ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2011 August 27; 3(8): 205-227

Baishideng Publishing Group
www.wjgnet.com

WJH World Journal of Hepatology

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

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WJH World Journal of Hepatology

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Monthly Volume 3 Number 8 August 27, 2011

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World Journal of Hepatology
Volume 3 Number 8 August 27, 2011

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a monthly, open-access, peer-reviewed journal supported by an editorial board of 573 experts in hepatology from 46 countries.

The major task of *WJH* is to report rapidly the most recent results in basic and clinical research on hepatology, including: liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology.

NAME OF JOURNAL
World Journal of Hepatology

LAUNCH DATE
October 31, 2009

SPONSOR
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PUBLISHING
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Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
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http://www.wjgnet.com

PUBLICATION DATE
August 27, 2011

ISSN
ISSN 1948-5182 (online)

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World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i8.205

World J Hepatol 2011 August 27; 3(8): 205-210
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: Current status

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Received: November 28, 2010 Revised: June 15, 2011
Accepted: July 28, 2011
Published online: August 27, 2011

Abstract

The treatment of choice for patients with severe alcoholic hepatitis (AH) is use of corticosteroids. Many randomized well designed studies have been reported from all over the world on the use of corticosteroids in the treatment of AH. However, the data on the efficacy of corticosteroids in these patients have been conflicting. Initial meta-analyses also failed to show beneficial effects of corticosteroids. Based on individual data meta-analysis showing clear benefit of corticosteroids amongst patients with severe AH (modified discriminant function of 32 or more), led American College of Gastroenterology to recommend use of corticosteroids as the first line treatment option amongst patients with severe AH. However, corticosteroids are relatively contraindicated amongst patients with severe AH and coexistent sepsis, gastrointestinal bleeding, and acute pancreatitis. These patients may be candidates for second line treatment with pentoxifylline. Further, specific treatment of AH with corticosteroids far from satisfactory with as many as 40%-50% of patients failing to respond to steroids, thus classified as non-responsive to steroids. The management of these patients is a continuing challenge for physicians. Better treatment modalities need to be developed for this group of patients in order to improve the outcome of patients with severe AH. This article describes at length the available trials on use of corticosteroids and pentoxifylline with their current status. Route of administration, dosage, adverse effects, and mechanisms of action of these two drugs are also discussed. Finally, an algorithm with clinical approach to management of patients who present with clinical syndrome of AH is described.

Key words: Corticosteroids; Pentoxifylline; Alcoholic hepatitis

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Singal AK, Walia I, Singal A, Soloway RD. Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: Current status. *World J Hepatol* 2011; 3(8): 205-210 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i8/205.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i8.205

INTRODUCTION

Patients with severe alcoholic hepatitis (AH) have a short-term mortality of about 40%-50%[1]. Therefore, these patients should be identified early and treated appropriately.

Two established specific agents for treating severe AH are corticosteroids and pentoxifylline.

CORTICOSTEROIDS

The choice for treating patients with established and diagnosed cases of severe AH is corticosteroids[1]. There have been 12 randomized placebo controlled trials (RCT) to assess the benefit of corticosteroids in AH patients (Table 1). Results from these RCTs, conducted during the last 40 years, have varied with the sample size, inclusion/exclusion criteria, disease severity, end-points, type of corticosteroid used and treatment duration. These studies have shown conflicting data on the benefit of steroids with only five studies showing a survival benefit (Table 1). Meta-analyses of RCTs provide the best evidence for efficacy. To date, four meta-analyses have been published on the efficacy of steroids in AH[2-5]. The latest Cochrane analysis concluded that there is no clear evidence that steroids are effective in the management of AH. The potential for bias is due to heterogeneous data[5]. However, the same meta-analyses concluded that steroids do have survival benefit for patients with severe AH (discriminant function index, DFI ⩾ 32)[5].

One of the means to tackle the issue of heterogeneity is to perform meta-analysis on the individual patient data from each study[6]. This had been performed earlier by Mathurin and colleagues from France where they analyzed individual patient data from 3 RCTs. The results of this meta-analysis showed that steroids have survival advantage for severe AH with 28 d survival of 85% among treated patients and 65% for patients receiving placebo (P = 0.001). This was also associated with improvement of liver function starting within the first week of starting the steroids[4].

Corticosteroids act by reducing inflammatory cytokines such as tumor necrosis factor-α (TNF-α), intercellular adhesion molecule 1, interlukin (IL)-6 and IL-8[7,8]. Inflammation is a major component of AH pathogenesis. In fact, in one study, peripheral white blood cell count > 5500/cm and the amount of polymorphonuclear leucocytic infiltration on the liver biopsy specimen were independent predictors for response and survival on steroid treatment[9].

Although, many agents have been used across different studies, prednisolone is preferred (but not demonstrated to be better) over prednisone as the latter requires conversion within the liver to its active form, prednisolone. The drug is given orally in a dose of 40-60 mg/d for a total duration of 4 wk. The treatment is then tapered over next 2-3 wk. If the patient is unable to take it orally due to nausea, vomiting or altered sensorium, an intravenous preparation such as methylprednisolone may be used until the patient is capable to take medication by mouth.

It is prudent to screen patients for any contraindication prior to starting steroids. One of the most important contraindications is the presence of infection which is fairly common among patients with severe AH. This used to be considered an absolute contraindication for steroids[10]. However, the latest data from France have shown that if a patient is adequately treated for an established infection, steroids can be safely started and even improve the outcome in these patients. In this study, all 246 patients studied prospectively were treated with steroids. Patients with infection (25% of the group) were treated adequately with antibiotics prior to starting steroids. Survival with steroids at 2 mo was similar, irrespective of the presence of infection prior to starting steroids (71% *vs* 72%, P = 0.99)[11].

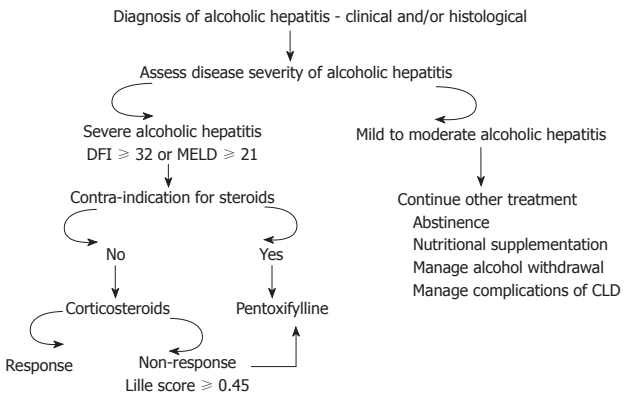

Figure 1 Specific treatment options for management of severe alcoholic hepatitis.

Other contra-indications are an active gastrointestinal bleeding, renal failure, acute pancreatitis, active tuberculosis, uncontrolled diabetes and psychosis. Patients should be assessed for response to steroids. It has been shown that a decrease in bilirubin at 1 wk (early change in bilirubin, ECBL) is a reliable and specific marker for response. Patients who achieved ECBL had a better survival at 6 mo compared to patients who did not achieve ECBL (98.3% *vs* 23%, P < 0.0001)[12]. Based on ECBL and other variables, French workers have derived a score (Lille score) based on the patient's age, serum albumin, ECBL, renal insufficiency and prothrombin time. Patients with a Lille score of ⩾ 0.45 are defined as non-responders to steroids (NRS). This score, with a cut off at 0.45, has an accuracy of 75% in predicting death at 3-6 mo[13]. Patients should also be screened for infective complications while on steroids. Occurrence of sepsis and infective complications while the patient is on steroids is a poor prognostic sign. A total of 57 patients developed infection after starting steroids which occurred more frequently among NRS than responders to steroids (42% *vs* 11%, P < 0.000001)[11]. Lille score was an independent predictor for the occurrence of infection after starting steroids.

PENTOXIFYLLINE

For patients who have contraindications to steroids, the second option for treatment is oral pentoxifylline (PTX), a phosphodiesterase and a possible TNF-α inhibitor[14] (Figure 1). The drug was first shown to have beneficial effect in AH in a double blind placebo controlled RCT.

Table 1 Randomized studies to assess corticosteroids for treatment of acute alcoholic hepatitis

Ref.	Study design	Sample size	Mean age (yr) males (%)	Drug schedule	Main outcome /findings	Secondary findings	Causes of death
Helman *et al*[19] 1971	Randomized controlled trial: 3 groups: severe, moderate without encephalopathy, and ambulatory	37 (20)	48 (32)	Prednisolone 40 mg/d × 4 wk	Mortality benefit seen only for group Ⅰ with severe alcoholic hepatitis (1/15 in treated *vs* 6/15 in untreated, $P < 0.01$)	No difference on histology at 4 wk and no effect on prevention to cirrhosis. Improved caloric intake was seen with steroids	Treated: (n = 1): liver failure. Untreated: (n = 6): hepatorenal syndrome (4), lower gastrointestinal bleed (1), variceal bleed (1)
Porter *et al*[20] 1971	Double blind Randomized controlled trial	20 (11)	45 (64)	6-Methylprednisolone 40 mg/d in 3 d × 10 d followed by oral if possible	Survival 45% *vs* 22%, P = NS	No effect on biochemical parameters	Treated: (n = 1): tuberculosis
Campra *et al*[21] 1973	Prospective controlled trial	45 (20)	43 (75)	Prednisone 0.5 mg/kg per day × 3 wk then 0.25 mg/kg per day × 3 wk	Survival was no different (36% *vs* 35%). Trend for improved survival with encephalopathy (P = 0.2)	No effect on biochemical parameters	Treated: (n = 7): hepatic failure. Untreated (n = 9): hepatic failure, GIB (5), renal failure (4)
Blitzer *et al*[22] 1977	Prospective double blind	28 (16)	48.4 (not reported)	Prednisolone 40 mg × 14 d then tapering × 2 wk	Overall mortality higher in the treated group	No effect on biochemical parameters. Prothrombin time higher in non-survivors	Treated: (n = 11): GIB, Hepatorenal syndrome, spontaneous bacterial peritonitis fungal infections (33% cases): disseminated aspergillosis, candidemia disclosed on autopsy; Untreated (31%): GIB, hepatorenal syndrome, spontaneous bacterial peritonitis, fungal infections
Shumaker *et al*[23] 1978	Randomized controlled trial	27 (12)	44 (75)	6 -methyl prednisolone 80 mg/d × 4-7 d *po*	No change in survival (50% *vs* 53%)	Patients with contraindication to steroids had higher mortality. Causes of death in the two groups were similar with > 50% dying from GIB	Treated: (n = 3): GIB, (n = 2): hepatic failure, (n = 1): acute pancreatitis. Untreated: (n = 3): GIB, (n = 2): sepsis, (n = 1): not reported
Maddrey *et al*[24] 1978	Randomized controlled trial	55	40 (60)	prednisolone 40 mg/d × 28-32 d	Improved short-term mortality but no effect on development of portal hypertension even in short term	Serum bilirubin > 20, prothrombin time > 8 s, prolonged and encephalopathy predicted mortality	Treated: (n = 2): hepatic failure, (n = 1): cytomegalic inclusion disease and pneumocystis carinii pneumonia mono-lineal esophagitis, (n = 2): severe liver disease. Untreated: (n = 5): hepatic failure, coma and hepatorenal syndrome
Lesesne *et al*[25] 1978	Randomized controlled trial	14 (7)	49 (not reported)	Prednisolone 40 mg/d × 30 d then 2 wk of tapering	Improved survival of the treated group. Improved nutrition alone is not a factor for better survival	Infrequent complications from steroids could be cause of death	Treated: (n = 2): hepatic failure and hepatorenal syndrome, (n = 1): hemorrhagic pancreatitis, (n = 1): pneumococcal pneumonia. Untreated: (n = 7): hepatic failure, (n = 4): GIB, (n = 3): hepatorenal syndrome, (n = 1): aspiration pneumonia, (n = 1): klebsiella bacteremia
Depew *et al*[26] 1980	Randomized controlled trial	28 (15)	49 (66)	Prednisolone 40 mg/d × 28 d then taper × 14 d	Mortality in both groups similar (53% *vs* 54%). LOS: 66 d with prednisolone and 56 d with placebo	No effect on biochemical parameters and complications higher with steroids	Treated: (n = 7): urinary tract infection, (n = 3) pneumonia, (n = 2) septicemia, (n = 1) perinephric abscess. Untreated: (n = 6): urinary tract infection, (n = 1) pneumonia

Ramond *et al*[27] 1992	Randomized controlled trial	61 (32)	48 (not reported)	prednisolone 40 mg/d × 28 d (IV if unable to take orally)	Improved survival at 6 mo (84% *vs* 45%, *P* = 0.002) irrespective of encephalopathy for patients with discriminant function > 32 (21/23 *vs* 10/19, *P* < 0.001)	Death in steroids group occurred early. Patients should be started on steroids while awaiting biopsy results	Treated: (*n* = 2): gastritis and GIB, (*n* = 2): septicemia lung. Untreated: (*n* = 16): GIB, ascites, variceal rupture, pancreatitis, (*n* = 1 each): septicemia
Theodossi *et al*[28] 1982	Randomized controlled trial	55 (27)	Not reported, 70% (treatment group), 30% (control group)	Methylprednisolone 1 g/d × 3 d	Patients survival predicted by: encephalopathy, discriminant function > 93, bilirubin 20 mg/dL, creatinine 3 mg/dL, and histological evidence of cirrhosis	Not reported	Treated: (*n* = 7): septicemia, (*n* = 2): pancreatitis. Untreated: (*n* = 6): septicemia, (*n* = 2): pancreatitis % mortality in patients of hepatic encephalopathy: 94% (treatment group) 69% (control group)
Richardet *et al*[29] 1993[1]	Randomized controlled trial	23 (12)	Not reported	Prednisolone 40 mg/d × 8 d	Tumor necrosis factor, interleukin-6, interleukin-8 decreased in treated group significantly at Day 8 from their baseline Day 0 levels	Not reported	Not reported

[1]Abstract publication. NS: Not significant; GIB: Gastrointestinal bleeding.

Table 2 Randomized controlled trial controlled trial studies to assess pentoxifylline for treatment of acute alcoholic hepatitis

Ref.	Sample size	Mean age (yr) males (%)	Drug schedule	Main outcome/findings	Secondary findings	Causes of death
McHutchison *et al*[30] 1991[1]	22 (12 pentoxifylline)	Not reported	Pentoxifylline 400 mg *tid* × 10 d	Renal impairment more with placebo (mean creatinine change -0.3 *vs* +2.1	No difference on other biochemical parameters. Plasma tumor necrosis factor increased in controls only. Survival trend better with pentoxifylline (3 deaths *vs* 1 death)	Not reported
Akriviadis *et al*[15] 2000	101 (49 pentoxifylline)	42 (71% males)	Pentoxifylline 400 mg *tid* × 28 d	Mortality during the admission 25% *vs* 46% (*P* = 0.037)	Age, creatinine at randomization, and pentoxifylline treatment predicted survival. Tumor necrosis factor levels were no different with pentoxifylline and placebo. However, among non-survivors tumor necrosis factor levels decreased more in pentoxifylline group	Hepatorenal syndrome: treated *vs* untreated (50% *vs* 92%, *P* = 0.009)
Paladugu *et al*[31] 2006[1]	30 (14)	50 (100%)	Pentoxifylline	Mortality at 28 d: 29% *vs* 46% (*P* = 0.09). Time to death 21 d *vs* 18 d (*P* = 0.041)	Tumor necrosis factor levels unchanged in both groups	Hepatorenal syndrome: treated *vs* untreated (50% *vs* 86%, *P* = 0.1)
Sidhu *et al*[32] 2006[1]	50	Not reported	Pentoxifylline 400 mg *tid* × 28 d	Mortality at 28 d (24% *vs* 40%, *P* = NS)	Pentoxifylline reduced creatinine, tumor necrosis factor, discriminant function index, prothrombin time	Hepatorenal syndrome: treated *vs* untreated (83% *vs* 60%)
Lebrec *et al*[33] 2007[1]	132	Not reported	Pentoxifylline	Mortality at 2 mo (14% *vs* 16%, *P* = 0.77) and at 6 mo (27% *vs* 31%, *P* = 0.3) were similar	No difference for serious adverse effects between the 2 groups. Subgroup with renal dysfunction also did not get benefit with pentoxifylline	Not reported

[1]Abstract publication.

The study showed survival benefit at 1 mo with the use of PTX compared to placebo (76% *vs* 54%)[15]. This benefit was attributed mainly to the prevention of the hepatorenal syndrome (HRS) among patients treated with PTX as compared to placebo (50% *vs* 92%, *P* < 0.05)[15]. Later, many studies (reported as abstracts) confirmed this observation of beneficial effect of PTX in the prevention of HRS (Table 2). A study published recently comparing steroids to PTX showed superiority of PTX in the treatment of AH patients with better survival rate at 3 mo (85% *vs* 65%, *P* = 0.04)[16]. This was again mainly due to prevention of HRS by PTX (6 of 34 patients receiving steroids developed HRS compared to none of 34 receiving PTX)[16]. However, the latest Cochrane systematic review of 5 RCTs (4 reported as abstracts) concluded that there is not enough evidence for survival benefit of PTX in the treatment of AH. However, the problem with these studies is a small sample size. Further, four of these

five studies are reported as abstracts[17].

The question of whether PTX is a salvage option for patients with NRS was answered by a study in which patients were identified as NRS at 1 wk (Lille score ⩾ 0.45) and randomized to PTX or placebo. Steroids were continued in both the groups for 28 d[18]. The use of additional PTX failed to demonstrate survival advantage at 2 mo (36% *vs* 31%, $P > 0.05$). Further, there was no benefit shown on the biochemical parameters. Clearly, PTX was not shown to be an option for patients with NRS[18]. However, the drug has not been studied in patients with NRS without additional steroids. Since patients with NRS are prone to develop infectious complications, this might have abrogated the benefit of PTX. Occurrence of infective complications and/or sepsis as cause of death was not reported in this study. Although the evidence for efficacy of PTX for severe AH is weak, this drug may be a second line option and is worth considering until newer and more effective agents are developed.

PTX is given orally at a dose of 400 mg three times a day for a total duration of 28 d. Although an anti-TNF agent, the TNF levels were not shown to be different among patients receiving PTX and those receiving placebo[15]. The exact mechanism of action of PTX is not entirely clear. Neutralization of TNF-α by PTX may explain the protective effect of this drug on HRS although the exact mechanism is not clear.

REFERENCES

1 **Lucey MR**, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; **360**: 2758-2769

2 **Daures JP**, Peray P, Bories P, Blanc P, Yousfi A, Michel H, Gremy F. [Corticoid therapy in the treatment of acute alcoholic hepatitis. Results of a meta-analysis]. *Gastroenterol Clin Biol* 1991; **15**: 223-228

3 **Imperiale TF**, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. *Ann Intern Med* 1990; **113**: 299-307

4 **Mathurin P**, Mendenhall CL, Carithers RL, Ramond MJ, Maddrey WC, Garstide P, Rueff B, Naveau S, Chaput JC, Poynard T. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002; **36**: 480-487

5 **Rambaldi A**, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis--a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. *Aliment Pharmacol Ther* 2008; **27**: 1167-1178

6 **Sutton AJ**, Higgins JP. Recent developments in meta-analysis. *Stat Med* 2008; **27**: 625-650

7 **Spahr L**, Rubbia-Brandt L, Pugin J, Giostra E, Frossard JL, Borisch B, Hadengue A. Rapid changes in alcoholic hepatitis histology under steroids: correlation with soluble intercellular adhesion molecule-1 in hepatic venous blood. *J Hepatol* 2001; **35**: 582-589

8 **Taïeb J**, Mathurin P, Elbim C, Cluzel P, Arce-Vicioso M, Bernard B, Opolon P, Gougerot-Pocidalo MA, Poynard T, Chollet-Martin S. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. *J Hepatol* 2000; **32**: 579-586

9 **Mathurin P**, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, Benhamou JP, Chaput JC, Rueff B, Poynard T. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. *Gastroenterology* 1996; **110**: 1847-1853

10 **McCullough AJ**, O'Connor JF. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**: 2022-2036

11 **Louvet A**, Wartel F, Castel H, Dharancy S, Hollebecque A, Canva-Delcambre V, Deltenre P, Mathurin P. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. *Gastroenterology* 2009; **137**: 541-548

12 **Mathurin P**, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, Valla D, Poupon R, Chaput JC, Naveau S. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. *Hepatology* 2003; **38**: 1363-1369

13 **Louvet A**, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; **45**: 1348-1354

14 **Reuter BK**, Wallace JL. Phosphodiesterase inhibitors prevent NSAID enteropathy independently of effects on TNF-alpha release. *Am J Physiol* 1999; **277**: G847-G854

15 **Akriviadis E**, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119**: 1637-1648

16 **De BK**, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. *World J Gastroenterol* 2009; **15**: 1613-1619

17 **Whitfield K**, Rambaldi A, Wetterslev J, Gluud C. Pentoxifylline for alcoholic hepatitis. *Cochrane Database Syst Rev* 2009; CD007339

18 **Louvet A**, Diaz E, Dharancy S, Coevoet H, Texier F, Thévenot T, Deltenre P, Canva V, Plane C, Mathurin P. Early switch to pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids. *J Hepatol* 2008; **48**: 465-470

19 **Helman RA**, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. *Ann Intern Med* 1971; **74**: 311-321

20 **Porter HP**, Simon FR, Pope CE, Volwiler W, Fenster LF. Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. *N Engl J Med* 1971; **284**: 1350-1355

21 **Campra JL**, Hamlin EM, Kirshbaum RJ, Olivier M, Redeker AG, Reynolds TB. Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. *Ann Intern Med* 1973; **79**: 625-631

22 **Blitzer BL**, Mutchnick MG, Joshi PH, Phillips MM, Fessel JM, Conn HO. Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. *Am J Dig Dis* 1977; **22**: 477-484

23 **Shumaker JB**, Resnick RH, Galambos JT, Makopour H, Iber FL. A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. *Am J Gastroenterol* 1978; **69**: 443-449

24 **Maddrey WC**, Boitnott JK, Bedine MS, Weber FL, Mezey E, White RI. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193-199

25 **Lesesne HR**, Bozymski EM, Fallon HJ. Treatment of alcoholic hepatitis with encephalopathy. Comparison of prednisolone with caloric supplements. *Gastroenterology* 1978; **74**: 169-173

26 **Depew W**, Boyer T, Omata M, Redeker A, Reynolds T.

Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. *Gastroenterology* 1980; **78**: 524-529
27 **Ramond MJ**, Poynard T, Rueff B, Mathurin P, Théodore C, Chaput JC, Benhamou JP. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; **326**: 507-512
28 **Theodossi A**, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. *Gut* 1982; **23**: 75-79
29 **Richardet JP**, Dehoux M, Mal F. Influence of corticosteroids (CS) on plasma cytokines concentrations in patients with severe alcoholic hepatitis (HA): results of a randomized study. *Hepatology* 1993; **18**: S75
30 **McHutchison JG**, Draguesku RB. Pentoxifylline may prevent renal impairment (hepatorenal syndrome) in severe acute alcoholic hepatitis. *Hepatology* 1991; **14**: 96A
31 **Paladugu H**, Sawant P, Dalvi L, Kudalkar J. Role of pentoxifylline in treatment of severe acute alcoholic hepatitis - a randomized controlled trial. *J Gastrenterol Hepatol* 2006; **21**: A459
32 **Sidhu S**, Singla M, Bhatia KL. Pentoxifylline reduces disease severity and prevents renal impairment in severe acute alcoholic hepatitis: a double blind, placebo controlled trial. *Hepatology* 2006; **44** Suppl 1: 373A–374A
33 **Lebrec D**, Dominique T, Oberti F, Perarnau JM, Condat B, Barraud H, Saliba F, Carbonell N, Renard P, Ramond MJ, Moreau R, Poynard T. Pentoxifylline for the treatment of patients with advanced cirrhosis. A randomized, placebo-controlled, double-blind trial. *Hepatology* 2007; **46** Suppl 1: 249A-250A

S- Editor Zhang SJ **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i8.211

World J Hepatol 2011 August 27; 3(8): 211-214
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Recent and currently emerging medical treatment options for the treatment of alcoholic hepatitis

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Received: November 26, 2011 Revised: June 13, 2011
Accepted: July 15, 2011
Published online: August 27, 2011

Abstract

Patients with severe alcoholic hepatitis (AH) need to be treated with specific treatment for better outcome. Currently available specific treatment modalities are use of corticosteroids or pentoxifylline. However, the response rate to these drugs is only about 50%-60%. Hence, there is an urgent need for better and more effective treatment options. Tumor necrosis factor plays an important role in the pathogenesis of AH. However, agents blocking the action of tumor necrosis factor have not been found to be effective. Rather the randomized studies evaluating these agents showed an adverse effect and more infections in treated patients. Critical role of tumor necrosis factor in hepatic regeneration explaining this contrast is discussed. Oxidative stress and inflammation derived from gut bacteria ate two main components in the pathogenesis of AH laying foundation for the role of antioxidants, probiotics, and antibiotics in the management of AH. This article reviews the current data and status of these newer agents for the treatment of AH. Of the various options available, Vitamin E and N-acetylcysteine (NAC) have shown great promise for clinical use as adjunct to corticosteroids. With these encouraging data, future well designed studies are suggested to assess Vitamin E and NAC before their routine use in clinical practice in the management of AH.

Key words: Alcoholic hepatitis; Tumor necrosis factor-α inhibitors; Infliximab; Etanercept; Antioxidants; Probiotics; Rifaximin; Betaine; Granulocytapheresis

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Reep GL, Soloway RD. Recent and currently emerging medical treatment options for the treatment of alcoholic hepatitis. *World J Hepatol* 2011; 3(8): 211-214 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i8/211.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i8.211

AGENTS WHICH BLOCK TUMOR NECROSIS FACTOR-α

Tumor necrosis factor-α (TNF-α) is involved with cytotoxicity, leukocyte activation, inflammatory cytokines and other aspects of the immune response[1]. Alcohol-induced stress leads to increased TNF-α production[2]. Therefore, TNF-α was studied as a target for therapeutic intervention. Two currently available TNF-α inhibitors, infliximab and etanercept, have been evaluated as possible treatments for alcoholic hepatitis (AH). A pilot study of infliximab in 2002 examined 20 patients with biopsy-proven, severe AH (Maddrey's discriminant function

score ⩾ 32). Patients were treated with 28 d of prednisone (40 mg/d) and a single dose of either infliximab (5 mg/kg iv) or placebo on day 0. At day 28, Maddrey's score was significantly improved in the infliximab group (39 to 12, $P < 0.05$) but not in the placebo group (44 to 22, $P > 0.05$). Infliximab infusions were well-tolerated[3]. A later open-label trial evaluated 19 patients with severe AH who were treated with infliximab monotherapy (single dose of 5 mg/kg iv). Significant improvement in median values of Maddrey's Discriminant Function at 1 mo (38 *vs* baseline of 66, $P = 0.002$) and at 2 mo (28 *vs* baseline of 66, $P = 0.006$) was shown with 1 and 2 mo survival of 89% and 68%, respectively.

However 5 (26%) patients developed infection and two subsequently died[4]. Another study, a double-blind randomized controlled trial (RCT), compared 3 groups of patients: infliximab, prednisolone and infliximab, prednisolone and placebo. Within 2 mo, 7 patients in the infliximab group and 3 from the placebo group died and the study was stopped prematurely. The frequency of severe infections was higher in the infliximab group. The authors concluded that infliximab may actually be harmful due to the increased infection risk[5].

Etanercept, another anti-TNF agent, was studied in a pilot study on 13 patients with moderate or severe AH. Etanercept was given in a loading dose on day 1 followed by 25 mg subcutaneously on days 4, 8 and 12. The 30 d survival rate was 92% but several significant adverse events were noted (infection, hepatorenal decompensation, gastrointestinal bleeding) which required premature discontinuation of etanercept therapy in 23% of patients[6]. A double-blinded RCT of 48 patients with moderate to severe AH compared a 3 wk course of etanercept (25 mg on days 1, 4, 8, 11, 15 and 18) with placebo. Steroid or pentoxifylline use was not allowed in this study. Mortality rates at 1 mo were similar between etanercept and placebo (36.4% and 22.7%; odds ratio = 1.8, 95% CI: 0.5-6.5). However, mortality at 6 mo was significantly higher for etanercept as compared to placebo (58% *vs* 23%, $P = 0.017$). Worse outcome with the study drug was due to a higher rate of serious infections in the etanercept group (34.6% *vs* 9.1%, $P = 0.04$)[7]. In summary, TNF-α inhibitors are not effective agents for treating AH and pose a risk of serious infections.

ANTIOXIDANTS

Oxidative stress (OS) is a strong component of AH and the existence of OS markers has been consistently shown[8,9]. Antioxidants such as vitamin E, N-acetylcysteine (NAC) have been tried as adjuvant treatment option for patients with severe AH.

An open label RCT by Phillips *et al*[10] examined 101 patients with severe AH, comparing prednisone to an antioxidant cocktail over a 4 wk treatment period. Mortality at 1 mo was lower with steroids compared to antioxidants (30% *vs* 46%, $P = 0.05$). However, mortality was similar at 1 year. More infections occurred with the antioxidant group but culture proven infection was more frequent in the steroid group[10]. In another RCT, 70 patients with severe AH were randomized, based on 4 wk of steroid use, to receive either a combination of antioxidants (including NAC) for 6 mo or no treatment. Survival at 6 mo was similar in the two groups (53% *vs* 56%, $P = 0.7$) and was also independent of the prior steroid use[11]. Another study evaluated 51 patients with AH who received daily supplementation with 1000 mg of vitamin E and showed improvement in serum hyaluronic acid levels, but no effect was seen on liver function or 1 year survival[12]. A recent RCT from France on 174 patients with AH compared steroids alone to steroids with intravenous NAC given over 4 wk. Mortality at 2 mo was lower in the patients who received steroids and NAC (15% *vs* 33%, $P = 0.007$). Similarly, complication rate at 6 mo was lower in the group receiving steroids and NAC (19% *vs* 42%, $P = 0.001$)[13]. In summary, these data indicate that antioxidants show some promise in the treatment of AH; however, further studies are needed to confirm these findings before their routine use in clinical practice.

PROBIOTICS AND ANTIBIOTICS

Several studies have shown that patients with liver disease have abnormal bowel flora overgrowth and thus probiotics, which help to restore normal bowel flora, have been proposed as a possible treatment for alcoholic liver disease[14,15]. A prospective pilot study randomized 66 patients with alcoholic psychosis to receive either a 5 d course of probiotics (Bifidobacterium or Lactobacillus) or placebo. Compared to controls, all subjects initially had decreased levels of Bifidobacterium and Lactobacillus and significantly elevated ALT, AST and GGT levels. After treatment, the subjects who received probiotics had significantly increased levels of Bifidobacterium and Lactobacillus and decreased liver enzyme levels compared to patients receiving placebo[16]. Another open-label study compared 12 alcoholic cirrhotics who received *Lactobacillus* probiotics for 4 wk to healthy controls. Baseline neutrophil phagocytic capacity in the experimental group was significantly lower compared to healthy controls (73% *vs* 98%, $P < 0.05$). This normalized at the end of the study ($P < 0.05$). *Ex vivo* endotoxin-stimulated levels of soluble TNF-receptor-1, soluble TNF-receptor-2 and interleukin-10 were also significantly lower at the end of the study ($P < 0.05$)[17].

Increased bowel permeability and elevated endotoxin levels are also now being considered as a target for antibiotic therapy. Rifaximin, a derivative of rifamycin with low systemic absorption and broad-spectrum activity against gastrointestinal tract micro-organisms that has been previously used to treat hepatic encephalopathy, is now being studied with regards to improving liver function in alcoholic cirrhosis[18]. A recent study evaluated endotoxin levels and hepatic vein portal gradients (HVPG)

in 30 patients who received a 28 d course of rifaximin. Median plasma endotoxin levels decreased significantly after rifaximin administration both in systemic (1.45 *vs* 0.7, $P < 0.0001$) and splanchnic circulation (1.8 *vs* 0.8, $P < 0.0001$). Median HVPG also decreased from 18 mmHg on day 0 to 14.7 mmHg on day 29 ($P < 0.0001$). Overall, the HVPG decreased in 23, remained stable in 2 and increased in 3 after intestinal decontamination with rifaximin[19]. These findings are in contrast to earlier studies on norfloxacin that showed reduction in serum endotoxin concentrations and partial reversal of hyperdynamic circulatory state in cirrhotics with no significant change on HVPG[20,21].

MISCELLANEOUS TREATMENT MODALITIES

Betaine, a naturally-occurring antioxidant and methionine metabolite, was evaluated in a case report of a 40-year-old female who developed recurrent steatohepatitis due to continued alcohol consumption following liver transplantation. The patient was treated with 10 mg of betaine orally twice daily and subsequent liver biopsies at 6 and 12 mo showed a significant improvement in hepatic steatosis as well as normalization of liver function[22]. Further studies are needed to see if this treatment would show some benefit in AH as well.

Another treatment option which has been tried is granulocytapheresis, a technique that uses an extracorporeal absorptive mechanism to remove up to 60% of activated granulocytes and monocytes from circulating blood and thereby reduces levels of circulating proinflammatory cytokines. This is based on the existence of qualitative functional defects of neutrophils in patients with AH[23,24]. In a case series on 6 patients with severe AH (5 of whom were corticosteroid non responders), use of granulocytapheresis did not provide any benefit. All patients tolerated the procedure without hemodynamic compromise or other complications; however, all but one of the patients died within a month of granulocytapheresis treatment. The sole survivor was the corticosteroid responder in the group[25].

In summary, currently corticosteroids and pentoxifylline remain the mainstay for treating AH. However, there is a need for newer, more efficacious agents to improve the outcome of patients who fail to respond to first line agents. Vitamin E and NAC have shown encouraging data in small studies and need to be explored further in larger trials as adjunctive treatment option for treating severe AH.

REFERENCES

1 **Strieter RM**, Kunkel SL, Bone RC. Role of tumor necrosis factor-alpha in disease states and inflammation. *Crit Care Med* 1993; **21**: S447-S463

2 **Maher JJ**. Cytokines: overview. *Semin Liver Dis* 1999; **19**: 109-115

3 **Spahr L**, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, Fischer M, Egger H, Hadengue A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002; **37**: 448-455

4 **Sharma P**, Kumar A, Sharma BC, Sarin SK. Infliximab monotherapy for severe alcoholic hepatitis and predictors of survival: an open label trial. *J Hepatol* 2009; **50**: 584-591

5 **Naveau S**, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, Oberti F, Broët P, Emilie D. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004; **39**: 1390-1397

6 **Menon KV**, Stadheim L, Kamath PS, Wiesner RH, Gores GJ, Peine CJ, Shah V. A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis. *Am J Gastroenterol* 2004; **99**: 255-260

7 **Boetticher NC**, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, Boardman L, Gores GJ, Harmsen WS, McClain CJ, Kamath PS, Shah VH. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology* 2008; **135**: 1953-1960

8 **Dey A**, Cederbaum AI. Alcohol and oxidative liver injury. *Hepatology* 2006; **43**: S63-S74

9 **Loguercio C**, Federico A. Oxidative stress in viral and alcoholic hepatitis. *Free Radic Biol Med* 2003; **34**: 1-10

10 **Phillips M**, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. *J Hepatol* 2006; **44**: 784-790

11 **Stewart S**, Prince M, Bassendine M, Hudson M, James O, Jones D, Record C, Day CP. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. *J Hepatol* 2007; **47**: 277-283

12 **Mezey E**, Potter JJ, Rennie-Tankersley L, Caballeria J, Pares A. A randomized placebo controlled trial of vitamin E for alcoholic hepatitis. *J Hepatol* 2004; **40**: 40-46

13 **Ngyen-Khac E**, Thevenot T, Piquet MA, Benferhat S, Hezam A, Goria O, Chatelain D, Tramier B, Dewaele F, Grhib S, Rudler M, Carbonell N, Tossou H, Bental A, Bernard-Chaber B, Dupas JL. Treatment of severe acute alcoholic hepatitis (AAH) with cortioids plus N-acetylcysteine (C+NAC) versus corticoids alone (C): a multicenter randomized controlled trial [Abstract]. *Hepatology* 2009; **50**: 346A

14 **Liu Q**, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Hepatology* 2004; **39**: 1441-1449

15 **Zhao HY**, Wang HJ, Lu Z, Xu SZ. Intestinal microflora in patients with liver cirrhosis. *Chin J Dig Dis* 2004; **5**: 64-67

16 **Kirpich IA**, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, Sidorov PI, Bazhukova TA, Soloviev AG, Barve SS, McClain CJ, Cave M. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. *Alcohol* 2008; **42**: 675-682

17 **Stadlbauer V**, Mookerjee RP, Hodges S, Wright GA, Davies NA, Jalan R. Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. *J Hepatol* 2008; **48**: 945-951

18 **Gillis JC**, Brogden RN. Rifaximin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential in conditions mediated by gastrointestinal bacteria. *Drugs* 1995; **49**: 467-484

19 **Vlachogiannakos J**, Saveriadis AS, Viazis N, Theodoropoulos I, Foudoulis K, Manolakopoulos S, Raptis S, Karamanolis DG. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009; **29**: 992-999

20 **Albillos A**, de la Hera A, González M, Moya JL, Calleja JL, Monserrat J, Ruiz-del-Arbol L, Alvarez-Mon M. Increased

lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology* 2003; **37**: 208-217

21 **Rasaratnam B**, Kaye D, Jennings G, Dudley F, Chin-Dusting J. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis. A randomized trial. *Ann Intern Med* 2003; **139**: 186-193

22 **Samara K**, Liu C, Soldevila-Pico C, Nelson DR, Abdelmalek MF. Betaine resolves severe alcohol-induced hepatitis and steatosis following liver transplantation. *Dig Dis Sci* 2006; **51**: 1226-1229

23 **Jaeschke H**. Neutrophil-mediated tissue injury in alcoholic hepatitis. *Alcohol* 2002; **27**: 23-27

24 **Jaeschke H**. Cellular adhesion molecules: regulation and functional significance in the pathogenesis of liver diseases. *Am J Physiol* 1997; **273**: G602-G611

25 **Morris JM**, Dickson S, Neilson M, Hodgins P, Forrest EH. Granulocytapheresis in the treatment of severe alcoholic hepatitis: a case series. *Eur J Gastroenterol Hepatol* 2010; **22**: 457-460

S- Editor Zhang SJ **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i8.215

World J Hepatol 2011 August 27; 3(8): 215-218
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

Liver transplantation in acute alcoholic hepatitis: Current status and future development

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Received: November 26, 2011 Revised: June 13, 2011
Accepted: July 15, 2011
Published online: August 27, 2011

Abstract

Acute alcoholic hepatitis (AH) is a distinct clinical entity amongst patients with chronic alcohol abuse. Patients with severe AH are at risk of dying in about 20%-25% cases despite specific treatment with corticosteroids and/or pentoxifylline. Clearly, a need for an additional more effective treatment option is unmet currently. Liver transplantation (LT), a definitive treatment option for alcoholic cirrhosis requires 6 mo abstinence. However, this rule cannot be applied to patients with AH as these patients are actively drinking prior to their presentation. Shortage of donors, ethical issues, and fear of recidivism after transplantation with less than 6 mo pretransplant abstinence are some of the reasons behind this rule of 6 mo of abstinence and hesitancy of transplanting patients with AH. These issues are debated at length in this manuscript. Further, retrospective studies have shown that patients undergoing transplantation for alcoholic cirrhosis and having histological changes of AH have been shown to fare as well when compared to patients without these histological changes. Recently, French workers have reported a case matched prospective study showing encouraging data on the usefulness of LT for patients who are non-responders to corticosteroid and/or pentoxifylline therapy. Future studies are needed to identify patients with severe AH who are going to benefit most with LT. In the light of emerging data on the efficacy of LT in improving survival of patients with severe acute AH who do not respond to corticosteroids, the time is ripe to re-evaluate our policy of LT in patients with AH.

Key words: Alcoholic hepatitis; Liver transplantation; Recidivism; Alcohol abstinence

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Singal AK, Duchini A. Liver transplantation in acute alcoholic hepatitis: Current status and future development. *World J Hepatol* 2011; 3(8): 215-218 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i8/215.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i8.215

NEED FOR LIVER TRANSPLANTATION IN ALCOHOLIC HEPATITIS

Acute alcoholic hepatitis (AH) is a distinct clinical syndrome that manifests as jaundice, abdominal pain, fever and acute hepatic decompensation of variable degrees depending on the severity of the disease, and may commonly be associated with underlying chronic liver disease[1]. It is caused by excessive alcohol consumption of prolonged duration which is invariably heavy and increased in the last few weeks to months prior to presentation[1]. Patients with mild to moderate AH may respond to conservative management and abstinence. However, patients with severe disease (discriminant function index or Maddrey score of $\geqslant$ 32) have an overall mortality of

about 40% within 6 mo[1]. Current available treatment options are corticosteroids and pentoxifylline but have limited efficacy, with a survival benefit of only around 50%[2,3]. Clearly, there is a need for more effective and definitive treatment options in order to improve prognosis and outcome of patients with severe AH.

CURRENT STATUS OF LIVER TRANSPLANTATION IN AH

Liver transplantation (LT) is a definitive treatment option for patients with end-stage liver disease who have > 10% risk of dying within 1 year. LT is an accepted treatment modality for patients with alcohol related chronic liver disease (ALD). The outcome after LT for ALD is as good as for other causes of liver disease[4]. However, LT as a treatment option for patients with severe AH remains controversial despite the fact that it is an established treatment option for most etiologies of acute liver failure (ALF)[1]. Many issues preclude physicians and transplant hepatologists to uniformly adopt this treatment modality for this group of acutely sick patients. These issues are related to (1) ethical concerns of transplanting patients with active alcohol abuse; (2) lack of applicability of 6 mo abstinence rule to these patients as by definition AH occurs among people who are currently actively drinking until at least a few weeks prior to presentation; and (3) risk of recidivism to alcohol drinking after LT that affects the graft and patient survival.

Ethical concerns and issues

One of the major ethical concerns is a shortage of organs for LT. The public opinion about a patient who is actively abusing alcohol is that this problem is self-inflicted by the patient and should be his or her own responsibility[5]. Why should the liver be given to someone who has reached this disease stage which could have been avoided with timely alcohol abstinence. However, in our opinion this argument is not justified for many reasons. First, alcoholism and ALD should not be clubbed together since significant liver disease develops in only 15% of all people who drink alcohol excessively[6]. So, clearly other etiologies such as genetic predisposition, hepatitis C and other viral infections, such as influenza[7-9], may contribute to the development of the disease. Further, there are other liver diseases such as hepatitis B, hepatitis C, non-alcoholic fatty liver disease and acetaminophen overdose where patient behavior is an important component either in the acquisition of these diseases or in their adequate management. The question therefore, is why should ALD be treated differently from these diseases?

The 6 mo abstinence rule

The criteria for listing patients with ALD on a LT recipient list are similar to any other chronic liver disease qualifying for LT except that in ALD there is an additional requirement for abstinence for ⩾ 6 mo ("6 mo rule")[10]. The same "6 mo rule" is being applied currently in transplant centers, including in the United States, for patients with AH[11,12]. Patients with severe AH who do not respond to corticosteroids or pentoxifylline have a mortality of 50%-75% at 6 mo[12]. Hence, this rule of 6 mo abstinence cannot be applied if these patients are to be better managed and salvaged. Clearly, there is an urgent need for changing this policy of abstinence of 6 mo[12]. Before we take this drastic action, let us examine critically what the effect of abstinence of 6 mo on the rate of alcohol relapse after LT (recidivism) has been.

The most authoritative prospective study on this issue is reported by DiMartini *et al*[13] on a follow up of 167 patients with orthotopic liver transplantation (OLT) who underwent OLT after a minimum abstinence period of 6 mo. The authors showed that although pre-OLT abstinence duration was a predictor on the frequency as well as time to relapse to alcohol abuse after OLT, even in patients who were sober for 36 mo, only 40% remained sober after OLT[13]. The lack of correlation of post-OLT recidivism with 6 mo abstinence prior to OLT was also shown by McCallum *et al*[14] in their systematic review of 11 studies. Only 2 of the studies showed an association while 9 studies did not show an association between 6 mo pre-OLT abstinence and post-OLT recidivism[14]. Does this mean that recidivism after OLT is not important? The answer is no. What we can say so far is that there is no evidence for the 6 mo abstinence rule to be considered as a necessary pre condition for OLT. Let us now examine recidivism after OLT, its frequency, its impact on the graft and patient survival and the factors predictive of recidivism.

Recidivism after orthotopic liver transplantation

The rate of alcohol relapse use after LT varies according to different authors. In a review of 22 studies on alcoholic liver disease, relapse ranged from 3% to 49%, with graft dysfunction and death ranging from 0% to 27% and 0% to 6.5%, respectively[6]. One problem is that these rates include any amount of drinking, including social drinking. For the purposes of graft and OLT outcome, the consideration should be a relapse to harmful drinking sufficient to cause liver damage[14]. Heavy drinking after LT in alcoholic liver disease as a whole is reported in less than 10% of patients[15]. Moreover, the definition of harmful drinking varies from study to study[14]. Further, documenting alcohol use by history taking is not always accurate since patients may not always tell the truth[16]. Even after accounting for recidivism for harmful drinking, the 5-year graft survival rates are better in patients with ALD compared to patients with hepatitis C induced liver disease[17]. This is because recurrence of HCV is almost universal after OLT with 20%-25% patients developing cirrhosis within 5 years of OLT[18]. However, in a retrospective study on long-term follow up (median follow up of 7.5 years), patients who relapsed to harmful drinking had poorer survival when compared to abstainers (45% *vs* 86%, $P < 0.05$)[19]. Therefore, the issue of recidivism is essential to accurately identify patients

prior to OLT who are likely to relapse to harmful drinking after the OLT. In a systematic review on 22 studies, McCallum *et al*[14] identified factors consistently associated with recidivism-younger age (2 studies), associated poly substance abuse (3 studies), lack of social support (7 studies), family history of alcohol abuse in a first degree relative (3 studies), poor response to previous rehabilitation programs (2 studies) and non-compliance (2 studies). Concomitant mental and psychiatric disorders were associated in 2 studies while 2 studies did not find this association. A lack of insight was not a predictor in any of the 3 studies[14].

DATA ON LIVER TRANSPLANTATION IN ALCOHOLIC HEPATITIS

Before implementing and rethinking our policy of LT in patients with severe AH, let us first examine the available data on the outcome of patients with AH after OLT. These data are limited and restricted to retrospective analyses. In one such study, among a series of 246 cases of ALD, 110 underwent OLT. About 7.2% (8 cases) had histological evidence of AH on the explants. Comparison of these 8 cases with the remaining 102 cases without histological AH in the explants showed similar patient survival post-OLT recidivism[20]. Similar data have been reported by other investigators[21-23]. Recidivism rates were similar irrespective of presence or absence of AH in the explant[21]. Further, there were no differences on the outcome between patients with mild AH and severe AH[21]. The problems with these studies is their retrospective design and the fact that histological changes of AH can persist for a long duration even after response to treatment[23]. Prospective data on the use of LT in this group of patients with severe AH are scant. In a recently reported study at the American association for the study of liver disease 2009 in Boston from the French group, 18 patients with severe AH non-responsive to steroids (NRS: defined as $\geqslant$ 0.45 Lille score) were studied prospectively to assess the role of LT[24]. Each case was matched to a control patient (who did not undergo LT and continued to receive medical management) for age, sex, DFI and Lille score. Patients received LT within an average of 9 d from the day they were labeled as NRS. At the end of 1 year, patient survival in the transplanted group was higher compared to those not receiving LT (83% *vs* 44%, $P = 0.009$)[24]. Among the non-transplanted patients, 50%-90% deaths occurred within first 2 mo. Only one patient relapsed to drinking about 2.5 years after LT. That patient was classified a social drinker without any impact on the graft function[24].

CURRENT STATUS AND FUTURE PROSPECTS

AH remains, for the moment, a contraindication for transplant in the majority of liver centers in the United States. However, we think that the time is right to re-evaluate our policy[12]. Current data clearly show that LT is a definitive treatment option for the group of patients with severe AH who continue to deteriorate despite intensive medical treatment. Further, 6 mo of abstinence does not affect recidivism after OLT. However, before we routinely use this modality of definitive treatment for severe AH, we need to (1) derive long-term outcome of patients and graft in this setting; (2) determine the best criteria to identify candidates with the least risk of recidivism to harmful drinking; and (3) develop homogeneity in the definition of harmful drinking, drinking patterns and alcohol abuse questionnaires. Then we will be able to implement guidelines that are fair and scientifically sound for the optimal utilization of available organs in the setting of AH in the same way we are doing for other etiologies of ALF. Although the destination is far, there seems to be light at the end of the tunnel which will allow us to make the right decision and a life or death difference in many cases of severe AH.

REFERENCES

1 **Lucey MR**, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; **360**: 2758-2769

2 **Mathurin P**, Mendenhall CL, Carithers RL, Ramond MJ, Maddrey WC, Garstide P, Rueff B, Naveau S, Chaput JC, Poynard T. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002; **36**: 480-487

3 **Whitfield K**, Rambaldi A, Wetterslev J, Gluud C. Pentoxifylline for alcoholic hepatitis. *Cochrane Database Syst Rev* 2009; CD007339

4 **Neuberger J**, Tang H. Relapse after transplantation: European studies. *Liver Transpl Surg* 1997; **3**: 275-279

5 **Neuberger J**, Adams D, MacMaster P, Maidment A, Speed M. Assessing priorities for allocation of donor liver grafts: survey of public and clinicians. *BMJ* 1998; **317**: 172-175

6 Anantharaju A, Van Thiel DH. Liver transplantation for alcoholic liver disease. National Institute of Alcohol Abuse and Alcoholism 2004. Available from: URL: http://pubs.niaaa.nih.gov/publications/arh27-3/257-269.htm

7 **Singal AK**, Anand BS. Mechanisms of synergy between alcohol and hepatitis C virus. *J Clin Gastroenterol* 2007; **41**: 761-772

8 **Singal AK**, Sagi S, Weinman SA, Snyder N. Impact of hepatitis C on the outcome and severity of acute alcoholic hepatitis. *Eur J Gastroenterol Hepatol* 2011; **23**: 204-209

9 **Duchini A**, Viernes ME, Nyberg LM, Hendry RM, Pockros PJ. Hepatic decompensation in patients with cirrhosis during infection with influenza A. *Arch Intern Med* 2000; **160**: 113-115

10 **Lucey MR**, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, Kneteman NM, Lake JR, Martin P, McDiarmid SV, Rakela J, Shiffman ML, So SK, Wiesner RH. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 1997; **3**: 628-637

11 **Mathurin P**. Is alcoholic hepatitis an indication for transplantation? Current management and outcomes. *Liver Transpl* 2005; S21-S24

12 **Dureja P**, Lucey MR. The place of liver transplantation in the treatment of severe alcoholic hepatitis. *J Hepatol* 2010; **52**: 759-764

13 **DiMartini A**, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, Fung JJ, Fontes P. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transpl* 2006; **12**: 813-820

14 **McCallum S**, Masterton G. Liver transplantation for alcoholic liver disease: a systematic review of psychosocial selection criteria. *Alcohol Alcohol* 2006; **41**: 358-363

15 **Mackie J**, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, Neuberger J. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. *Liver Transpl* 2001; **7**: 418-427

16 **Weinrieb RM**, Van Horn DH, McLellan AT, Lucey MR. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: fostering candor is the key to recovery. *Liver Transpl* 2000; **6**: 769-776

17 **Webb K**, Neuberger J. Transplantation for alcoholic liver disease. *BMJ* 2004; **329**: 63-64

18 **Firpi RJ**, Clark V, Soldevila-Pico C, Morelli G, Cabrera R, Levy C, Machicao VI, Chaoru C, Nelson DR. The natural history of hepatitis C cirrhosis after liver transplantation. *Liver Transpl* 2009; **15**: 1063-1071

19 **Pfitzmann R**, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nüssler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2007; **13**: 197-205

20 **Immordino G**, Gelli M, Ferrante R, Ferrari C, Piaggio F, Ghinolfi D, Sturdevant M, Andorno E, Morelli N, Bottino G, Casaccia M, Valente U. Alcohol abstinence and orthotopic liver transplantation in alcoholic liver cirrhosis. *Transplant Proc* 2009; **41**: 1253-1255

21 **Tomé S**, Martinez-Rey C, González-Quintela A, Gude F, Brage A, Otero E, Abdulkader I, Forteza J, Bustamante M, Varo E. Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. *J Hepatol* 2002; **36**: 793-798

22 **Wells JT**, Said A, Agni R, Tome S, Hughes S, Dureja P, Lucey MR. The impact of acute alcoholic hepatitis in the explanted recipient liver on outcome after liver transplantation. *Liver Transpl* 2007; **13**: 1728-1735

23 **Shakil AO**, Pinna A, Demetris J, Lee RG, Fung JJ, Rakela J. Survival and quality of life after liver transplantation for acute alcoholic hepatitis. *Liver Transpl Surg* 1997; **3**: 240-244

24 **Castel H**, Moreno C, Antonini T, Duclos-Vallée JC, Dumortier J, Leroy V, Dharancy S, Boleslawski E, Lucidi V, Letoublon C, Samuel D, Francoz C, Durand F, Pruvot FR, Mathurin P. Early transplantation improves survival of non-responders to steroids in severe alcoholic hepatitis: a challenge to the 6 month rule of abstinence. *Hepatology* 2009; **50** Suppl 4 : 307A

S- Editor Zhang SJ **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i8.219

World J Hepatol 2011 August 27; 3(8): 219-227
ISSN 1948-5182 (online)

BRIEF ARTICLE

Noninvasive predictors for liver fibrosis in patients with nonalcoholic steatohepatitis

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Received: March 9, 2011 Revised: June 6, 2011
Accepted: July 18, 2011
Published online: August 27, 2011

Abstract

AIM: To evaluate certain anthropometric, clinical and laboratory features indicating liver fibrosis in nonalcoholic steatohepatitis and to establish the noninvasive markers for liver fibrosis.

METHODS: Eighty-one patients (40 male, 41 female) who were diagnosed with fatty liver by ultrasonographic examination and fulfilled the inclusion criteria participated in the study. Anamnesis, anthropometric, clinical and laboratory features of all cases were recorded and then liver biopsy was performed after obtaining patient consent. Steatosis, necroinflammation and liver fibrosis were examined according to age ⩾ 45, gender, body mass index, central obesity, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 1, γ-glutamyltransferase (GGT)/ALT > 1, platelet count, insulin, c-peptide levels and the presence of hypertension, diabetes, hypertriglyceridemia and insulin resistance.

RESULTS: Eighty-one patients with non-alcoholic steatohepatitis (NASH) enrolled in the study. 69 of 81 patients were diagnosed with NASH, 11 were diagnosed with simple fatty liver and 1 was diagnosed with cirrhosis. AST/ALT > 1, GGT/ALT > 11, high serum ferritin and fasting insulin levels, the presence of diabetes, hypertension, hypertriglyceridemia and insulin resistance seemed to enhance the severity of steatosis, necroinflammation and fibrosis but these results were not statistically significant.

CONCLUSION: Liver steatosis and fibrosis can occur in individuals with normal weight. There was no significant concordance between severity of liver histology and the presence of predictors for liver fibrosis including metabolic risk factors.

Key words: Liver fibrosis; Predictors; Nonalcoholic fatty liver disease; Steatohepatitis

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Uslusoy HS, Nak SG, Gülten M. Noninvasive predictors for liver fibrosis in patients with nonalcoholic steatohepatitis. *World J Hepatol* 2011; 3(8): 219-227 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i8/219.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i8.219

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a hepatic pathology which includes fat accumulation and inflammation in hepatocytes accompanied by fibrosis in various degrees, with neglible or no alcohol consumption.

This entity may progress to cirrhosis and liver failure[1]. Although NAFLD is supposed to be in association with certain metabolic disorders like obesity, diabetes and hyperlipidemia, it can also occur in lean individuals and those without diabetes[2,3]. The natural progression of fatty liver is not definitely estimated previously. While approximately 7%-37.6% of patients with non-alcoholic steatohepatitis (NASH) may have advanced fibrosis and 20% of patients with NASH may silently progress to cirrhosis, fatty liver should not always be considered as an innocent condition[4-7]. Due to the difficulties in extensive application of liver biopsy, many anthropometric, clinical and laboratory features in NASH patients were investigated for their currency and worthiness in the prediction of liver fibrosis. Our aim is to research and reveal the validity, accuracy and convenience of certain anthropometric, clinical and laboratory features to predict liver fibrosis and their concordance with liver histology.

MATERIALS AND METHODS

Patients

Eighty-one patients, diagnosed with fatty liver as mild, moderate and severe by ultrasonographic examination and with an elevation in alanine aminotransferase (ALT) levels of at least 1.5 fold of the normal range and persistent liver steatosis, were enrolled in the study in Uludag University Gastroenterology Division. After complete anthropometric, clinical and laboratory assessments, liver biopsy was performed. Exclusion criteria were alcohol consumption ⩾ 20 g/d, pregnancy, positive tests indicating the presence of hepatitis B and C virus, autoimmune liver diseases, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cirrhosis, primary sclerosing cholangitis and toxic liver diseases. Data handling and liver biopsy were performed with patient consent. The study was approved by the hospital ethics committee.

Laboratory studies

All cases underwent liver examination by ultrasonography and subsequently anamnesis; anthropometric, clinical, complete blood count and biochemical assessments were performed. Biochemical evaluation consisted of ALT, aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, high-density lipoprotein (HDL)-cholesterol, triglycerides, fasting glucose and insulin levels and oral glucose tolerance test. Anthropometric measurements included height, weight, body mass index (BMI), waist and hip circumferences and waist/hip ratio values. Diagnosis of obesity was dependent on World Health Organization (WHO) criteria[8]. American Diabetes Association criteria were used to signify type 2 diabetes, impaired glucose intolerance and impaired fasting glycemia. Patients on oral antidiabetics or insulin therapy were accepted as diabetics. Hypertension was recognized when resting blood pressure was ⩾ 140/90 mmHg or when patients were on antihypertensive drug therapy. Triglycerides ⩾ 1500 mg/L were accepted as hypertriglyceridemia. The measurement of insulin resistance was made using homeostatic model assessment (HOMA) method and patients were classed as insulin resistant while HOMA value was ⩾ 2.70. ALT levels 1.5 or more times the upper normal values marked an elevation. The diagnosis of metabolic syndrome was made using WHO criteria[9]: BMI ⩾ 30 kg/m^2, waist/hip circumference ratio > 0.90 in men and > 0.85 in women, fasting blood glucose ⩾ 1100 mg/L, overt diabetes, presence of impaired glucose tolerance and/or IR, triglycerides ⩾ 1500 mg/L, HDL-cholesterol < 400 mg/L in men and < 500 mg/L in women, arterial blood pressure ⩾ 140/90 mmHg and presence of microalbuminuria. Patients had at least three of these criteria to be diagnosed with metabolic syndrome. The study was approved by the hospital ethics committee.

Pathology

All 81 patients underwent liver biopsy according to the severity of clinical and laboratory features and patient consent. Liver biopsy specimens were examined by liver pathologists in the Department of Pathology at the Medical Faculty in Uludag University. Necroinflammation and fibrosis in liver were evaluated using the histopathological criteria defined by Brunt *et al*[10]. Diagnosis of NASH was dependent on steatosis (mild: < 33% of lobules, moderate: 33%-66% of lobules and severe: > 66% of lobules) and 2 of the 3 features: (1) necroinflammation with mononuclear cells and/or polymorphonuclear leucocytes; (2) ballooning degeneration of hepatocytes, Mallory bodies; and (3) pericellular, perisinusoidal and/or bridging fibrosis. Steatosis and necroinflammation were categorized as grade 1, 2 and 3 and fibrosis as grade 1, 2, 3 and 4 (cirrhosis).

Statistical analysis

Statistical significance was not reached due to the small number of patients and statistical evaluation and *P* values were not available. Evaluations were performed using percentage values. Hence, patient features were evaluated according to their percentage values.

RESULTS

Anthropometric, clinical and laboratory results

Eighty-one patients (40 male, 41 female) who were diagnosed with fatty liver by ultrasonographic examination participated in the study at Uludag University Gastroenterology Division. All patients underwent liver biopsy. 69 (35 male, 34 female) of 81 patients were diagnosed with NASH, 11 (4 male, 7 female) were diagnosed with simple fatty liver and 1 (male) was diagnosed with cirrhosis. Initial characteristics of all patients were obtained and recorded as shown in Table 1. We used the most pronounced independent risk factors such as age ⩾ 45 years, gender, BMI > 30 kg/m^2, central obesity (waist/hip ratio

Table 1 General aspects of all non-alcoholic steatohepatitis cases *n* (%)

Nonalcoholic steatohepatitis (*n* = 70)	
Average age (yr)	47.9 ± 8.74
Gender (male/female)	36/34
Hepatomegaly	16 (23.9)
BMI (kg/m^2)	30.4 ± 4.79
Normal weight (BMI < 24.9 kg/m^2)	3 (4.30)
Overweight (BMI = 25-29.9 kg/m^2)	34 (48.5)
Obese (BMI = 30-39.9 kg/m^2)	29 (41.4)
Morbid obese (BMI > 40 kg/m^2)	4 (5.80)
Waist/hip cir (E > 0.90, K > 0.85)	49 (71)
Systolic blood pressure (mmHg)	124 ± 16.2
Diastolic blood pressure (mmHg)	75.6 ± 11.9
Hypertension	21 (30.4)
HDL-cholesterol (mg/dL)	46.3 ± 8.07
Low-HDL-cholesterol	28 (40.5)
Triglycerides (mg/dL)	163 ± 79.5
Hypertriglyceridemia	36 (52.1)
Fasting glucose (mg/dL)	107 ± 26.2
Diabetes mellitus	20 (28.8)
Fasting insulin (μU/mL)	16.6 ± 13.0
Homeostatic model assessment-insulin resistance value	3.91 ± 2.45
Fasting c-peptid	4.35 ± 2.15
aspartate aminotransferase (U/L)	48.2 ± 23.9
Alanine aminotransferase (U/L)	76.2 ± 35.2
Gama glutamyl transpeptidase (U/L)	59.2 ± 46.8
Alkaline phosphatase (U/L)	93.4 ± 32.3
İnsulin resistance	30 (43.4)
Metabolic syndrome	46 (66.6)

This table shows that numbers of non obese patients are much higher than obese patients and 33.4% of non-alcoholic steatohepatitis patients have no metabolic syndrome. BMI: Body mass index; HDL: High-density lipoprotein.

> 0.90 in men and > 0.85 in women), AST/ALT > 1, GGT/ALT > 1, platelet count, fasting serum levels of ferritin, c-peptid and insulin and presence of hypertension, diabetes, hypertriglyceridemia and insulin resistance.

Table 1 shows that the numbers of normal and overweight patients were higher than those of obese and morbidly obese patients. This indicates that the risk for liver steatosis could be higher when BMI values exceed 25 kg/m^2. Prevalences of other components of metabolic syndrome were not significantly increased, as stated in Table 1. These results indicate that NASH could occur in patients with only one risk factor or even in patients without any risk factors.

Although the simple fatty liver group is small (11 patients), we determined that two patients had 2, seven patients had 3, one patient had 4 and one patient had 5 risk factors. These results have shown that the presence and numbers of metabolic risk factors did not give information about liver histology. It seems that discrimination between NASH and simply fatty liver will not be made according only to clinical, epidemiological, anthropometrical or laboratory results.

Furthermore, the presence of predictors for liver fibrosis were also searched for in patients with simple fatty liver. However, in patients with age ⩾ 45, obesity, hypertension, diabetes and hypertriglyceridemia, it seemed to be increased but these results were not significant.

Table 2 shows that female gender, age > 45 years seem to have severe steatosis and necroinflammation. Interestingly, patients with normal BMI seem to have severe steatosis and necroinflammation. However, AST/ALT > 1, GGT/ALT > 1 and low platelet count, increase in fasting serum ferritin, insulin and c-peptide levels and presence of metabolic risk factors (diabetes, hypertriglyceridemia, hypertension and insulin resistance) seem to increase severe steatosis and necroinflammation but due to the small number of cases, these results are not significant.

Table 3 shows that gender and age > 45 did not seem to influence the development of fibrosis significantly. Patients with normal BMI seemed to have severe fibrosis but because of the small number of cases, these results were not significant. Central obesity, AST/ALT > 1, GGT/ALT > 1, elevated serum ferritin and fasting insulin levels, presence of hypertension, diabetes, hypertriglyceridemia and insulin resistance seemed to increase fibrosis but these findings were not significant. We diagnosed one patient with cirrhosis who had normal AST/ALT and AST/GGT ratio, normal platelet count and serum ferritin, fasting insulin and c-peptide levels. This patient had no metabolic risk factors apart from diabetes.

Histopathology

The detailed features of liver histology of our 81 cases were examined using the presence of "predictors for liver fibrosis". Tables 2 and 3 present the influences of predictors on liver histology in our 70 NASH cases. The remaining 11 patients were diagnosed with simple fatty liver.

DISCUSSION

In the present study, we aimed to reveal simple, confident and feasible noninvasive parameters to assign the severity of nonalcoholic steatohepatitis. General aspects of our patients are presented in Table 1.

Advanced obesity was stated as a risk factor for the development of liver fibrosis by Sobhonslidsuk *et al*[11], Ong *et al*[12] and Ratziu *et al*[13]. Recent studies revealed that the people with normal body weight but high visceral fat ratio (central obesity) could have NAFLD, metabolic syndrome and insulin resistance[2,3]. Sobhonslidsuk *et al*[11] and Cheung *et al*[14] stated that abdominal obesity correlated only with liver inflammation and so waist circumference predicts metabolic risk condition with the most significance. Angelico *et al*[15] and Marchesini *et al*[16] found a correlation between various degrees of liver steatosis and BMI but we did not detect any relationship between steatosis and BMI (Table 2). Boza *et al*[17] found no significant association between BMI and histological changes. In the latest study, high HOMA-IR values and ALT levels were the only independent predictors of NASH. Gholam *et al*[18] stated that except for BMI and hyperglycemia, insulin resistance and the metabolic syndrome were associated with the presence of NASH and fibrosis. Rocha

Table 2 Predictors of liver fibrosis and liver histology (steatosis and necroinflammation) in patients with nonalcoholic steatohepatitis

	Steatosis (n = 70)			Necroinflammation (Grade) (n = 70)		
	Mild (%)	Moderate (%)	Severe (%)	Mild (%)	Moderate (%)	Severe (%)
Gender						
Male	38.9	38.9	22.1	36.1	55.5	8.3
Female	41.2	35.3	23.5	20.6	64.7	14.7
Age (yr)						
> 45	35.4	37.5	27.0	25.0	62.5	12.5
< 45	45.4	36.3	18.1	36.3	59.0	4.5
Body mass index (kg/m^2)						
18.5-24.9	0	66.6	34.4	33.3	33.4	33.3
25.0-29.9	34.2	42.9	22.9	31.4	60.0	8.6
30.0-39.9	50.0	21.5	28.5	32.1	53.6	14.3
> 40	25.0	75.0	0	50.0	50.0	0
Central obesity						
+	40.0	38.0	22.0	28.5	61.2	10.2
-	35.0	35.0	30.0	28.5	57.1	14.2
AST/ALT > 1	40.0	20.0	40.0	20.0	40.0	40.0
AST/ALT < 1	37.5	39.0	23.4	29.6	60.9	9.3
GGT/ALT > 1	36.3	27.2	36.3	31.8	50.0	18.1
GGT/ALT < 1	38.2	42.5	19.1	25.5	65.9	8.6
Platelet count						
Low	33.4	0	66.6	33.4	33.3	33.4
Normal	39.3	37.8	22.7	36.3	53.0	10.6
Ferritin						
Elevated	0	33.4	66.6	0	33.4	66.6
Normal	39.3	37.8	22.7	28.7	62.1	10.6
Fasting insulin						
Elevated	14.4	28.5	57.1	14.4	71.4	14.4
Normal	42.0	35.5	22.5	30.6	62.0	11.2
Fasting c-peptid						
Elevated	31.2	37.5	31.2	15.6	71.8	12.5
Normal	45.9	35.1	18.9	37.8	51.3	10.8
Hypertension						
Present	38.1	33.4	28.5	19.0	62.0	19.0
Absent	38.7	38.7	22.4	32.6	59.2	8.2
Diabetes						
Present	38.1	33.4	28.5	23.8	57.1	14.2
Absent	36.7	38.7	24.4	28.5	61.2	10.2
Hypertriglyceridemia						
Present	36.2	38.8	25.0	19.4	66.6	13.8
Absent	41.0	35.2	23.5	38.2	52.9	8.8
Insulin resistance						
Present	37.9	34.4	27.5	24.1	65.5	10.3
Absent	40.0	40.0	20.0	50.0	40.0	10.0

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-glutamyltransferase.

et al[19] said that the prevalence of NAFLD was 2.3% in 199 patients with central obesity. Nevertheless, we observed no connection between central obesity and fibrosis/necroinflammation. It is a remarkable point that necroinflammation and fibrosis could progress even in patients with normal weight (Tables 2 and 3).

Females aged over 45 years were considered to influence liver histology in nonalcoholic steatohepatitis[20]. Daryani *et al*[21] and Shimada *et al*[22] have found that females over 55 had a relationship with liver steatosis and advanced fibrosis and other metabolic parameters (e.g. obesity, diabetes, hypertension) but these were not statistically significant predictors[23]. Harrison *et al*[24] and Yatsuji *et al*[25] said that advanced age was related to advanced fibrosis. Singh *et al*[26] and Liew *et al*[27] found that older females were identified as independent predictors of fibrotic severity. Ong *et al*[12], Helling *et al*[28] and Arun *et al*[29] stated that male gender was associated with NASH. Prashanth *et al*[30] said that older age, duration of diabetes mellitus, degree of glycemic control, BMI, waist circumference and family history of diabetes mellitus did not predict the presence or severity of NAFLD or fibrosis. In our study, age over 45 years and gender did not seem to have more severe steatosis/necroinflammation and fibrosis (Tables 2 and 3).

Elevated ALT and AST levels were assessed as remarkable markers for NASH and liver fibrosis. Hossain *et al*[31] found that diabetes mellitus and aminotransferase levels are independent predictors of fibrosis in NAFLD. Chavarría-Arciniega *et al*[32] stated that fibrosis showed correlation only with AST. Rodríguez-Hernández *et al*[33] stressed that ALT was correlated with inflammation and

Table 3 Predictors of liver fibrosis and histological stage in nonalcoholic steatohepatitis cases (n = 70)

	Absent	Fibrosis (%)		Bridging	Cirrhosis (%)
		Perisinusoidal/ pericellular	Periportal		
Gender					
Male	50.0	22.2	16.6	8.3	2.7
Female	38.2	47.0	5.9	8.9	-
Age (yr)					
> 45	45.8	39.7	6.25	6.25	2.1
< 45	41.0	22.7	22.7	13.6	-
Body mass index (kg/m^2)					-
18.5-24.9	33.3	0	33.3	33.3	
25.0-29.9	44.4	41.6	8.3	5.5	-
30.0-39.9	50.0	21.4	14.2	10.7	3.5
> 40	25.0	75.0	0	0	-
Central obesity					
Present	38.0	36.0	16.0	8.0	2.0
Absent	60.0	30.0	0	10.0	-
AST/ALT > 1	20.0	20.0	20.0	40.0	-
AST/ALT < 1	53.1	29.6	10.9	4.6	1.5
GGT/ALT > 1	52.1	26.0	13.0	8.63	-
GGT/ALT < 1	54.3	30.4	8.6	6.5	2.1
Platelet count					
Low	66.6	33.4	0	0	0
Normal	44.0	35.0	10.5	9.0	1.5
Ferritin					
Elevated	33.4	0	66.6	0	0
Normal	44.0	36.5	9.0	9.0	1.5
Fasting insulin					
Elevated	28.5	14.5	28.5	28.5	-
Normal	43.6	37.1	9.7	8.0	1.6
Fasting c-peptid					
Elevated	59.0	27.2	6.8	6.8	-
Normal	44.0	32.0	16.0	8.0	2.3
Hypertension					
Present	28.5	52.3	9.5	9.5	-
Absent	53.0	26.5	12.2	6.1	2.0
Diabetes					
Present	19.0	47.6	14.2	14.2	4.7
Absent	55.1	28.5	10.2	6.1	-
Hypertriglyceridemia					
Present	38.8	33.4	16.6	8.3	-
Absent	47.0	38.2	5.8	5.8	3.0
Insulin resistance					
Present	37.0	40.7	18.5	3.7	3.7
Absent	77.2	13.6	-	9.2	-

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-glutamyltransferase.

fibrosis. Prashanth *et al*[30] also said that serum alanine aminotranferase (ALT) and ALP levels were significantly higher in patients with steatohepatitis. Gholam *et al*[18] also said that elevated transaminase levels correlated with NASH and fibrosis. However, 46% of their subjects with NASH had normal transaminases. Shi *et al*[34] denoted that elevated serum level of ALT is an independent predictor of the degree of inflammation but not of steatosis and fibrosis. Nevertheless, recent certain studies expressed that ALT and AST were not reliable markers for NASH or for fibrosis[34,35]. Ong *et al*[12] said that waist/hip ratio and AST were independently associated with advanced fibrosis but in the latest study the majority of the patients with either NASH or advanced fibrosis had normal AST. Nomura *et al*[36] and Mofrad *et al*[37] stated that significant liver disease could exist with normal liver enzyme levels. Fracanzani *et al*[38] also stressed that normal ALT is not a valuable parameter to exclude patients from liver biopsy. We also found that there was no relationship between ALT and AST levels and liver fibrosis.

Furthermore, the ratio of AST/ALT higher than 1 was asserted to be a marker for liver fibrosis in NASH. Prashanth *et al*[30] found that serum AST/ALT ratio was significantly higher in patients with severe fibrosis and, additionally, all patients with severe fibrosis had metabolic syndrome. Gramlich *et al*[20], Harrison *et al*[24] and McPherson *et al*[39] said that the presence of AST/ALT > 1 could exclude liver fibrosis in patients with NAFLD. Myers[35] and Amarapurkar *et al*[40] revealed that elevation in AST,

ALT levels and AST:ALT > 1 did not show significant association with fibrosis. In the latest study, there was no accurate noninvasive method available that could previously determine the risk of fibrosis in patients with NASH and the elevated levels of transaminases were non-specific with the disease. Hence, liver biopsy remains the gold standard in staging and predicting progression in patients with NASH. Myers[35] said that an AST/ALT ratio above 1 might indicate advanced fibrosis; however, its sensitivity was poor. Bahrami *et al*[41] determined that the value of AST/ALT < 1 was present in 65.3% of patients with NAFLD. Shimada *et al*[22] said that the AST: ALT ratio was less specific. In our study, the presence of AST/ALT > 1 seemed to increase steatosis, necroinflammation and fibrosis, but these results were not significant. Furthermore, 20% of patients with AST/ALT > 1 had no fibrosis, the other 20% of patients with AST/ALT > 1 had only slight necroinflammation. In addition, in patients with AST/ALT < 1 the rate of fibrosis was approximately 47%. For example, in our study, one patient with cirrhosis was male, 55 years old and had AST/ALT < 1 but no metabolic syndrome. We observed that the presence of GGT/ALT > 1 also had no relationship with liver histopathology.

Metabolic disorders are considered to influence liver histology in NAFLD[42,43]. Prashanth *et al*[30] pointed out that the prevalence of NASH increased with the components of metabolic syndrome. Diabetes mellitus influences liver histology in NAFLD[40,44]. Singh *et al*[26] signified that female gender, BMI, waist:hip ratio, hypercholesterolemia and LDL levels are independent predictors of liver damage in patients with NASH. According to Helling *et al*[28], only increased triglycerides and decreased prealbumin correlated with NASH. Assy *et al*[45] defined hypertriglyceridemia and diabetes as the only risk factors that increase the risk of fatty infiltration in hyperlipidemic patients. Liew *et al*[27] featured that serum cholesterol and low-density lipoprotein cholesterol levels were risk factors associated with gallbladder disease and fatty liver disease. Rodríguez-Hernández *et al*[33] said that diabetes and ALT correlated with histological hepatic changes. Amarapurka *et al*[44] found that diabetes mellitus does not always precede NASH and risk factors like central obesity, dyslipidemia and family history do not forebode the occurrence of NASH in diabetic patients. We also did not detect any significant correlation between individual metabolic risk factors and liver fibrosis in NASH patients (Tables 2 and 3). Moreover, in our study one patient, female and over 45 years, with NASH had no metabolic risk factor.

Ryan *et al*[42] said that except for defined metabolic syndrome, other individual features of metabolic syndrome did not correlate with hepatic fibrosis. Nonetheless, all patients with NASH did not fulfil the criteria of metabolic syndrome and liver histology, even in association with metabolic syndrome which has always represented severe steatohepatitis or advanced fibrosis. Kim *et al*[3] stated that NAFLD could occur in non obese and non diabetic individuals. The prevalences of metabolic syndrome were 40% in men and 26% in women according to Hamaguchi *et al*[46]. Pagano *et al*[47] defined the prevalence of metabolic syndrome in NASH cases as 47%. Lizardi-Cervera *et al*[48] signified the prevalence of metabolic syndrome in patients with NAFLD as 22.8%. Moon *et al*[49] studied whether metabolic risk factors had a relationship with the stage of liver fibrosis but no significant differences between histological features in NASH patients with or without metabolic syndrome were found. Kang *et al*[43] stated that as low a proportion of 34% of NAFLD patients had metabolic syndrome. Xanthakos *et al*[50] stressed that in morbidly obese adolescents, severe NASH was uncommon and the presence of metabolic syndrome did not distinguish NASH from steatosis alone. In our study, severity of steatosis, necroinflammation and fibrosis were not significant different in NASH patients with metabolic syndrome when compared to those without it.

Fasting c- peptid and insulin levels were asserted to tend to increase in NAFLD. Patients with fatty liver seem to have lower c-peptid and insulin levels than those with NASH[47,51]. Recent studies claimed that metabolic risk factors and insulin resistance could influence liver histology[52]. Sobhonslidsuk *et al*[11] represented that insulin resistance and elevated visceral fat are risk factors for the presence of NASH. Gholam *et al*[18] said that individuals with NASH had a high level of insulin resistance when compared to those with simple fatty liver. The prevalence of insulin resistance was 85% in the study by Willner *et al*[53]. But Marchesini *et al*[54] revealed the prevalence of insulin resistance in NAFLD was 61%.

However, Dixon *et al*[55] reported that HOMA-IR value, ALT and arterial hypertension were independent predictors for NASH, but they also found that 7.8% of their study patients had NASH even although they had normal AST and HOMA-IR values. Bahrami *et al*[41] found the rate of insulin resistance was only 54.7% in 53 patients with NASH. Guidorizzi de Siqueira *et al*[52] said that insulin resistance was detected in only 33% of NAFLD patients but there was a high frequency of IR in patients with advanced fibrosis. Sakurai *et al*[56] have specified that only steatosis was significantly and independently associated with elevated HOMA values but there was no similar association with the grade or stage of NASH.

An interesting observation expressed by Machado *et al*[57] is that the rates of insulin resistance in NAFLD patients could vary from 47% to 98% and in their study, 36% fulfilled three criteria of metabolic syndrome. We detected that, although high c-peptid and insulin levels and presence of insulin resistance seemed to increase the severity of steatosis, steatohepatitis and liver fibrosis, the findings were not significant.

Low platelet count was proposed to be a marker of fibrosis according to Shimada *et al*[22] and Stepanova *et al*[58]. According to the literature, this parameter was not significant alone as a combination of fibrosis markers are advisable[19,59-62]. In the present study, the relationship between

low platelet count and the severity of steatosis, steatohepatitis and fibrosis were not significant.

Licata *et al*[63] pointed out that high serum ferritin level is a risk factor for steatosis. Fracanzani *et al*[38] said that fibrosis was independently associated with elevated serum ferritin and normal ALT level is not a reliable parameter to exclude patients from liver biopsy. However, Loguercio *et al*[64] revealed that abnormal GGT or ALT, age and ferritin were associated with steatosis but that no single factor was found to be an independent predictor. Pagano *et al*[47] also said that parameters related to iron metabolism did not differ when comparing patients with NASH to the control group. Dixon *et al*[55] represented that there was no difference in ferritin levels between patients with NASH and without NASH. Friis-Liby *et al*[65] stated that abnormalities in iron indices were detected in 31 patients of 102 (39%) and elevated ferritin in 29 patients of 102 (28.4%). Pagadala *et al*[59] signified that elevated serum ferritin in NAFLD has not been confirmed by other studies. Chitturi *et al*[51], Angulo *et al*[62] and Younossi *et al*[66] did not observe any relationship between iron metabolism and the clinical or pathological outcomes in patients with NAFLD. Nevertheless, in our study high ferritin levels seemed to raise steatosis, necroinflammation and fibrosis but these results were not significant.

In conclusion, none of the present tools yield all that is needed for the "perfect" fibrosis marker as each non invasive predictor lacks accuracy and reliability and hence, combination algorithms of fibrosis markers are needed[35,59,67,68]. Although noninvasive, simple, reproducible and reliable biomarkers are still greatly needed, none of them can substitute for a liver biopsy[62,69,70].

COMMENTS

Background

Nonalcoholic fatty liver disease is a condition which is described as fat accumulation, especially triglycerides, in liver cells. This condition may lead the function of liver to deteriorate. So liver diseases including liver cirrhosis and liver failure may occur. Hence to detect this fat accumulation and to predict the probable evil outcomes are very important.

Research frontiers

To avoid the harmful consequences of NAFLD apart from liver biopsy many noninvasive methods were improved. These methods are generally based on blood tests. The studies on noninvasive methods are still going on to determine the most sensitive and specific tools. The authors also searched simple, available, applicable and reliable methods.

Innovations and breakthroughs

New predictive markers should be investigated before severe outcomes of NAFLD have occured. This study aimed to reveal and establish simple, available and accurate noninvasive markers for liver fibrosis which are applicable in every health center.

Applications

If predictive tools could be applicable even in small health centers with high accuracy well then they are really reliable so people with fatty liver can have a check-up for prognosis of liver steatosis. The variables we used to predict liver fibrosis are even though usable and beneficial in health centers but still more investigations are needed.

Terminology

Fatty liver or liver steatosis can occur without alcohol consumption and progress to steatohepatitis which means an inflammation in liver then this condition can deteriorate so fibrous tissue begin to form after liver cell destruction. Once liver cell destruction begins somehow the event may progress to cirrhosis and liver failure. Hence to prevent this process is now an important problem and early determination of coming hazardous results of NAFLD became remarkable and developing issue in whole liver diseases.

Peer review

This descriptive study suggest that follow-up of the individuals with fatty liver should not be neglected. Especially studies on simple, accurate, reliable and above all applicable noninvasive markers for liver fibrosis in every health center should go on.

REFERENCES

1 **Angulo P.** Nonalcoholic fatty liver disease. *N Engl J Med*, 2002; **346**: 1221-1231

2 **Chen CH**, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, Yueh SK. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. *J Clin Gastroenterol* 2006; **40**: 745-752

2 **Kim HJ**, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch Intern Med* 2004; **164**: 2169-2175

3 **Sakurai M**, Takamura T, Ota T, Ando H, Akahori H, Kaji K, Sasaki M, Nakanuma Y, Miura K, Kaneko S. Liver steatosis, but not fibrosis, is associated with insulin resistance in nonalcoholic fatty liver disease. *J Gastroenterol* 2007; **42**: 312-317

4 **Leite NC**, Villela-Nogueira CA, Pannain VL, Bottino AC, Rezende GF, Cardoso CR, Salles GF. Histopathological stages of nonalcoholic fatty liver disease in type 2 diabetes: prevalences and correlated factors. *Liver Int* 2011; **31**: 700-706

5 **Hashimoto E**, Tokushige K. Prevalence, gender, ethnic variations, and prognosis of NASH. *J Gastroenterol* 2011; **46** Suppl 1: 63-69

6 **Wong VW**, Wong GL, Choi PC, Chan AW, Li MK, Chan HY, Chim AM, Yu J, Sung JJ, Chan HL. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut* 2010; **59**: 969-974

7 **Caldwell S**, Argo C. The natural history of non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 162-168

8 **World Health Organisation**. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity, Geneva, 1997 June 3-5. Geneva: World Health Organization, 1998

9 **World Health Organization**. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: World Health Organization, 1999

10 **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

11 **Sobhonslidsuk A,** Jongjirasiri S, Thakkinstian A, Wisedopas N, Bunnag P, Puavilai G. Visceral fat and insulin resistance as predictors of non-alcoholic steatohepatitis. *World J Gastroenterol* 2007; **13**: 3614-3618

12 **Ong JP**, Elariny H, Collantes R, Younoszai A, Chandhoke V, Reines HD, Goodman Z, Younossi ZM. Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. *Obes Surg* 2005; **15**: 310-315

13 **Ratziu V**, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, Khalil L, Turpin G, Opolon P, Poynard T. Liver fibrosis in overweight patients. *Gastroenterology* 2000; **118**: 1117-1123

14 **Cheung O**, Kapoor A, Puri P, Sistrun S, Luketic VA, Sargeant CC, Contos MJ, Shiffman ML, Stravitz RT, Sterling RK, Sanyal AJ. The impact of fat distribution on the severity of nonalcoholic fatty liver disease and metabolic syndrome. *Hepatology* 2007; **46**: 1091-1100

15 **Angelico F,** Del Ben M, Conti R, Francioso S, Feole K, Maccioni D, Antonini TM, Alessandri C. Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases. *J Gastroenterol Hepatol* 2003; **18**: 588-594

16 **Marchesini G,** Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923

17 **Boza C**, Riquelme A, Ibañez L, Duarte I, Norero E, Viviani P, Soza A, Fernandez JI, Raddatz A, Guzman S, Arrese M. Predictors of nonalcoholic steatohepatitis (NASH) in obese patients undergoing gastric bypass. *Obes Surg* 2005; **15**: 1148-1153

18 **Gholam PM**, Flancbaum L, Machan JT, Charney DA, Kotler DP. Nonalcoholic fatty liver disease in severely obese subjects. *Am J Gastroenterol* 2007; **102**: 399-408

19 **Rocha R**, Cotrim HP, Bitencourt AG, Barbosa DB, Santos AS, Almeida Ade M, Cunha B, Guimarães I. Nonalcoholic fatty liver disease in asymptomatic Brazilian adolescents. *World J Gastroenterol* 2009; **15**: 473-477

20 **Gramlich T**, Kleiner DE, McCullough AJ, Matteoni CA, Boparai N, Younossi ZM. Pathologic features associated with fibrosis in nonalcoholic fatty liver disease. *Hum Pathol* 2004; **35**: 196-199

21 **Daryani NE**, Daryani NE, Alavian SM, Zare A, Fereshtehnejad SM, Keramati MR, Pashaei MR, Habibollahi P. Nonalcoholic steatohepatitis and influence of age and gender on histopathologic findings. *World J Gastroenterol* 2010; **16**: 4169-4175

22 **Shimada M**, Hashimoto E, Kaneda H, Noguchi S, Hayashi N. Nonalcoholic steatohepatitis: risk factors for liver fibrosis. *Hepatol Res* 2002; **24**: 429-438

23 **Argo CK**, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol* 2009; **51**: 371-379

24 **Harrison SA**, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. *Gut* 2008; **57**: 1441-1447

25 **Yatsuji S**, Hashimoto E, Tobari M, Tokushige K, Shiratori K. Influence of age and gender in Japanese patients with nonalcoholic steatohepatitis. *Hepatol Res* 2007; **37**: 1034-1043

26 **Singh DK**, Sakhuja P, Malhotra V, Gondal R, Sarin SK. Independent predictors of steatohepatitis and fibrosis in Asian Indian patients with non-alcoholic steatohepatitis. *Dig Dis Sci* 2008; **53**: 1967-1976

27 **Liew PL**, Lee WJ, Wang W, Lee YC, Chen WY, Fang CL, Huang MT. Fatty liver disease: predictors of nonalcoholic steatohepatitis and gallbladder disease in morbid obesity. *Obes Surg* 2008; **18**: 847-853

28 **Helling TS**, Helzberg JH, Nachnani JS, Gurram K. Predictors of nonalcoholic steatohepatitis in patients undergoing bariatric surgery: when is liver biopsy indicated? *Surg Obes Relat Dis* 2008; **4**: 612-617

29 **Arun J**, Clements RH, Lazenby AJ, Leeth RR, Abrams GA. The prevalence of nonalcoholic steatohepatitis is greater in morbidly obese men compared to women. *Obes Surg* 2006; **16**: 1351-1358

30 **Prashanth M**, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, Shah SR, Rathi PM, Joshi AS, Thakkar H, Menon PS, Shah NS. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. *J Assoc Physicians India* 2009; **57**: 205-210

31 **Hossain N**, Afendy A, Stepanova M, Nader F, Srishord M, Rafiq N, Goodman Z, Younossi Z. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1224-1229, 1229.e1-1229.e2

32 **Chavarría-Arciniega S**, López-Alvarenga JC, Uribe-Uribe NO, Herrera-Hernández M, González-Barranco J. [Relationship between morphological diagnosis of NASH (non-alcoholic steatohepatitis) and liver function tests in a group of patients with morbid obesity]. *Rev Invest Clin* 2005; **57**: 505-512

33 **Rodríguez-Hernández H**, Gonzalez JL, Márquez-Ramirez MD, Flores-Hernandez M, Rodríguez-Morán M, Guerrero-Romero F. Risk factors associated with nonalcoholic fatty liver disease and its relationship with the hepatic histological changes. *Eur J Gastroenterol Hepatol* 2008; **20**: 399-403

34 **Shi JP**, Xun YH, Hu CB, Zhang L, Liu H, Lou GQ, Fan JG. [Clinical and histological features of non-alcoholic fatty liver disease]. *Zhonghua Ganzangbing Zazhi* 2009; **17**: 812-816

35 **Myers RP**. Noninvasive diagnosis of nonalcoholic fatty liver disease. *Ann Hepatol* 2009; **8** Suppl 1: S25-S33

36 **Nomura K**, Yano E, Shinozaki T, Tagawa K. Efficacy and effectiveness of liver screening program to detect fatty liver in the periodic health check-ups. *J Occup Health* 2004; **46**: 423-428

37 **Mofrad P**, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003; **37**: 1286-1292

38 **Fracanzani AL**, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, Bertelli C, Fatta E, Bignamini D, Marchesini G, Fargion S. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology* 2008; **48**: 792-798

39 **McPherson S**, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010; **59**: 1265-1269

40 **Amarapurkar DN**, Patel ND, Kamani PM. Evaluating risk factors for development of non-alcoholic steatohepatitis in type-II diabetes mellitus. *J Hepatitis Monthly* 2008; **8**: 197-200

41 **Bahrami H**, Daryani NE, Mirmomen S, Kamangar F, Haghpanah B, Djalili M. Clinical and histological features of nonalcoholic steatohepatitis in Iranian patients. *BMC Gastroenterol* 2003; **3**: 27

42 **Ryan MC**, Wilson AM, Slavin J, Best JD, Jenkins AJ, Desmond PV. Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. *Diabetes Care* 2005; **28**: 1222-1224

43 **Kang H**, Greenson JK, Omo JT, Chao C, Peterman D, Anderson L, Foess-Wood L, Sherbondy MA, Conjeevaram HS. Metabolic syndrome is associated with greater histologic severity, higher carbohydrate, and lower fat diet in patients with NAFLD. *Am J Gastroenterol* 2006; **101**: 2247-2253

44 **Amarapurka DN**, Amarapurkar AD, Patel ND, Agal S, Baigal R, Gupte P, Pramanik S. Nonalcoholic steatohepatitis (NASH) with diabetes: predictors of liver fibrosis. *Ann Hepatol* 2006; **5**: 30-33

45 **Assy N**, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. *Dig Dis Sci* 2000; **45**: 1929-1934

46 **Hamaguchi M**, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005; **143**: 722-728

47 **Pagano G**, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin P, Rizzetto M. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. *Hepatology* 2002; **35**: 367-372

48 **Lizardi-Cervera J**, Laparra DI, Chávez-Tapia NC, Ostos ME, Esquivel MU. [Prevalence of NAFLD and metabolic syndrome in asymtomatics subjects]. *Rev Gastroenterol Mex* 2006; **71**: 453-459

49 **Moon KW**, Leem JM, Bae SS, Lee KM, Kim SH, Chae HB, Park SM, Youn SJ. [The prevalence of metabolic syndrome in patients with nonalcoholic fatty liver disease]. *Korean J Hepa-*

tol 2004; **10**: 197-206
50 **Xanthakos S**, Miles L, Bucuvalas J, Daniels S, Garcia V, Inge T. Histologic spectrum of nonalcoholic fatty liver disease in morbidly obese adolescents. *Clin Gastroenterol Hepatol* 2006; **4**: 226-232
51 **Chitturi S**, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M, George J. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 2002; **35**: 373-379
52 **Guidorizzi de Siqueira AC**, Cotrim HP, Rocha R, Carvalho FM, de Freitas LA, Barreto D, Gouveia L, Landeiro L. Nonalcoholic fatty liver disease and insulin resistance: importance of risk factors and histological spectrum. *Eur J Gastroenterol Hepatol* 2005; **17**: 837-841
53 **Willner IR**, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. *Am J Gastroenterol* 2001; **96**: 2957-2961
54 **Marchesini G**, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med* 1999; **107**: 450-455
55 **Dixon JB**, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001; **121**: 91-100
56 **Sakurai M,** Takamura T, Ota T, Ando H, Akahori H, Kaji K, Sasaki M, Nakanuma Y, Miura K, Kaneko S. Liver steatosis, but not fibrosis, is associated with insulin resistance in nonalcoholic fatty liver disease. *J Gastroenterol* 2007; **42**: 312-317
57 **Machado M**, Cortez-Pinto H. Non-alcoholic fatty liver disease and insulin resistance. *Eur J Gastroenterol Hepatol* 2005; **17**: 823-826
58 **Stepanova M**, Aquino R, Alsheddi A, Gupta R, Fang Y, Younossi Z. Clinical predictors of fibrosis in patients with chronic liver disease. *Aliment Pharmacol Ther* 2010; **31**: 1085-1094
59 **Pagadala M**, Zein CO, McCullough AJ. Predictors of steatohepatitis and advanced fibrosis in non-alcoholic fatty liver disease. *Clin Liver Dis* 2009; **13**: 591-606
60 **Sumida Y**, Eguchi Y, Ono M. Current status and agenda in the diagnosis of nonalcoholic steatohepatitis in Japan. *World J Hepatol* 2010; **2**: 374-383
61 **Loaeza-del-Castillo A**, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Voráčková F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol* 2008; **7**: 350-357
62 **Angulo P,** Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; **45**: 846-854
63 **Licata A**, Nebbia ME, Cabibbo G, Iacono GL, Barbaria F, Brucato V, Alessi N, Porrovecchio S, Di Marco V, Craxì A, Cammà C. Hyperferritinemia is a risk factor for steatosis in chronic liver disease. *World J Gastroenterol* 2009; **15**: 2132-2138
64 **Loguercio C**, De Simone T, D'Auria MV, de Sio I, Federico A, Tuccillo C, Abbatecola AM, Del Vecchio Blanco C. Nonalcoholic fatty liver disease: a multicentre clinical study by the Italian Association for the Study of the Liver. *Dig Liver Dis* 2004; **36**: 398-405
65 **Friis-Liby I**, Aldenborg F, Jerlstad P, Rundström K, Björnsson E. High prevalence of metabolic complications in patients with non-alcoholic fatty liver disease. *Scand J Gastroenterol* 2004; **39**: 864-869
66 **Younossi ZM**, Gramlich T, Bacon BR, Matteoni CA, Boparai N, O'Neill R, McCullough AJ. Hepatic iron and nonalcoholic fatty liver disease. *Hepatology* 1999; **30**: 847-850
67 **Wieckowska A**, McCullough AJ, Feldstein AE. Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. *Hepatology* 2007; **46**: 582-589
68 **Wieckowska A**, Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. *Semin Liver Dis* 2008; **28**: 386-395
69 **Sebastiani G**, Alberti A. Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. *World J Gastroenterol* 2006; **12**: 3682-3694
70 **Sakugawa H**, Nakayoshi T, Kobashigawa K, Yamashiro T, Maeshiro T, Miyagi S, Shiroma J, Toyama A, Nakayoshi T, Kinjo F, Saito A. Clinical usefulness of biochemical markers of liver fibrosis in patients with nonalcoholic fatty liver disease. *World J Gastroenterol* 2005; **11**: 255-259

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Online Submissions: http://www.wjgnet.com/1948-5182office
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World J Hepatol 2011 August 27; 3(8): I
ISSN 1948-5182 (online)

Acknowledgments to reviewers of *World Journal of Hepatology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Hepatology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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World J Hepatol 2011 **August 27; 3(8): I**
ISSN 1948-5182 (online)

MEETING

Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Franz-Josef-Strauss-Allee 11
Regensburg 93053, Germany

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver
Bangkok, Thailand

February 22, 2011-March 04, 2011
Canadian Digestive Diseases Week 2011
Vancouver, BC, Canada

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 7-11, 2011
Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings
Sarasota, FL 34234, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA 94143, United States

March 25-27, 2011
MedicReS IC 2011
Good Medical Research, Istanbul, Turkey

March 26-27, 2011
26th Annual New Treatments in Chronic Liver Disease
San Diego, CA 94143, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Av. Diagonal, 661-671
Barcelona 08028, Spain

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn, Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV SPIGC, II ESYS
Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 2, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

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World J Hepatol 2011 August 27; 3(8): I-V
ISSN 1948-5182 (online)

INSTRUCTIONS TO AUTHORS

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The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJH* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJH* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJH* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

Indexed and Abstracted in

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Published by

Baishideng Publishing Group Co., Limited

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Acknowledgments

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L

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