Institute of Medical Sciences is a major referral center in north India, particularly for ALF, and we evaluated 1223 consecutive patients with ALF from 1986 to 2009; surprisingly, we have not been able to document paracetamol or other drugs or indigenous medicine as a cause of ALF in these patients.[1] These reports indicate that ATT is indeed the major cause of DILI in India. As indicated by Devarbhavi et al., other drugs may cause DILI, but the frequency is very low. During a 10-year period (1997-2008), Devarbhavi et al. documented that 76.6% of DILI-ALF cases were due to ATT, and 15 patients had ALF due to other drugs. The authors have not provided the exact number of ALF patients. However, when we reanalyzed this figure, we found that probably there were 64 patients with DILI-ALF, and for 49, DILI-ALF was due to ATT; this indicates that ATT is the most important cause of DILI in India. Paracetamol, which is the most frequent cause of DILI-ALF in the United Kingdom and United States, was documented in only one patient in Devarbhavi et al.'s report over a 10-year period. The cultural practices in the West and East are different. Paracetamol is a drug sold over the counter in the West and is available in almost all households; therefore, people have easy access to this drug for suicide, and on rare occasions, accidental consumption causing ALF has also been reported. In the households of India, an agriculture-based country, organophosphorous compounds used as pesticides are readily available and are consumed for the purpose of suicide. Furthermore, Indians are a distinct race and may have different genetic drug-metabolizing capabilities, about which information is lacking. Therefore, even though DILI-ALF due to agents other than ATT may occur in this country, as indicated by Devarbhavi et al., the frequency is probably very low; this is also supported by multiple reports on ALF from India.[2-5]

The other issue raised by Devarbhavi et al. is that, despite an increase in the prevalence of acquired immune deficiency syndrome (AIDS) and tuberculosis, in our study, the frequency of ATT-induced ALF was reported to be less during the last decade (1998-2009) than the frequency of ATT-induced ALF in the previous decade (1986-1997). Seventy-four percent of our patients with ATT-induced ALF (52/70) were documented from 1986 to 1997, whereas 26% (18/70) were diagnosed from 1998 to 2009.[1] Devarbhavi et al. suggested that because of increases in the frequency of AIDS and consequently tuberculosis, an increase in the number of ATT-induced ALF cases would be expected. However, an increase in the frequency of AIDS and tuberculosis would not necessarily lead to an increase in the number of ATT-induced DILI cases. There is no evidence to date that an increase in the frequency of AIDS and tuberculosis would increase ATT-induced toxicity. Even Devarbhavi et al. have not been able to provide any data showing an increase in ATT-induced ALF in their series during the last decade, and no information on the human immunodeficiency virus (HIV) status is available either. However, none of our ATT-induced ALF cases had HIV. During the last decade in India, antitubercular treatment has been administered through the DOTS (Directly Observed Treatment, Short-Course) program, in which ATT is administered to patients under supervision. In such a situation, the empirical use of ATT is likely to be less frequent, and this may explain the lower frequency of ATT-induced ALF during the last decade in our report.

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References

1. Kumar R, Shalimar, Bhatia V, Dattagupata S, Panda SK, Acharya SK. Antituberculous therapy-induced acute liver failure: magnitude, profile, prognosis, and early predictors of outcome. Hepatology 2010;51: 1665-1674.
2. Khuroo MS. Acute liver failure in India. Hepatology 1997;26: 244-246.
3. Jaiswal SB, Chitnis DS, Asolkar MV, Naik G, Aswini KK. Aetiology and prognostic factors in hepatic failure in central India. Trop Gastroenterol 1996;17:217-220.
4. Tandon BN, Joshi YK, Tandon M. Acute liver failure: experience with 145 cases. J Clin Gastroenterol 1986;8:664-668.
5. Acharya SK, Dasarathy S, Kumar TL, Sushma S, Prasanna KS, Tandon A, et al. Fulminant hepatitis in a tropical population; clinical course, cause and early predictor of outcome. Hepatology 1996;23:1448-1455.

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Transient Elastography in the Early Prediction of Progressive Recurrent Hepatitis C Following Liver Transplantation

To the Editor:

Early recognition of recipients with rapidly evolving recurrent hepatitis C following orthotopic liver transplantation (OLT) is the only practical approach to improve outcome of these patients.[1] Recently, transient elastography (TE) was shown to identify patients with rapidly progressive hepatitis C in the first year following OLT, differentiating them from patients with slowly progressive hepatitis C.[2]

Thirty-seven consecutive liver graft recipients with recurrent hepatitis C, who underwent transplantation from June 2005 to December 2007, were prospectively investigated with repeated TE examinations at 3, 6, 9, and 12 months after OLT and underwent a liver biopsy at month 12. Significant liver fibrosis was scored as Ishak staging (S) $\geq$ 3. Patients with S $<$ 3 at month 12 were defined slow fibrosers compared to rapid fibrosers, who had S $\geq$ 3.

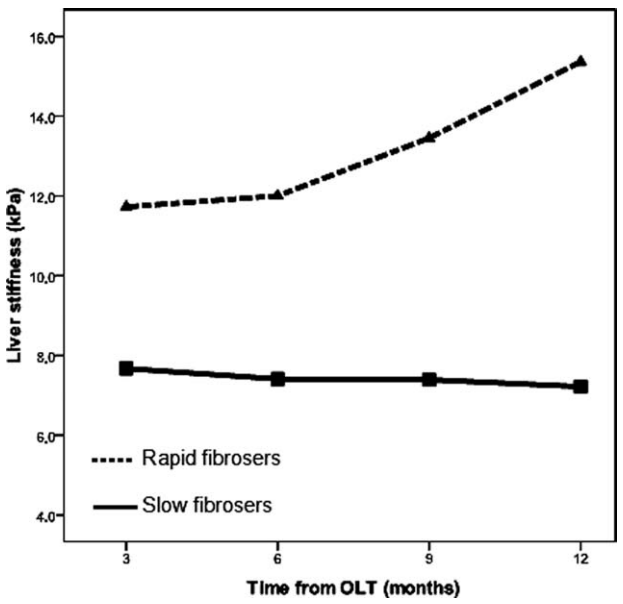

Fig. 1. The course of liver stiffness assessed by transient elastography during the first year following liver transplantation in slow and rapid fibrosers with recurrent hepatitis C, by a longitudinal mixed model for repeated measurements.

Of the 33 patients who completed the follow-up (four died within month 6), 21 (64%) were slow fibrosers and 12 (36%) were rapid fibrosers, thus confirming the 63% and 37% rates of slow and rapid fibrosers previously reported.[2] Slow fibrosers had significantly lower TE measurements at 3, 6, 9, and 12 months (median 7.5, 7.0, 6.9, and 6.4 kPa) compared to rapid fibrosers (median 8.9, 10.9, 11.8, and 13.0 kPa). The 12-month staging was significantly correlated with TE values at month 6 (rho = 0.48, $P = 0.006$), at month 9 (rho = 0.78, $P < 0.0001$), and at month 12 (rho = 0.83, $P < 0.0001$). Rapid fibrosers had significantly higher aspartate aminotransferase serum levels at 3, 6, 9, 12 months, γ-glutamyl transferase serum levels at 6 and 12 months, bilirubin at 6 months, and TE values at 6, 9, and 12 months compared to slow fibrosers. Moreover, rapid fibrosers were more often recipients of aged grafts compared to slow fibrosers, further confirming the prognostic relevance of donor age in this setting of patients. In results from a longitudinal mixed model for repeated measurements, the slope of TE variations was significantly greater in rapid fibrosers (0.40 kPa/month) than in slow fibrosers (−0.05 kPa/month) ($P < 0.0001$; Fig. 1), further confirming the results of the study by Carrion et al. (0.42 and 0.05 kPa/month in rapid and slow fibrosers, respectively).[2] The rates of patients with TE $>$ 7.9 kPa, the optimal TE cut-off for S $\geq$ 3 diagnosis previously identified by us,[3] at 3, 6, 9, and 12 months were 29%, 26%, 31%, and 28% in slow fibrosers and 60%, 67%, 100%, and 95% in rapid fibrosers ($P = 0.22$, $P = 0.06$, $P = 0.001$, and $P = 0.001$, respectively). By logistic regression analysis, TE $>$ 7.9 kPa at month 6 was the only independent predictor of significant fibrosis at month 12 ($P = 0.02$, odds ratio = 6.0, 95% confidence interval = 1.2-28.8).

By applying in our cohort the bilirubin plus TE model constructed by Carrion et al.[2] for identifying rapid fibrosers at month 6, we could correctly classify 67% of our rapid fibrosers, compared to 70% of rapid fibrosers identified by Carrion et al. Interestingly, the 7.9 kPa TE cut-off at month 6 could identify the same proportion (67%) of rapid fibrosers in our cohort. In conclusion, in an external validation group of liver graft recipients with recurrent hepatitis C, repeated TE examinations early after OLT helped to identify patients at risk of progressive graft disease, with a potential benefit for clinical management.

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References

1. Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transpl 2008;14(Suppl 2):S36-S44.
2. Carrion JA, Torres F, Crespo G, Miquel R, Garcìa-Valdecasas JC, Navasa M, et al. Liver stiffness identifies two different patterns of fibrosis progression in patients with hepatitis C virus recurrence after liver transplantation. HEPATOLOGY 2010;51:23-34.
3. Rigamonti C, Donato MF, Fraquelli M, Agnelli F, Ronchi G, Casazza G, et al. Transient elastography predicts fibrosis progression in patients with recurrent hepatitis C after liver transplantation. Gut 2008;57:821-827.

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Targeting Heme Oxygenase/Adiponectin Axis for Chronic Hepatitis C Treatment

To the Editor:

We read with great interest the article by Lehmann et al. in which the authors demonstrate that heme oxygenase-1 (HO-1) induction by cobalt protoporphyrin (CoPP) markedly inhibits the replication of hepatitis C virus (HCV) by increasing interferon response *in vitro*.[1] The heme oxygenase system plays a key role in the antioxidant defenses of many tissues and organs,[2] and a number of evidence suggests that HO-1 induction could exert therapeutic effects in a variety of liver conditions, including viral hepatitis and nonalcholic steatohepatitis.[3] The study by Lehmann et al. is consistent with previous reports showing the potent anti-HCV activity of HO-1 and further proposes HO-1 as a promising tool for the treatment of chronic hepatitis C. Nonetheless, there are some issues that we would like to point out in order to better underline the putative *in vivo* HO-1 activity against HCV through the modulation of interferon response. These issues regard the HO-1/adiponectin axis.

Adiponectin is an adipose tissue cytokine exerting potent anti-inflammatory effects in the liver, and has been demonstrated to play a key role in various liver diseases.[4] In particular, adiponectin is decreased in patients with obesity and insulin resistance,[5] which are strongly associated with a negative sustained virological response (SVR) following antiviral treatments.[6] Of note, it has been clearly demonstrated that HO-1 induction may favorably affect insulin sensitivity by increasing adiponectin levels.[7,8] L'Abbate et al. first showed that induction of HO-1 by CoPP increases serum adiponectin levels in mice with experimental diabetes.[7] Successively, the same group confirmed the potent insulin-sensitizing action of CoPP in ob/ob mice through the increase of adiponectin and its downstream target adenosine monophosphate kinase.[8] Therefore, it is conceivable that *in vivo* HO-1 induction could also be important not only for its classical antioxidant activity but also for the insulin-sensitizing action, which could be exploited to achieve more SVR in patients with chronic hepatitis C. Furthermore, far from the strict metabolic action of the adiponectin system, it has been also demonstrated that adiponectin displays a direct role in immune response against HCV. Palmer et al. elegantly showed that administration of adiponectin to *ex vivo* peripheral blood mononuclear cells from patients with chronic hepatitis C enhances interferon γ production.[9] Thus, in our opinion, the existence of an HO/adiponectin axis should be taken into account when considering the potent modulation of interferon response by HO-1 induction. In conclusion, besides the classical antioxidant action of HO-1, we think that the brilliant results of Lehmann et al. should be further extended to the contribution of adiponectin on *in vivo* response to interferon in patients with chronic hepatitis C, and, in particular, in those patients presenting with insulin resistance. We do agree with the authors' conclusions, which further confirm HO-1 as a key element in the liver antioxidant defenses and as a therapeutical target to develop future hepatoprotective strategies.[10]

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References

1. Lehmann E, El-Tantawy WH, Ocker M, Bartenschlager R, Lohmann V, Hashemolhosseini S, et al. The heme oxygenase 1 product biliverdin interferes with hepatitis C virus replication by increasing antiviral interferon response. HEPATOLOGY 2010;51:398-404.
2. Abraham NG, Kappas A. Pharmacological and clinical aspects of heme oxygenase. Pharmacol Rev 2008;60:79-127.
3. Yu J, Chu ES, Wang R, Wang S, Wu CW, Wong VW, et al. Heme oxygenase-1 protects against steatohepatitis in both cultured hepatocytes and mice. Gastroenterology 2010;138:694-704.
4. Marra F, Bertolani C. Adipokines in liver diseases. HEPATOLOGY 2009;50:957-969.
5. Bajaj M, Suraamornkul S, Piper P, Hardies LJ, Glass L, Cersosimo E, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab. 2004;89:200-206.
6. Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodrıguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology 2005;128:636-641.
7. L'Abbate A, Neglia D, Vecoli C, Novelli M, Ottaviano V, Baldi S, et al. Beneficial effect of heme oxygenase-1 expression on myocardial ischemia-reperfusion involves an increase in adiponectin in mildly diabetic rats. Am J Physiol Heart Circ Physiol 2007;293:H3532-H3541.
8. Li M, Kim DH, Tsenovoy PL, Peterson SJ, Rezzani R, Rodella LF, et al. Treatment of obese diabetic mice with a heme oxygenase inducer reduces visceral and subcutaneous adiposity, increases adiponectin levels, and improves insulin sensitivity and glucose tolerance. Diabetes 2008;57:1526-1535.
9. Palmer C, Hampartzoumian T, Lloyd A, Zekry A. A novel role for adiponectin in regulating the immune responses in chronic hepatitis C virus infection. HEPATOLOGY 2008;48:374-384.
10. Li Volti G, Sacerdoti D, Di Giacomo C, Barcellona ML, Scacco A, Murabito P, et al. Natural heme oxygenase-1 inducers in hepatobiliary function. World J Gastroenterol 2008;14:6122-6132.

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The Curative Efficiency of Tenofovir for Patients with Chronic Hepatitis B After Failure of Nucleoside/Nucleotide Analogues

To the Editor:

Recently, we read with interest the article by van Bömmel et al.[1] on tenofovir disoproxil fumarate (TDF) monotherapy for patients who failed to improve with other nucleoside/nucleotide analogues (NUC). Their findings showed that TDF monotherapy could induce a potent and long-lasting antiviral response in other NUC failure patients. However, we still have some questions to discuss.

According to Asian Pacific Association for the Study of the Liver (APASL) and European Association for the Study of the Liver (EASL) guidelines,[2,3] primary nonresponse (PNR) is defined as a decrease in hepatitis B virus (HBV) DNA by <1 log10 IU/mL at week 12. But in the American Association for the Study of Liver Diseases (AASLD) guidelines,[4] it is defined as a decrease in HBV DNA by <2 log10 IU/mL at week 24. Thus, we can see the time point at which determination of PNR in NUC treatment is still controversial. In this study, we thought it might not be good to define PNR at week 12 as treatment failure. We also speculated that some of the included patients might not represent "true failure" of a preceding treatment. For example, in adefovir-treated patients with nonresponse at week 12, if preceding treatment was continued but not switched to TDF, good virological response also might be reached. We suspected the efficacy of TDF for those patients may be not as good as reported. If patients with nonresponse were excluded from 131 eligible patients, the efficacy data of TDF may be more reasonable and valuable to us. If possible, we expect professor van Bömmel to be able to share relevant results with us.

We are also interested whether there were patients who presented with so-called nonresponse during TDF treatment. In the present study, the decrease of HBV DNA in TDF treatment was only assessed at 12 months and at the end of follow-up. If specific data on a decrease in HBV DNA at week 12 or 24 of TDF treatment were also shared, it would give us a more comprehensive understanding of the curative efficacy of TDF rescure therapy.

In addition, we would like to point out there was a typographic error of the age in table 1. The range of age should be 18-77, not 17-77.

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References

1. van Bömmel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology 2010;51:73-80.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227-242.
3. Liaw Y-F, Leung N, Kao J-H, Piratvisuth T, Gane E, Han K-H, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2008;2:263-283.
4. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661-662.

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Hepatitis B in Refugees, Guessing the Prevalence

To the Editor:

I read with great interest the article by Rein et al.[1] In this manuscript, the authors attempt to address the prevalence of hepatitis B surface antigen (HBsAg) in foreign-born persons living in the United States. The authors did so by requesting data on hepatitis B screening from refugee health coordinators around the country.

The authors indicate that estimates for HBsAg prevalence from the study correspond to estimates from the literature for each country (where comparison is available). One should be very careful when extrapolating the findings of one group of refugees to an entire nation. Generally, refugees that enter one jurisdiction come from the same area in the country of origin. In sub-Saharan Africa, rates of hepatitis B virus (HBV) for each country vary according to regional areas; this is likely related to the habits and customs of each region within a country. The authors report a prevalence of HBsAg of 3.1% in refugees from Tanzania. The rates of HBsAg for Tanzania range from 4.2% in individuals negative for human immunodeficiency virus (HIV),[2] 9.9% in the general population,[3] to 17% in HIV-infected individuals.[4]

Most african countries in the study by Rein et al. are areas of high endemicity for HIV.[5] Prevalence of HIV infection in a population is of importance when addressing prevalence, and relevance, of HBV infection. Patients infected with HIV are known to have higher rates of occult hepatitis B.[6] This means that individuals will be negative for HBsAg, with positive anticore antibody and detectable HBV viral load. The consequences of occult hepatitis B are still under investigation. However, occult hepatitis B has been reported to reactivate in patients with HIV.[7] Moreover, the effects and protection of vaccination against HBV in this population are unknown. Any study attempting to address prevalence of HBsAg in individuals from African countries should take into account the presence of HIV infection, in order to better evaluate the significance of the findings.

I applaud the initiative of Rein et al. to try to achieve a much-needed clarification on the prevalence of HBsAg in refugees entering the United States. However, well-conducted prospective or cross-sectional studies with larger samples for each country are needed.

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References

1. Rein DB, Lesesne SB, O'Fallon A, Weinbaum CM. Prevalence of hepatitis B surface antigen among refugees entering the United States between 2006 and 2008. HEPATOLOGY 2010;51:431-434.
2. Msuya SE, Mbizvo EM, Hussain A, Sam NE, Stray-Pedersen B. Seroprevalence of hepatitis B and C viruses among women of childbearing age in Moshi Urban, Tanzania. East Afr Med J 2006;83:91-94.
3. Jacobs B, Mayaud P, Changalucha J, Todd J, Ka-Gina G, Grosskurth H, et al. Sexual transmission of hepatitis B in Mwanza, Tanzania. Sex Transm Dis 1997;24:121-126.
4. Nagu TJ, Bakari M, Matee M. Hepatitis A, B and C viral co-infections among HIV-infected adults presenting for care and treatment at Muhimbili National Hospital in Dar es Salaam, Tanzania. BMC Public Health 2008;8:416.
5. Kilmarx PH. Global epidemiology of HIV. Curr Opin HIV AIDS 2009; 4:240-246.
6. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. J Acquir Immune Defic Syndr 2004;36:869-875.
7. Bloquel B, Jeulin H, Burty C, Letranchant L, Rabaud C, Venard V. Occult hepatitis B infection in patients infected with HIV: report of two cases of hepatitis B reactivation and prevalence in a hospital cohort. J Med Virol 2010;82:206-212.

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Is Cigarette Smoking an Independent Risk Factor or a Cofactor for Nonalcoholic Fatty Liver Disease?

To the Editor:

We read with great interest the article by Azzalini et al. showing that cigarette smoking causes significant oxidative stress and worsens the severity of nonalcoholic fatty liver disease (NAFLD) in obese Zucker rats. Their results indeed provide important data for improving our understanding of the relationship between cigarette smoking and NAFLD. However, whether this association also holds true in humans remains unclear, nor is it clear whether cigarette smoking independently increases the risk for NAFLD.

Recently, we conducted a cross-sectional study to analyze the association of cigarette smoking with NAFLD. We included 8442 employees (5369 males; mean age = 46.6 years) of Zhenhai Refining and Chemical Company, Ltd. (Ningbo, China), who were attending their annual health examination between January 1, 2008 and December 31, 2008. Most of the subjects were also included in our previous studies.[1,2] Here we observed that the prevalence rate of NAFLD was significantly higher among cigarette smokers versus nonsmokers (28.27% versus 19.18%, $P < 0.001$). We further classified all the subjects into four groups according to their smoking severity. In comparison with nonsmokers, the prevalence ratios for mild (1-10 cigarettes daily), moderate (11-20 cigarettes daily), and severe smokers (>20 cigarettes daily) were 1.33, 1.51, and 1.71, respectively (P for trend < 0.001). These results suggest that cigarette smokers are more likely to develop NAFLD than nonsmokers, and the likelihood increases with increasing severity of cigarette smoking.

Metabolic syndrome is a well-established risk factor for NAFLD.[3,4] An analysis of the relationship between cigarette smoking and metabolic syndrome may indirectly reflect the relationship between cigarette smoking and NAFLD. Therefore, the impact of cigarette smoking on the prevalence ratio of metabolic syndrome and its components was studied. We observed that the prevalence ratios of metabolic syndrome, central obesity, hypertriglyceridemia, elevated blood pressure, and elevated fasting plasma glucose all tended to increase with increases in cigarette smoking severity (Fig. 1). These results not only confirm that cigarette smoking is an important factor for metabolic syndrome[5,6] but also indirectly indicate that cigarette smoking may be a significant factor for NAFLD, which is closely related to metabolic syndrome.

Finally, we performed logistic regression analysis to evaluate whether cigarette smoking is an independent risk factor for NAFLD. In a univariate model, cigarette smoking was observed to be a significant risk factor for NAFLD with an odds ratio of 1.31 (95% confidence interval = 1.23-1.40). However, adjustments for age, gender, and body mass index significantly attenuated the odds ratio to 1.09 (1.00-1.18). In a multivariate model, cigarette smoking was not significantly statistically associated with the risk for NAFLD. This analysis indicated that the relationship between cigarette smoking and NAFLD may be somehow influenced by other variables.

Together, our results provide evidence that the association between cigarette smoking and NAFLD observed in rats may also hold true in humans. Our results also indicate that cigarette

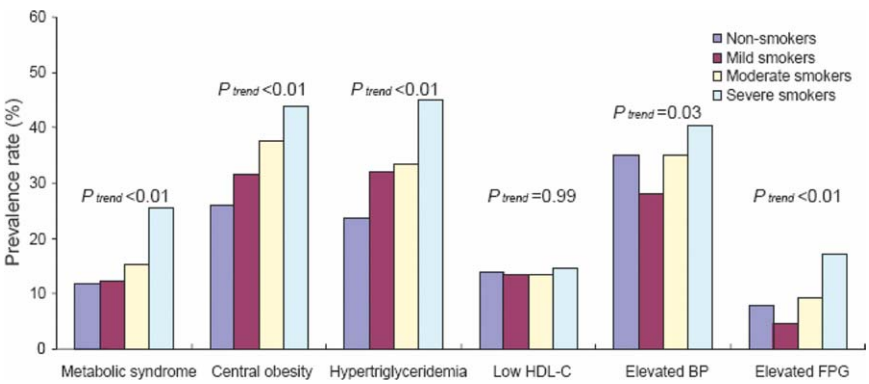

Fig. 1. Prevalence rate of metabolic syndrome with different severities of cigarette smoking. The prevalence rates of metabolic syndrome and its components, including central obesity, hypertriglyceridemia, elevated blood pressure (BP) and elevated fasting plasma glucose (FPG), all showed increasing trends with increasing severity of cigarette smoking.

smoking may act as a cofactor but not as an independent factor for NAFLD.

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References

1. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009;50:1029-1034.
2. Xu L, Xu CF, Yu CH, Miao M, Li YM. Haemoglobin and non-alcoholic fatty liver disease: further evidence from a population-based study. Gut 2009;58:1706-1707.
3. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37:917-923.
4. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med 2005;143:722-728.
5. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M. Association between cigarette smoking, metabolic syndrome, and carotid arteriosclerosis in Japanese individuals. Atherosclerosis 2005;181:381-388.
6. Oh SW, Yoon YS, Lee ES, Kim WK, Park C, Lee S, et al. Association between cigarette smoking and metabolic syndrome: the Korea National Health and Nutrition Examination Survey. Diabetes Care 2005;28:2064-2066.

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Histological Subclassification of Cirrhosis

To the Editor:

We read with great interest the review by Garcia-Tsao and colleagues[1] on the pathophysiological classification of cirrhosis. We agree that a simple one-stage description for advanced fibrotic liver disease is inadequate, especially for the prediction of clinical outcomes and the assessment of specific therapies. As the authors reported, currently cirrhosis is classified only as a single stage histologically, and this is a categorical assignment based on descriptive architectural changes and not a measurement of the amount of fibrosis.[2] Garcia-Tsao et al. also discuss the hepatic venous pressure gradient (HVPG), which we agree is a validated prognostic marker in cirrhosis[3] and possibly also in precirrhotic stages,[4] as we have shown in hepatitis C virus (HCV) transplant patients,[5] similarly to Blasco et al.[6]

Garcia-Tsao and colleagues[1] acknowledge the need to expand histological criteria. Two studies have evaluated the parenchymal nodule size and the thickness of fibrous septa for substaging cirrhosis,[7,8] and they have demonstrated a relationship between the nodule size, septal thickness, and HVPG. However, this evaluation is imprecise because of nodules of different sizes and septa of different thicknesses are present in the same or different histological sections.

Thus, how can histological staging, including cirrhosis, be improved? We believe that a formal quantification of liver collagen is one answer to this question.

We have evaluated a new histological maker, the collagen proportionate area (CPA), by digital image analysis and have correlated it with HVPG.[9] CPA was superior to the Ishak stage and was independently associated by logistic regression with an HVPG $\geq$6 mm Hg (odds ratio = 1.206, 95% confidence interval = 1.094-1.331, $P < 0.001$) and an HVPG $\geq$10 mm Hg (i.e., clinically significant portal hypertension; odds ratio = 1.105, 95% confidence interval = 1.026-1.191, $P < 0.009$).

At the last American Association for the Study of Liver Diseases meeting, we presented the results for CPA measured by 1-year biopsy in 96 patients after liver transplantation for HCV, which predicted decompensation. CPA measurement was highly predictive with good sensitivity (90%) and specificity (97.8%) and was better than the Ishak stage or HVPG.[10] CPA and HVPG together correctly identified all but one patient who decompensated. Although these results seem to contrast with other results in abstract,[11] this may reflect methodological differences. In patients diagnosed with early or established cirrhosis histologically (Ishak stages 5 and 6, respectively), CPA was more discriminatory than HVPG and again predicted clinical outcome.

We also have evaluated the relationships between liver collagen (CPA), transient elastography (TE), HVPG, and Ishak stage in 45 HCV transplant patients. Univariately, CPA, Ishak stage, and TE were associated with portal hypertension (HVPG $\geq$6 mm Hg), whereas multivariately, CPA was the only independent factor (odds ratio = 1.377, 95% confidence interval = 1.137-1.169, $P = 0.001$), and this resulted in a better correlation with TE than HVPG.

As CPA is a continuous variable measuring only collagen and not inflammation, it probably represents a better histological index to act as a histological standard for TE or other noninvasive markers of fibrosis. CPA had a better association than the Ishak stage or TE with an HVPG $\geq$6 mm Hg and an HVPG $\geq$10 mm Hg.[12]

Our data strongly suggest that CPA is a histological variable that scores cirrhosis with a continuous scale and predicts clinical outcomes.

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References

1. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445-1449.
2. Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. Gut 2006; 55:569-578.
3. Armonis A, Patch D, Burroughs A. Hepatic venous pressure measurement: an old test as a new prognostic marker in cirrhosis? Hepatology 1997;25:245-248.
4. Burroughs AK, Groszmann R, Bosch J, Grace N, Garcia-Tsao G, Patch D, et al. Assessment of therapeutic benefit of antiviral therapy in chronic hepatitis C: is hepatic venous pressure gradient a better end point? Gut 2002;50:425-427.
5. Samonakis DN, Cholongitas E, Thalheimer U, Kalambokis G, Quaglia A, Triantos CK, et al. Hepatic venous pressure gradient to assess fibrosis and its progression after liver transplantation for HCV cirrhosis. Liver Transpl 2007;13:1305-1311.
6. Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilabert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. Hepatology 2006;43:492-499.
7. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis—a histological classification of the severity of cirrhosis. J Hepatol 2006;44:111-117.
8. Kutami R, Girgrah N, Wanless IR, Sniderman K, Wong FS, Sherman M, et al. The Lannec grading system for assessment of hepatic fibrosis: validation by correlation with wedged hepatic vein pressure and clinical features [Abstract]. Hepatology 2000;32(Part 1):407A.
9. Calvaruso V, Burroughs AK, Standish R, Manousou P, Grillo F, Leandro G, et al. Computer-assisted image analysis of liver collagen: relationship to Ishak scoring and hepatic venous pressure gradient. Hepatology 2009;49:1236-1244.
10. Manousou P, Burroughs AK, Isgró G, Calvaruso V, Luong TV, Tsochatzis E, et al. Computer assisted image analysis of liver collagen at one year biopsy can predict clinical outcome in HCV post LT patients [Abstract]. Hepatology 2009;50(Suppl):302A-303A.
11. Viola A, Garcia-Tsao G. Quantitative histological assessment in cirrhosis: septal thickness predicts clinical decompensation [Abstract]. J Hepatol 2009;50:S94.
12. Isgró G, Calvaruso V, Manousou P, Luong TV, Andreana L, Patch D, et al. Correlation of Ishak stage, transient elastography, HVPG and collagen proportionate area in HCV transplanted patients [Abstract]. Hepatology 2009;50(Suppl):481A-482A.

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