CORRESPONDENCE

Reduced Plasma Adiponectin in NASH: Central Obesity as an Underestimated Causative Risk Factor

To the Editor:

We read with interest the recent article on adiponectin in nonalcoholic steatohepatitis (NASH) by Hui et al.[1] The authors reported that plasma adiponectin levels (1) are reduced in patients with NASH and (2) are inversely correlated with the histologically assessed degree of necroinflammation. These observations are highly relevant and bear therapeutic potential for the treatment of NASH; however, we feel that a potentially important point regarding the underlying basis of reduced adiponectin in NASH is underestimated in this report. In a number of studies, plasma adiponectin is negatively associated with body fat mass.[2,3] Although body mass index and waist/hip ratio were given, Hui and colleagues did not provide a direct assessment of body fat mass.

We measured plasma adiponectin levels using enzyme-linked immunosorbent assay (B-Bridge International, San Jose, CA[4]) in 34 patients with a histological diagnosis of NASH and in 23 controls (all values are given as the mean $\pm$ SD) matched for age (46.9 $\pm$ 12.2 vs. 46.0 $\pm$ 13.5 years), sex (female/male: 23:11 vs. 15:8), body mass index (29.8 $\pm$ 5.2 vs. 28.1 $\pm$ 3.6 kg/m^2), and body fat mass (37.9% $\pm$ 10.0% vs. 37.4% $\pm$ 8.7%) as determined via bioelectrical impedance analysis.[5] Although body fat mass was identical, the waist-to-hip ratio as measure of central obesity was significantly higher in the subjects with NASH compared with controls (0.95 $\pm$ 0.09 vs. 0.88 $\pm$ 0.13, respectively; $P < .05$). In the study by Hui et al., the waist-to-hip ratio was also significantly higher in the patients presenting with NASH compared with the control group, despite having a similar body mass index. In our study population, plasma adiponectin was significantly decreased in patients with NASH compared with controls (6.0 $\pm$ 2.7 vs. 10.7 $\pm$ 5.1 μg/mL; $P < .001$), consistent with the report by Hui et al. Taken together, although the control group had exactly the same degree of obesity, the patients with NASH had a significantly altered body fat distribution toward central obesity and significantly lower plasma adiponectin levels.

Data in the literature indicate that different fat stores might have different metabolic and inflammatory activity and that central obesity, as indicated by a high waist-to-hip ratio, is associated with unfavorable factors.[6–8] Obesity is an established risk factor for the development of hepatic steatosis.[9] Based on our data and the literature, we propose that the transition toward a hepatic inflammatory response and the development of NASH within a fatty liver are dependent on a shift in body fat distribution. Increasing visceral obesity results in (1) increased production of proinflammatory cytokines and adipokines such as leptin, tumor necrosis factor α, and interleukin 6[8,10,11] and (2) decreased production of protective adipokines such as adiponectin.[8,12] This abnormal balance might ultimately lead to the clinical and histopathological occurence of NASH.

In conclusion, visceral obesity might be an important causative risk factor for NASH. Prospective multicenter studies with long-term follow-ups are necessary to further investigate the role of visceral obesity in the pathogenesis of NASH to identify patients at risk and thus provide early treatment for them.

Uwe J. F. Tietge
Hartmut H.-J. Schmidt
Tatjana Schütz
Patrizia Dippe
Herbert Lochs
Matthias Pirlich
Division of Gastroenterology, Hepatology, and Endocrinology, Department of Medicine, Charité Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

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Reply:

We thank Tietge and colleagues for their interest in our recent study on the role of adiponectin in the pathogenesis of nonalcoholic steatohepatitis (NASH).[1] They provide data to support our conclusion that hypoadiponectinemia is a key feature of NASH. In addition, Tietge and collegues draw attention to the possible role of central obesity in the pathogenesis of this condition. We clearly recognized that central obesity was a critical determinant of the adipokine levels as indicated in our conclusion that "hypoadiponectinemia and elevated HOMA-IR (insulin resistance by homeostasis model) . . .. . . may be one of the pathogenic links between central obesity and the development of necroinflammatory forms of NAFLD".[1] The focus of our study was to determine the alterations in adipokine levels in NASH and their relationship to the severity of histological changes. The possible role of visceral obesity as the causative factor for insulin resistance and hypoadiponectinemia has been established in previous studies[2-4] and this point was not further highlighted in our study.

Tietge et al. use waist-to-hip ratio as an indirect measure of visceral fat mass and demonstrate that subjects with NASH has a greater extent

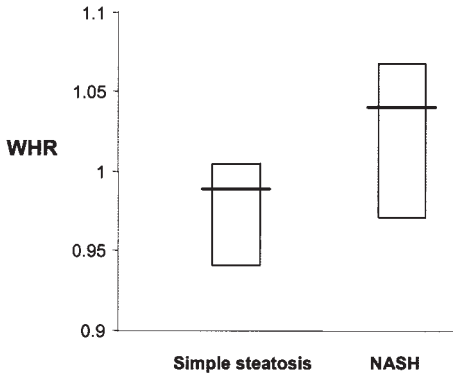

Fig. 1. Box-plot representation of waist-to-hip ratio (WHR) in subjects with nonalcoholic steatohepatitis (NASH) compared to those with simple steatosis matched by age, gender, body mass index, and body fat percent. The horizontal bar indicates the median values and 50% of values (*i.e,* between 25th and 75th percentiles) are within the box.

of visceral obesity compared to control subjects matched by percent body fat. Similar results have been published previously in a study which used single slice computed tomography (CT) to directly measure visceral obesity.[5] However, the comparison between subjects with NASH and matched controls does not justify the proposition by Tietge et al. that "transition towards a hepatic inflammatory response and the development of NASH within a fatty liver are dependent on a shift in body fat distribution". A more appropriate study to assess the role of central obesity in the development of the necroinflammatory response is to compare patients with NASH to those with simple steatosis who are matched by percent body fat. We measured body composition using dual energy x-ray absorptiometry in 37 of our 109 subjects (28 with NASH and 9 with simple steatosis).[6] The subjects with NASH were of similar age (47.2 ± 13.0 vs. 44.9 ± 14.6 years), gender proportion (male/female: 20/8 vs. 7/1), body mass index (31.1 ± 4.8 vs. 30.9 ± 4.0 kg/m^2), and percent body fat (35 ± 8 vs. 35 ± 9 %) compared with those with simple steatosis (results expressed as mean ± SD). Despite the similar degree of overall obesity, there was a trend toward increased central obesity in subjects with NASH compared to those with simple steatosis as indicated by the waist-to-hip ratio (WHR) (Fig. 1, $P = .1$, Mann-Whitney U test). These data support the hypothesis that visceral obesity may underlie the metabolic alterations which precipitate a necroinflammatory response in the fatty liver. Our findings need to be validated in a larger cohort. Direct measurement of visceral mass by computed tomography[7] or magnetic resonance imaging[8] will provide a more accurate assessment of the relationship between the fat compartments, the biochemical milieu and the histological features of NASH.

JASON M. HUI
JACOB GEORGE
Storr Liver Unit,
Westmead Millennium Institute,
Westmead Hospital,
Westmead, NSW 2145, Australia

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Preprocedure Coagulation Tests Are Unnecessary Before Abdominal Paracentesis in Emergency Departments

To the Editor:

We read with great interest the article of Grabau et al.[1] regarding performance of therapeutic abdominal paracentesis, because the authors highlight no significant procedure-related complications even in patients with marked thrombocytopenia or prolongation in the prothrombin time (PT) in an outpatient setting. We have launched a comparable study in an emergency setting and would like to share our results.

For a 1-year period starting in August 2003 in an emergency department of a tertiary center, a total of 186 abdominal paracenteses were carried out in 60 patients. The number of procedures carried out in a single patient ranged between 1 and 17. All patients underwent complete blood cell counts, biochemistries, and PT before the procedure. In the absence of a cutoff for coagulation parameters that would restrict paracentesis,[2] all patients were eligible. The emergency physicians performed the procedures using ultrasonography to define the puncture site in the outer-left lower abdomen and an 18-gauge aspirating catheter (Surflo, Terumo Corporation, Tokyo, Japan) using sterile technique. Their age (mean ± SD) was 59.0 ± 14.0 years. The underlying diseases were hepatocellular carcinoma in 46, viral-related liver cirrhosis in 107, alcoholic cirrhosis in 7, and other malignancies in 26. The status of Child classification of patients was A in 8, B in 81, and C in 97. The preprocedure mean international normalized ratio (INR) for PT was 1.6 ± 0.5 (range, 0.9-4.7), and the mean platelet count was 124 ± 103 $\times 10^3/\mu$L (range, 6-641 $\times 10^3/\mu$L). Details of the data are given in Table 1.

Table 1. Preprocedure Prothrombin Times and Platelet Counts, and Complications

	Diagnostic Paracentesis*, n	Therapeutic Paracentesis†, n	Complications, n
PT (INR)			
≤1.4	27	77	0
1.5–1.9	1	55	0
2.0–2.4	0	13	0
2.5–2.9	0	9	2
≥3.0	0	4	0
Platelet count ($\times 10^3/\mu$L)			
≥100	28	69	0
50–99	0	55	2
40–49	0	17	0
30–39	0	9	0
20–29	0	0	0
≤19	0	8	0

*The volume (mean ± SD) of ascites removed for diagnostic paracentesis (n = 28) was 157 ± 105 mL.

†The volume (mean ± SD) of ascites removed for therapeutic paracentesis (n = 158) was 3,020 ± 1,570 mL.

There were no procedure-related complications that required hospitalization, transfusions, or plasma volume expansion. Only two of 186 procedures (incidence, 1.1%; 95% CI, 0.3%-3.8%) were associated with minor complications in the same patient (incidence, 1.7%; 95% CI, 0.3%-8.9%) at different visits. One minor complication with removal of 1,200 mL of ascitic fluid for this 45-year-old male, a patient with hepatitis B virus-related cirrhosis, was local ecchymosis at the puncture site, with a platelet count of 81 $\times 10^3/\mu$L and an INR of 2.6. The diameter of ecchymosis was 3.5 cm. The other episode of cutaneous bleeding (estimated 10 mL) occurred with removal of 4,000 mL of ascitic fluid when he had a platelet count of 51 $\times 10^3/\mu$L and an INR of 2.9. It was promptly controlled within 10 minutes with local compression.

From our data, it appears that bleeding complications of abdominal paracentesis in an emergency department are rare, and even if present, appear to be very mild, regardless of preprocedure INR or platelet count. Considering the results of Grabau et al. in an outpatient setting, we propose such tests are unnecessary before abdominal paracentesis in an emergency setting. A limitation to the procedure is clinically evident fibrinolysis or disseminated intravascular coagulation.[3] Otherwise, our data should translate into the avoidance of unnecessary transfusion and related complications, cost savings, and shortening of the length of stay for patients in emergency departments.

CHIH-HAO LIN, M.D.[1]
SHYR-CHYR CHEN, M.D.[1]
PATRICK CHOW-IN KO, M.D.[1,2]
[1]*Department of Emergency Medicine*
National Taiwan University
Taipei, Republic of China
[2]*Division of Gastroenterology and Hepatology*
Department of Internal Medicine
National Taiwan University
Taipei, Republic of China

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A Challenge on the Use of the Words *Embryonic* and *Perinatal* in the Context of Biliary Atresia

To the Editor:

Zhang et al.[1] report an elegant study looking at the expression of a large number of genes and gene products in infants with biliary atresia, the main aim being to demonstrate gene or gene expression differences between two distinct clinical phenotypes. However, both the underlying general assumption and the specific nature of the patients in this study need to be challenged before one can accept the results as conclusive.

Use of the terms *embryonic* and *perinatal* in association with biliary atresia is widespread in the literature. Both terms imply an explicit assumption regarding the timing of the etiological cause; however, for a number of reasons this approach may be somewhat simplistic. The "perinatal" form of biliary atresia implies that there is destruction of an already fully formed biliary tree by a virus (presumably) at or around the time of birth. The two elements of this assumption are controversial. First, many viral studies in humans are not referenced in the article that are entirely negative but still perfectly valid.[2,3] Second, the assumption that the timing of an etiological insult is perinatal has little actual evidence to support it. Antenatally detected biliary atresia, although it represents a small proportion of most series (≈5%) and has an unusual biliary appearance (cystic), has implications on the timing of biliary atresia occurrence. In our recently reported series of 9 infants with biliary atresia, all occurrences were detected between 18 and 20 weeks' gestation, with 8 of 9 being nonsyndromic.[4] Furthermore, the key studies of Francoise Muller, who measured various gastrointestinal enzymes (specifically γ-glutamyltranspeptidase) in serial samples of amniotic fluid, have also shown that in those cases of nonsyndromic biliary atresia detected "incidentally," there was definite evidence of bile obstruction early in the second trimester.[5-7]

In the current study, the authors have chosen very unusual examples of biliary atresia and classified them as "embryonic." Infants with the embryonic form of biliary atresia typically have a constellation of extrahepatic anomalies characterized by splenic anomalies (100%), situs inversus (50%), preduodenal portal vein (60%), absence of the inferior vena cava (40%), and cardiac anomalies (50%) (all percentages are based on the King's College series, currently n = 50). We have used the term *biliary atresia splenic malformation syndrome*,[8] and others, *polysplenia*[9] or *polyasplenia syndrome* when describing such infants.

So why were the infants in Zhang's study exceptional? Of the 5 "embryonic" infants, only one was a typical example, with polysplenia and a preduodenal portal vein (infant 2). Infant 3 did not have a splenic anomaly but had other typical features (preduodenal portal vein, annular pancreas, and malrotation). Infant 5 had congenital cardiac abnormalities but only an interrupted inferior vena cava to suggest syndromic biliary atresia. Infant 1 was extremely abnormal and very atypical with diaphragmatic hernia, vaginovesicular fistula, cleft lip and palate, and so forth. Finally, the preterm infant (infant 4) had

absolutely no features to suggest an embryonic cause for its biliary atresia, certainly not with a patent ductus arteriosum or hydronephrosis.

Nevertheless, using these infants, the authors then extrapolate their molecular and genetic findings and conclusions based on the more usual syndromic variant described above. For example, they searched for and found abnormal expression of laterality genes (*i.e.*, *Sprouty-4 like*, *Zinc family member-3-heterotaxy-1*), when in fact not one of the "embryonic" infants had any clinical evidence of axial determination defects.

Searching for the roots of biliary atresia lies in unraveling the key molecular differences between the syndromic and nonsyndromic forms. The groups to be discriminated, however, need far better definition and a much higher degree of within-group homogeneity before we can speculate on any difference in their genes.

MARK DAVENPORT
Department of Paediatric Surgery
King's College Hospital
London, United Kingdom

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Reply:

We welcome Dr. Davenport's interest in our article reporting hepatic transcriptional signatures that differentiate two clinical phenotypes in infants with biliary atresia. His comments underscore two important issues that need to be carefully considered in any patient-based studies addressing the pathogenesis of biliary atresia: etiology and time of onset of disease. Both issues are interrelated and, when used in conjunction with the presence or absence of nonhepatic malformations, have been used in the literature to identify clinical forms. In regards to *etiology*, there are sufficient data to suggest that viral insults are a plausible etiology despite the variable identification of specific viruses in published studies from different populations of patients with biliary atresia. This is further supported by an experimental mouse model of rotavirus-induced biliary atresia, in which the virus is efficiently cleared from the liver after obstruction of the extrahepatic bile duct.[1,2] The inability to detect viral elements in these mice even when sensitive techniques are used (such as PCR) underscores the concept that a negative result does not rule out a previous infection by a virus, which may have triggered an inflammatory and obstructive injury to the bile ducts. Therefore, patient- and animal-based studies support the existence of a "perinatal" form of acquisition in a group of infants with biliary atresia, perhaps due to an infectious insult. The exact timing of the proposed viral insult is currently unknown.

Dr. Davenport's comments about the *time of onset of disease* and the use of the term "*embryonic*" to describe a group of patients included in our study highlight an important gap in our understanding of pathogenic mechanisms of disease and the need to develop a uniform system to classify clinical subtypes of biliary atresia. In regards to the *time of onset of disease*, although experimentally the administration of rotavirus to pregnant mice at term results in biliary obstruction in their offspring,[3] an association between a viral insult to the developing human fetus and the postnatal diagnosis of biliary atresia has not been fully established. However, the early onset of jaundice and the coexistence of congenital nonhepatic malformations in a subset of infants with biliary atresia imply, at least in part, a prenatal onset of disease. As described in the literature cited by Dr. Davenport, the high prevalence of unique malformations in these infants, especially splenic malformations and laterality defects, allows for the grouping of these patients into the biliary atresia–splenic malformation or polysplenia syndrome. However, the nomenclature to describe infants with biliary atresia presenting with other types of nonhepatic malformations is far from clear or uniformly accepted. For example, two additional phenotypic groups have been proposed based on the presence of associated anomalies that do not follow any recognizable syndromic pattern/sequence or the presence of intestinal malrotation and atresia; notably some of the abnormalities included minor cardiovascular and urogenital malformations.[4] These differences notwithstanding, common to all patients with nonhepatic malformations is the *coexistence of one or more congenital malformation*s. In this context, we applied the term "embryonic" to all five infants with biliary atresia who also had nonhepatic malformations. Despite the phenotypic heterogeneity among these infants, they shared unique transcriptional profiles, as demonstrated by the coordinated expression of regulatory genes and the overexpression of imprinted genes when compared to infants with biliary atresia without nonhepatic malformations (termed "perinatal").

Our experimental design and the limited number of subjects were not adequate to analyze the hepatic transcriptome in search of molecular signatures that are unique to subtypes of infants with biliary atresia and nonhepatic malformations, such as those with the biliary atresia–splenic malformation syndrome. These studies will need a population size that allows for much greater discriminatory (statistical) power of the gene expression profiling, and enable the testing of hypotheses relating to the expression of laterality genes in the subgroup of infants with laterality defects. We agree with Dr. Davenport that critical to these analyses is a rigorous phenotypic definition of clinical groups and a much higher degree of within-group homogeneity. When such a population is assembled, it will be equally important to use mathematical models to explore the existence of novel subtypes based on molecular signatures, to determine how they correlate with clinical phenotypes, and to explore their impact on long-term outcome.

JORGE A. BEZERRA, M.D.[1]
RONALD J. SOKOL, M.D.[2]
[1] *Cincinnati Children's Hospital Medical Center, Cincinnati, OH*
[2] *The Children's Hospital, Denver, CO*

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p18(INK4c) Expression in Hepatocellular Carcinoma

To the Editor:

Morishita and colleagues[1] reported an interesting study investigating the expression of the cell cycle inhibitor p18(INK4c). The authors demonstrated that loss of p18 expression occurred especially in lower-differentiated hepatocellular carcinomas (HCCs) and correlated with an unfavorable prognosis. A decreased expression in advanced tumor stages and a very similar prognostic role has been demonstrated in previous studies for p27(KIP1), but not for p21(CIP1/WAF1).[2,3] The association of a lack in p18 and p27 expression in human liver tumors reflects data gained in basic animal studies. In contrast to $p21^{-/-}$ mice, $p18^{-/-}$ and $p27^{-/-}$ mice display increased body size and develop the same tumors at a higher age.[4] The induction patterns of p18 and p27 messenger RNA in mouse embryonic development are strikingly similar.[5] We recently performed a study using knockout mice for p18, p21, p27, or p18/p21 and p18/p27 in combination.[6] In partial hepatectomy experiments, we demonstrated that the effect of a p18 knockout on hepatocyte cell cycle progression is similar to a p27 knockout, whereas it differs from a p21 knockout. The present study by Morishita and colleagues therefore highlights the relevance of observations made in the partial hepatectomy model for liver carcinogenesis in humans.

However, the authors suggest in their article that the loss of p18 in the development of HCC is mediated through an upregulation of cyclin-dependent kinase 4 (CDK4) activity. In our study, we showed that loss of p18 expression alone did not influence CDK4 activation after partial hepatectomy, whereas lack of p21 lead to an earlier activation of CDK4. This phenotype was enhanced in p18/p21 double knockout animals. Moreover, combined p18/p27 knockout mice displayed increased amounts of hepatocytes entering S phase after partial hepatectomy compared with the respective single knockouts.[6] Because p21 and p27 expression are frequently downregulated in HCC,[7] it remains unclear if the effect on CDK4 activity observed by Morishita and colleagues might be caused by a simultaneous loss of p18 and p21 or p27 expression. Although p18 single mutant mice develop liver tumors in a model of chemical carcinogenesis,[8] these tumors were not HCCs but hemangiosarcomas from the hepatic sinusoidal endothelial cells, suggesting that a single lack of p18 might not be sufficient for increased carcinogenesis in hepatocytes. Additionally, it is unclear why the authors observed changes in CDK4 but not CDK6 activity depending on the p18 status, whereas it was shown that p18 *in vivo* preferentially associates with CDK6.[9] Therefore, further studies should be conducted evaluating the expression status of p18, p21, and p27 in parallel to examine their functional collaboration in HCC development. Because mutations or increased promoter methylation appear not to be involved in the downregulation of p18 expression in HCC, an additional analysis of p21 and p27 expression might even reveal a functional dependency between these proteins with regard to their expression during liver carcinogenesis, as suggested previously for p16(INK4a) and p27.[10] A thorough understanding of the role of CDK inhibitors in hepatic cell cycle regulation may ultimately provide new insights into molecular hepatocarcinogenesis and may uncover new targets for therapeutic approaches.

TOM LUEDDE, M.D., PH.D.
FRANK TACKE, M.D., PH.D.
MICHAEL P. MANNS, M.D.
CHRISTIAN TRAUTWEIN, M.D.
Department of Gastroenterology, Hepatology, and Endocrinology
Hannover Medical School
Hannover, Germany

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Reply:

We appreciate the comments of Luedde et al.[1] We read the interesting article reported by Luedde et al.[2] In the partial hepatectomy (PH) experiments using knockout mice for various cyclin-dependent kinase (Cdk) inhibitors, the authors have shown that a loss of $p18^{INK4C}$ alone did not influence Cdk4 activity, but the lack of $p21^{CIP1/WAF1}$ led to Cdk 4 activation. On the other hand, we have reported that the kinase activity of Cdk4 was higher in $p18^{INK4C}$-negative hepatocellular carcinomas (HCCs) than in $p18^{INK4C}$-positive ones.[3] Based on the results, we concluded that $p18^{INK4C}$ expression might play an important role in the development of HCC through the upregulation of Cdk4 activity. These two reports appear to be contradictory. However, our experiments are different from the study of Leudde and colleagues. The reasons are as follows. Liver regeneration after PH reflects the proliferation of normal hepatocytes, and the process is completed after one week. Thus, changes induced by liver regeneration after PH are quite short, and are reversible. On the other hand, proliferation of HCC is a chronic and continuous process in transformed cells (cancer cells), and it is irreversible. Therefore, although the kinetic changes of cell cycle-related molecules in liver regeneration after PH provide important hints for the mechanism of hepatocarcinogenesis, they may not be directly applied to the proliferation of cancer cells. To solve this problem, it may be necessary to study Cdk 4 activity in carcinogen-induced HCC of $p18^{INK4C}$ knockout animals.

It has been shown that the expression of $p21^{CIP1/WAF1}$, $p27^{KIP1}$ and $p57^{KIP2}$ were frequently downregulated in HCC.[4,5] Therefore, we agree with the suggestion that the effect on Cdk4 activity in HCC may be caused by a simultaneous loss of $p18^{INK4C}$, $p21^{CIP1/WAF1}$ and/or $p27^{KIP2}$. In the future, it will be needed to determine what Cdk inhibitors influence Cdk4 activation in HCC. In addition, we would like to address the following point. Luedde et al. have stated that a loss of $p18^{INK4C}$ expression alone did not influence Cdk4 activation after PH. However, a clear band corresponding to the retinoblastoma protein phosphorylated at Ser-780 was visible 36 and 48 hours after PH in $p18^{INK4C}$ knockout animals (Fig. 5C in the text of Luedde et al.[2]). This result suggests that a loss of $p18^{INK4C}$ alone may also influence Cdk4 activation in liver regeneration after PH. We previously reported that the overexpression of Cdk4 was detected in HCC of Long Evans cinnamon rats and human.[6,7] In addition, Pascale et al.[8] have also demonstrated that the overexpression of cyclin D1/Cdk4 complex occurred in chemically induced HCC of Fischer 344 rats. Conversely, it has been shown that Cdk6 protein was not increased in HCC.[4,5] Therefore, we assume that the amount of Cdk4 (cyclin D/Cdk4) may be higher than that of Cdk 6 (cyclin D1/Cdk6), and $p18^{INK4C}$ may dominantly interact with Cdk4 rather than with Cdk6 in $p18^{INK4C}$-positive HCCs, suggesting that $p18^{INK4C}$ in HCC may contribute only to the up-regulation of Cdk4. Finally, expression levels of $p18^{INK4C}$, $p21^{CIP1/WAF1}$, $p27^{KIP1}$, $p57^{KIP2}$ and other Cdk inhibitors should be evaluated to examine their functional collaboration in the development of HCC.

TSUTOMU MASAKI, M.D.
ASAHIRO MORISHITA, M.D.
SHIGEKI KURIYAMA, M.D.
Third Department of Internal Medicine
Kagawa University School of Medicine
Kagawa, Japan

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Measurement of Hepatic Venous Pressure Gradient in Patients With Active Variceal Bleeding

To the Editor:

I read with interest the article on measurement of hepatic venous pressure gradient in patients with active variceal bleeding.[1] I would like to mention one therapeutic aspect in this article that I suggest is not appropriate. The authors randomized the patients with cirrhosis and active bleeding into two arms—injection sclerotherapy and band ligation—and measured the hepatic venous pressure gradient before and after the procedure until the 5th day of admission. They concluded that injection sclerotherapy had caused a sustained increase in hepatic venous pressure gradient, which is followed by a higher rebleeding rate. The authors did not administer any pharmacological treatment to the patients who exhibited signs and symptoms of acute variceal bleeding within 12 hours of admission.

I believe it is inappropriate to withhold vasoactive drugs from patients who experience active variceal bleeding. The authors claim that at the time they designed the study, endoscopic treatment was the treatment of choice for acute variceal bleeding.[2] However, in an American Association for the Study of Liver Diseases single-topic symposium in 1998, pharmacological treatment was established as an effective treatment for variceal bleeding.[3] Furthermore, D'Amico et al.[4] published an elegant meta-analysis in 1999 in which they concluded that pharmacological treatment should be started immediately even if variceal bleeding is suspected before endoscopic confirmation.

The present study was performed between 1998 and 2001, the period in which the pharmacological treatment consensus had already been accepted. I believe that researchers should either stop or modify a study when a consensus on treatment modalities is altered completely during the study period.

OSMAN CAVIT OZDOGAN, M.D.
Department of Gastroenterology
Liver Unit
Marmara University School of Medicine
Istanbul, Turkey

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Reply:

We are grateful to Dr. Ozdogan for his interest in our article aimed to investigate the possible influence of emergency endoscopic treatment on HVPG in patients with cirrhosis and with bleeding esophageal varices (BEV). We completely agree with him that the investigators should stop a trial if during the study period a consensus has been reached regarding the treatment modalities under evaluation. However, this does not appear to be the issue in our study. The author refers to a single topic symposium on portal hypertension and variceal bleeding reported in HEPATOLOGY in 1998. At that period there was consensus suggesting only that endoscopic measures are the first choice of treatment for the control of BEV. It is true that the metaanalyses of D'Amico et al. (1999)[1] and de Franchis and Primignani (1999)[2] favored the early administration of a vasoactive drug when variceal bleeding is suspected. However, their data were based only on two double blind controlled trials one of which suffered from difficulties in interpretation since the placebo group contained patients with more severe liver disease at randomization versus the treated group.[2,3] Later on, the question on the optimal role of vasoactive drugs was again brought out by an excellent review from Garcia-Tsao.[4] The author recommends endoscopic therapy as the therapy of choice for the management of acute variceal bleeding since it stops bleeding in 80%-90% of patients. The goal of vasoactive drugs would be the prevention of early rebleeding. Recently, Banares et al.[5] showed the superiority of combination therapy in achieving the 5-day haemostasis in BEV without, however, any improvement in mortality. Furthermore, D'Amico et al. (2003)[6] concluded that emergency sclerotherapy should not be performed as the first line treatment of BEV because vasoactive drugs achieve control of bleeding in 83% of patients and therefore, endoscopic therapy might be added only in pharmacological treatment failures. However, the definitions of the end points and the selection of trials included in the above metaanalysis have been seriously criticized.[7] Hence it is obvious than even in 2003 more trials were required in order to determine further potential advantages of combined therapy in the management of these patients. Therefore, our study which was conducted (1998-2001) under the guidelines of good clinical practice is absolutely documented according to the recommendations for the management of patients with BEV. As we have shown, in BEV endoscopic therapy increases HVPG which is sustained after sclerotherapy, but not band ligation, and this resulted in a higher rebleeding rate. Taking into consideration (1) the above results; (2) the available data suggesting that vasoactive drugs may reduce HVPG[8]; and (3) the safety, efficacy and easy of administration of these drugs compared to endotherapy,[6] we consider that the early administration of vasoactive drugs is mandatory in all patients with cirrhosis and with BEV. Therefore, in the forthcoming era of future trials, we believe that withholding vasoactive drugs in patients with BEV is not justified.

ALEC AVGERINOS[1,2]
JIANNIS VLACHOGIANNAKOS[1]
SPILIOS MANOLAKOPOULOS[1]
SOTIRIOS A. RAPTIS[2]
[1]2nd Department of Gastroenterology, Evangelismos Hospital
Athens, Greece
[2]2nd Department of Medicine Propaedeutic and Research Unit
Attikon University Hospital
Chaidari, Greece

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