Nonalcoholic fatty liver disease in a district general hospital: clinical presentation and risk factors

Wing-Kin Syn · Peter Nightingale · Jeffrey M. Bateman

Received: 11 September 2007 / Accepted: 16 January 2008 / Published online: 28 February 2008
© Asian Pacific Association for the Study of the Liver 2008

Abstract

Introduction Nonalcoholic fatty liver disease (NAFLD) affects one-fifth of the adult population and is currently the commonest liver problem in the western world. The prevalence of NAFLD is likely to rise over the coming decades in parallel to the obesity and diabetes epidemics. A retrospective study was undertaken in a UK district general hospital (DGH) to determine the clinical and laboratory features of patients with NAFLD.

Methods and findings A total of 48 patients with NAFLD were identified. Most (54%) were asymptomatic on presentation and 90% had an echogenic liver on ultrasonography (USS). Liver tests were elevated in the majority, but did not distinguish between simple steatosis and steatohepatitis. Having features of the metabolic syndrome and a low platelet count ($P = 0.028$) may help identify patients with advanced hepatic fibrosis.

Conclusions NAFLD is common in the DGH and should be considered in all patients with metabolic risk factors. A liver biopsy should be considered in those with low platelets, type II diabetes mellitus, and the metabolic syndrome.

Keywords District general hospital · Liver tests · Metabolic syndrome · Nonalcoholic fatty liver · Ultrasonography

Abbreviations

NASH	(Nonalcoholic) steatohepatitis
USS	Ultrasound
WCC	White cell count
INR	International normalized ratio
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
GGT	Gamma gluteryltransferase
AST	Aspartate aminotransferase
BMI	Body mass index
ATP	Adult treatment panel

Introduction

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by the accumulation of excess fat in the liver in the absence of significant alcohol consumption. Histologically, NAFLD ranges from simple bland steatosis to steatohepatitis (NASH), where there is a risk of progressive liver damage, leading to cirrhosis [1, 2]. Although NAFLD has no specific clinical or laboratory features, a *presumed* diagnosis of NAFLD can often be made in a patient with a combination of a mildly elevated liver biochemistry, negative liver screen, “bright” liver on abdominal ultrasonography (USS), and the presence of metabolic risk factors such as hypertension, noninsulin-dependent diabetes mellitus and insulin-resistance, hyperlipidemia, and obesity [2–4]. The definitive diagnosis of NAFLD is made on a liver biopsy [5, 6] as patients with NAFLD may present with “normal” liver biochemistry [7–9] and at least 20% of people with persistently abnormal

W.-K. Syn · J. M. Bateman
Princess Royal Hospital, Apley Castle, Telford,
Shropshire TF1 6TF, UK

J. M. Bateman
e-mail: Jeffrey.Bateman@sath.nhs.uk

W.-K. Syn (✉)
Liver Unit and Hepatobiliary Unit, Queen Elizabeth Hospital,
3rd Floor Nuffield House, Birmingham B15 2TH, UK
e-mail: wsyn@doctors.org.uk

P. Nightingale
Wellcome Trust Clinical Research Facility, Birmingham, UK
e-mail: peter.nightingale@uhb.nhs.uk

alanine aminotransaminase values have an alternative diagnosis. More important, a liver biopsy is currently the only reliable method in distinguishing simple steatosis from NASH and allows an assessment of disease severity [5, 6].

Nonalcoholic fatty liver disease is a major public health concern as it affects nearly 20% of the adult population, is the commonest liver problem in the western world, and is the commonest cause of cryptogenic cirrhosis in the United States [10]. Recent studies have suggested that NAFLD may also be a marker and mediator of coronary artery disease [11]. Despite a lack of proven therapy for NAFLD, indirect evidence suggests that controlling certain risk factors may reduce the risks of progressive liver damage [12]. In the UK, the health and economic burden from NAFLD is expected to rise in parallel to the increasing prevalence of noninsulin-dependent diabetes mellitus and childhood obesity [13–16]. As secondary health care in the UK continues to be provided in district general hospitals (DGH) by general physicians, it can be envisaged that DGH will have to cope with an increasing number of patients with NAFLD and NAFLD-related diseases.

Given the paucity of published (NALFD) experience from DGH, we reviewed data from a single gastroenterology unit in the district of Shropshire, UK. We studied the initial clinical presentations and laboratory results and identified risk factors of advanced liver disease.

Methods

In this study, a *probable* diagnosis of NAFLD was defined by an “echogenic” or “bright” liver on USS, while a *definite* diagnosis of NAFLD was made on a liver biopsy [5]. Between 2006 and 2007, all patients with a new *probable* or *definite* diagnosis of NAFLD from the gastroenterology department were recruited into this retrospective analysis. Patients were excluded from the study if they had known liver disease, had recent sepsis, were on medications that are known to cause a fatty liver, or consumed over 5 units of alcohol per week. The alcohol consumption was determined by directquestioning of the patient, interviews with family members, and measurement of random blood alcohol levels.

Abdominal imaging

“Fatty” changes within a liver may be detected by abdominal USS [6, 17, 18]. All patients with nonspecific abdominal pain, hepatomegaly, features of portal hypertension (splenomegaly, ascites, and varices), and abnormal liver biochemistry undergo USS.

Liver biopsy and histology

In the absence of contraindications, liver biopsies were performed when clinically indicated as directed by the supervising clinician. Liver biopsies were performed either as a “blind” procedure or under USS-guidance, depending on the availability of an interventional radiologist.

Liver sections were routinely stained with hematoxylin and eosin, hematoxylin van Gieson, reticulin, orcein, Perl, and periodic acid–Schiff with and without diastase pretreatment. NASH is characterized by perivenular hepatocyte ballooning in setting of macrovesicular steatosis, mixed lobular inflammation, and pericellular fibrosis with or without Mallory bodies [19]. Disease severity is based on the Brunt grading and staging classification [20]. Briefly, inflammation was graded as mild, moderate, or severe, depending on the severity of steatosis, zone three ballooning, and lobular inflammation, while fibrosis stage was assigned as stage one (pericellular or perivenular fibrosis), stage two (stage one with portal fibrosis), stage three (bridging fibrosis), and stage four (cirrhosis).

Full blood count, liver biochemistry, serology, and immunology

All patients had routine blood tests for full blood count (hemoglobin, white cell count [WCC], platelets), international normalized ratio (INR), and liver biochemistry (serum bilirubin, alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma gluteryltransferase [GGT]) taken on the day of clinical assessment. Normal ranges are as follows: INR, 1; platelets, $150\text{--}500 \times 10^9/\text{L}$; bilirubin, $1\text{--}17 \mu\text{mol}/\text{L}$; ALT, $10\text{--}31 \text{ U}/\text{L}$; ALP, $45\text{--}145 \text{ U}/\text{L}$; GGT, $0\text{--}50 \text{ U}/\text{L}$. Serum aspartate transaminase (AST) is not part of the routine liver panel at our center. Immunological tests (antinuclear antibodies, antimitochondrial antibodies, antismooth muscle antibodies) for autoimmune diseases, serological tests for hepatitis B and C viruses (hepatitis B surface antigen, antihepatitis C antibodies), and serum levels for metabolic disease (ceruloplasmin, alpha-1 antitrypsin, ferritin) were performed in patients with abnormal liver biochemistry or abnormal USS. Patients with elevated ferritin levels (normal range $30\text{--}350 \mu\text{g}/\text{L}$) have additional blood samples taken for hemochromatosis gene (C282Y/H63D) mutation analysis. Those with low ceruloplasmin levels had blood and urine analyzed for copper levels.

Clinical analysis

Relevant clinical and anthropometric data were collected through a retrospective notes review. Note was made to the

presence of any metabolic risk factors such as hypertension, type II diabetes mellitus, hyperlipidemia, and hyperuricemia. A patient is overweight when the body mass index (BMI) is between 25 and 29.9 kg/m² and is obese when BMI is over 30 kg/m².

The diagnosis of the metabolic syndrome is based on meeting three or more of the National Institute of Health (Adult Treatment Panel) ATP III criteria, which consists of hypertension, central obesity, elevated fasting blood sugar, high triglycerides, and low high-density lipoproteins [21].

Statistical analysis

Data were analyzed with SPSS for Windows 15.0 (SPSS, Chicago, IL). Variables studied included patients' age, BMI, presence or absence of the metabolic syndrome, ALT, bilirubin, GGT, ALP, and platelet counts. Comparisons of groups were made with the Mann–Whitney test or Fisher exact test. The Spearman correlation coefficient was used to measure association with age. A *P*-value less than 0.05 is considered statistically significant.

Results

Study population (Table 1)

Between 2006 and 2007, 48 patients were newly identified as having either *probable* or *definite* NALFD. A total of 15 (31%) patients had biopsy-proven and hence *definite* NALFD. The majority were Caucasians; three (6%) were Asians (Indian subcontinent).

Clinical features (Table 1)

Over half (26/48) with *probable* or *definite* NALFD were asymptomatic and were identified by referring physicians or general practitioners from elevated liver tests. None of the patients had stigmata of chronic liver disease. At the time of diagnosis, the median values of routine liver biochemistry were as indicated in Table 1. INR were less than 1.2. None had hepatitis B or C infection. Five patients (10%) had elevated ferritin level (median 300 microgram/L; range 130–734), but none carried the common hemochromatosis gene mutation. One patient had a moderately elevated antinuclear antibody titre of

Table 1 Demographics and clinical features

	Patients with <i>Definite</i> or <i>Probable</i> NALFD
Number recruited	48
Age (median, years)	62 (range: 30–78)
Sex	F 23 (48%); M 25 (52%)
<i>Symptoms</i>	
No symptoms	26 (54%)
Abdominal pain	16 (33%)
Chest pain	5 (10%)
Others (renal failure)	1 (2%)
<i>Liver biochemistry (normal values)</i>	
ALT (10–31 U/L)	64 (range, 9–511)
Bilirubin (1–17 umol/L)	11 (range, 4–51)
GGT (0–50 U/L)	152 (range, 17–1848)
ALP (45–145 U/L)	109 (range, 53–555)
Platelets (normal value; 150–500 × 10 ⁹ / L)	253 × 10 ⁹ (range, 137–442)
<i>Ultrasonography</i>	
Echogenic liver	43 (90%)
Normal liver	5 (10%)
<i>Metabolic risk factors</i>	
Obesity	43 (90%)
Hypertension	33 (69%)
Type II diabetes mellitus	19 (40%)
Hyperlipidaemia	27 (56%)
Gallstones / Previous cholecystectomy	17 (35%)

1:160, but no other immunological features of autoimmune hepatitis.

Abdominal imaging and liver histology

All patients underwent USS examination, and 90% had increased echogenicity in the liver (Table 1). In total, 16 (33%) patients (11 “echogenic” liver and five normal liver) went on to have a liver biopsy. 15 (31%) biopsies showed macrovesicular steatosis, but only three (6%) had evidence of NASH (one patient had stage one fibrosis, one patient had stage two fibrosis while another had stage three fibrosis). None had cirrhosis. One biopsy was normal. There were no complications from liver biopsies.

Complications of liver disease

One patient with NASH fibrosis (stage three) had small-volume ascites and esophageal varices.

Metabolic risk factors and cardiovascular disease

A total of 37 (77%) patients had at least one feature of the metabolic syndrome and 26 (54%) patients fulfilled the criteria for the metabolic syndrome (Table 1). The median BMI was 32 kg/m² (range 22–55). Uric acid levels were checked in only 20 patients; 12 (60%) had elevated levels.

Five patients had previous cardiovascular, cerebrovascular, or peripheral vascular ischemic events; three of them also had the metabolic syndrome.

Subgroup analysis

- (a) Neither BMI nor the presence or absence of the metabolic syndrome showed any significant associations with routine blood tests (Table 2).
- (b) Biopsy-proven simple steatosis versus NASH.

Platelet counts were lower in NASH compared with simple steatosis (244 vs. 274.5; $P = 0.028$). There were no significant differences in ALT (89 vs. 98, $P = 0.83$), bilirubin (13 vs. 10, $P = 0.72$), ALP (120 vs. 150, $P = 0.59$), and GGT levels (267 vs. 229.5, $P = 0.47$).

Neither BMI ($P = 1$) nor age (median years; NASH 63 vs. simple steatosis 60; $P = 0.65$) was significantly different between groups. While all three patients with NASH had four or more features of the metabolic syndrome, all 12 patients with simple steatosis had three or less features. Type II diabetes mellitus was present in all (100%) NASH patients, but occurred in less than half of those (42%) with simple steatosis.

Discussion

NAFLD is a common medical condition, but may be easily overlooked, as patients are often asymptomatic [22]. Over 50% of our patients were referred only after the detection of elevated liver tests, while the rest presented with non-specific abdominal and chest discomfort. Fatigue and right upper discomfort are common and are probably related to liver capsule distension [4]. Although previously considered a disease of exclusion, NAFLD should now be suspected in all patients with associated metabolic risk factors such as hypertension, type 2 diabetes, hyperlipidemia, and truncal obesity [23]. Over 70% of those with NAFLD had at least one of these factors and 90% had a BMI greater than 25 kg/m². Over 50% also fulfilled the ATP III criteria for the metabolic syndrome. Our findings were comparable to a study of 304 consecutive NAFLD patients, where one-third of men and two-thirds of women fulfilled the criteria for the metabolic syndrome [24] and the prevalence of metabolic syndrome was found to increase with BMI. No measurements of insulin-resistance were taken in our patients, which probably reflects clinical practice in the UK. The diagnosis of NAFLD is important

Table 2 Relationship between Age, BMI, presence or absence of the metabolic syndrome with routine blood tests

	Age		BMI			Metabolic syndrome		
	rho	P-value	Normal ^a	Obese ^a	P-value*	No ^a	Yes ^a	P-value*
ALT	−0.31	0.037	35 (21–164)	67 (41–114)	0.17	64 (41–166)	56 (35–104)	0.47
Bil	−0.10	0.50	10 (7–23)	11 (7–15)	0.96	10 (7–15)	12 (6–17)	0.57
ALP	0.07	0.63	121 (94–350)	107 (75–150)	0.33	111 (77–166)	109 (74–150)	0.79
GGT	0.16	0.29	172 (63–790)	127 (52–244)	0.54	96 (35–426)	162 (57–257)	0.70
Platelets	−0.10	0.57	300 (263–313)	252(198–296)	0.45	262 (189–321)	247 (216–292)	0.74

rho = Spearman correlation coefficient; Bil = Bilirubin

* For comparison of two groups using Mann–Whitney test

^a Values are medians (lower quartile–upper quartile)

as up to a quarter of patients with steatohepatitis may progress to cirrhosis [25]. Moreover, NAFLD may be associated with progressive liver disease from alcoholic liver disease and viral hepatitis and may increase sensitivity to drug or toxin-induced hepatotoxicity [26–30]. In an autopsy study, atherosclerosis was found more commonly in children with NAFLD [11], and NAFLD was also shown to be associated with greater severity of coronary disease [31]. In this study, five patients with NAFLD had concurrent cardiovascular or cerebrovascular disease.

Currently, a liver biopsy is considered the gold standard for the diagnosis of NAFLD [5]. In this study, we found that ALT and GGT levels were 2 times and 3 times above the upper limit of normal. Although GGT is the most common abnormality in NAFLD [22], this is not specific and there is currently no agreement on the liver enzymes used to make the diagnosis [32]. Moreover, individual values of ALT and GGT fell within the normal limit (17% and 21%, respectively) and were therefore unhelpful in predicting the presence or absence of NAFLD. USS, computed tomography, and magnetic resonance imaging have all been used to assess hepatic fat deposition and have been shown to be equally accurate in assessing the degree of steatosis [6]. In a recent study, over 80% of patients with indicative USS appearances have NAFLD on a liver biopsy [33]. Nearly 90% of our patients with NAFLD had “echogenic” liver on USS. 10 out of 11 patients with echogenic liver, who went on to have a liver biopsy, had NAFLD. Insensitivity of the USS occurs when steatosis affects less than one-third of the liver volume [6, 34, 35]. This probably explained the normal USS appearances of five patients with biopsy-proven NAFLD and highlights the usefulness of a liver biopsy. It is essential to identify patients who have a higher risk of disease progression, as they should be treated more aggressively and should undergo cancer surveillance [36, 37]. At present, a liver biopsy is the only reliable way of differentiating simple steatosis from steatohepatitis and also allows the staging of disease [5, 38]. Several studies have shown that age at the time of diagnosis, obesity, diabetes, and AST:ALT ratio may be useful, indirect predictors of advanced disease [39–41]. We found that neither age ($P = 0.65$), nor BMI ($P = 1$) or routine liver tests (above) were able to distinguish simple steatosis from steatohepatitis. In contrast, platelet counts were significantly lower ($P = 0.028$) in those with NASH. As AST was not measured at our center, we were unable to validate the prognostic value of AST:ALT ratio in the DGH setting.

Although this study was not designed to assess the prevalence or incidence of disease, it provided a “snapshot” of current clinical burden in a DGH. It is likely that even more patients have NAFLD as only those from the gastroenterology department were recruited. Up to 75% of

patients with type II diabetes mellitus and over 50% of patients with a history of myocardial infarct have NAFLD [31, 42, 43]. Many patients undergoing bariatric surgery will also have NAFLD [44–46]. With the rapidly increasing prevalence of obesity and diabetes [13, 15], the overall number of patients who will develop NAFLD will only increase. These observations are important as they allow departments to predict areas of clinical expansion, and therefore, appropriate resource allocation. Despite a small study population, we have shown that a majority of patients with echogenic livers on USS have NAFLD on biopsies and found that liver tests are poor predictors of fibrosis.

In conclusion, the clinical burden from NAFLD is significant. Many patients are asymptomatic and the diagnosis of NAFLD should be considered in all patients with metabolic risk factors. Routine liver biochemistry is unhelpful in identifying patients with NAFLD and only platelet counts correlate with advanced disease. A liver biopsy is currently still the best way of staging NAFLD and should be considered in patients with multiple metabolic risk factors.

References

1. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: mayo clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc.* 1980;55:434–8.
2. Chitturi S, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. *Semin Liver Dis.* 2001;21:27–41.
3. Powell EE, Cooksley WG, Hanson R, et al. The natural history of non-alcoholic steatohepatitis: a follow-up study of 42 patients for up to 21 years. *Hepatology.* 1990;11:74–80.
4. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-tetri BA. Non-alcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology.* 1994;107:1103–9.
5. Bianchi L. Liver biopsy in elevated liver function tests? An old question revisited. *J Hepatol.* 2001;35:290–4.
6. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in non-alcoholic fatty liver disease. *Gastroenterology.* 2002;123:745–50.
7. Mofrad P, Contos M, Haque M, et al. Clinical and histologic spectrum of non-alcoholic fatty liver disease with normal ALT values. *Hepatology.* 2003;37:1286–92.
8. Clark JM, Diehl AM. Defining non-alcoholic fatty liver disease: implications of epidemiological studies. *Gastroenterology.* 2003;124:248–50.
9. Yu AS, Keefe EB. Elevated AST or ALT to non-alcoholic fatty liver disease: accurate predictor of disease prevalence? *Am J Gastroenterol.* 2003;98:955–6.
10. Clark JM, Diehl AM. Non-alcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. *JAMA.* 2003;289(22):3000–4.
11. Schwimmer JB, Deutsch R, Behling C, et al. Fatty liver as a determinant of atherosclerosis. *Hepatology.* 2005;42:610A.
12. George J, Farrell GC. Management of NASH: current and future perspectives on treatment. In: Farrell G, George J, de la Hall PM, McCullough AJ, editors. *Fatty liver disease: NASH and related disorders*. Malden: Blackwell Publishing; 2005. p. 194–207.
13. Office for National Statistics. Obesity among adults: by sex and NS-SeC. *Social Trends* 2001;34.

14. Livingstone MB. Childhood obesity in Europe: a growing concern. *Public Health Nutr.* 2001;4(1A):109–16.
15. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995–2005: a population-based study. *Lancet.* 2007;369(9563):750–6.
16. Ehtisham S, Barrett TG. The emergence of type 2 diabetes in childhood. *Ann Clin Biochem.* 2004;41(Pt 1):10–6.
17. Ricci C, Longo R, Gioulis E, et al. Noninvasive in vivo quantitative assessment of fat content in human liver. *J Hepatol.* 1997;27(1):108–13.
18. Siegelman ES, Rosen MA. Imaging of hepatic steatosis. *Semin Liver Dis.* 2001;21(1):71–80.
19. Neuschwander-Tetri BA, Caldwell SH. Non-alcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology.* 2003;37:1202–19.
20. 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;94:2467–74.
21. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *J Am Med Assoc.* 2001;285:2486–97.
22. Cua IH, George J. Non-alcoholic fatty liver disease. *Hosp Med.* 2005;66(2): 106–11.
23. George J, Farrell GC. Practical approach to the diagnosis and management of people with fatty liver diseases. In: Farrell G, George J, de la Hall PM, McCullough AJ, editors. *Fatty liver disease: NASH and related disorders.* Oxford: Blackwell Publishing; 2005. p. 181–93.
24. Marchesini G, Bugianesi E, Forlani G, et al. Non-alcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology.* 2003;37:917–23.
25. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology.* 1999;116: 1413–9.
26. Powell EE, Jonsson JR, Clouston AD. Steatosis: co-factor in other liver diseases. *Hepatology.* 2005;42(1):5–13.
27. Donthamsetty S, Bhawe VS, Mitra MS, Latendresse JR, Mehendale HM. Nonalcoholic fatty liver sensitizes rats to carbon tetrachloride hepatotoxicity. *Hepatology.* 2007;45(2):391–403.
28. Bondini S, Younossi ZM. Non-alcoholic fatty liver disease and hepatitis C infection. *Minerva Gastroenterol Dietol.* 2006;52(2): 135–43.
29. Donthamsetty S, Bhawe VS, Mitra MS, et al. Non alcoholic steatohepatitis (NASH) sensitizes liver to hepatotoxicity. *Hepatology.* 2005;42:631A.
30. Kon K, Ikejima K, Okumura K, et al. Acetaminophen induces severe liver injury in obese and diabetic KK-Ay mice. *Hepatology.* 2005;42:512A.
31. Kessler A, Levy Y, Roth A, et al. Increased prevalence of NAFLD in patients with acute myocardial infarction independent of BMI. *Hepatology.* 2005;42:623A.
32. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol.* 2003;98(5):960–7.
33. Prati D, Taioli E, Zanella A, et al. Updated definitions of health ranges for serum amino transferase levels. *Ann Intern Med.* 2002;137:1–9.
34. Graif M, Yanuka M, Baraz M. Quantitative estimation of attenuation in ultrasound video images: correlation with histology in diffuse liver disease. *Invest Radiol.* 2000;35:319–24.
35. Joseph A, Savarymattu S, Al-Sam S, et al. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol.* 1991;43:26–31.
36. Marrero JA, Fontana RJ, Fu S, et al. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol.* 2005;42:218–24.
37. Hashimoto E, Yatsuji S, Kaneda H, et al. The characteristics and natural history of Japanese patients with nonalcoholic fatty liver disease. *Hepatol Res.* 2005;33:72–6.
38. Pinto HC, Baptista A, Camilo ME, et al. Non-alcoholic steatohepatitis: clinicopathological comparison with alcoholic hepatitis in ambulatory and hospitalized patients. *Dig Dis Sci.* 1996;41: 172–9.
39. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with non-alcoholic steatohepatitis. *Hepatology.* 1999;30:1356–62.
40. Ratziu V, Giral P, Charlotte F, et al. Liver fibrosis in overweight patients. *Gastroenterology.* 2000;118:1117–23.
41. Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. *J Clin Gastroenterol.* 2006;40(3 Suppl 1):S5–10.
42. Medina J, Fernandez-Salazar LI, Garcia-Buey L, et al. Approach to the pathogenesis and treatment of nonalcoholic steatohepatitis. *Diabetes Care.* 2004;27:2057–66.
43. Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care.* 2007;30(5):1212–8. [Epub 2007 Feb 2].
44. DelGaudio A, Boschi L, DelGaudio GA, Mastrangel L, Munars D. Liver damage in obese patients. *Obes Surg.* 2001;11:254–7.
45. Silverman EM, Sapala JA, Appelman HD. Regression of hepatic steatosis in morbidly obese persons after gastric bypass. *Am J Clin Pathol.* 1995;104:23–31.
46. Klain J, Fraser D, Goldstein J, et al. Liver histology in the morbidly obese. *Hepatology.* 1989;10:873–6.