P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(5):1106-1110
World Journal of Gastroenterology
 ISSN 1007-9327

• CLINICAL RESEARCH •

Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey

Lei Shen, Jian-Gao Fan, Yan Shao, Min-De Zeng, Jun-Rong Wang, Guo-Hao Luo, Ji-Qiang Li, Si-Yao Chen

Lei Shen, Min-De Zeng, Guo-Hao Luo, Ji-Qiang Li, Department of Gastroenterology, Renji Hospital, Second Medical University, Shanghai 200001, China
Jian-Gao Fan, Yan Shao, Department of Gastroenterology, First People' s Hospital, Shanghai, China
Jun-Rong Wang, Central Hospital of Putou District, Shanghai, China
Si-Yao Chen, Zhongshan Hospital, Fudan University, Shanghai, China
Correspondence to: Dr Jian-Gao Fan, Department of Gastroenterology, First People' s Hospital, Shanghai 200080, China. fanjg@citiz.net
Telephone: +86-21-63240090-3141 **Fax:** +86-21-63240825
Received: 2002-06-28 **Accepted:** 2002-07-25

Abstract

AIM: To determine the prevalence of nonalcoholic fatty liver in a specific population in Shanghai by an epidemiological survey, and to analyze risk factors of fatty liver.

METHODS: Total 4009 administrative officers who denied regular alcohol drinking participated in the survey, and underwent physical examination and laboratory tests. The important parameters were body mass index (BMI), waist hip circumferences ratio (WHR) and levels of serum lipids. Diagnosis of fatty liver was based on established real-time ultrasonographic criteria, the presence of an ultrasonographic pattern consistent with "bright liver", with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins. Analysis of data was performed through SPSS for Windows statistical package.

RESULTS: The overall prevalence of fatty liver was 12.9 %, 15.8 % in males and 7.5 % in females, and the prevalence of fatty liver in males younger than 50 years old, was significantly higher (13.3 %) than that of in females (2.7 %). But the difference between the sexes became less significant in people older than 50 years (19.1 % *vs* 18.1 %). The prevalence of fatty liver was increased with age; this was markedly presented in females younger than 50 years. Multiple variant regression analysis demonstrated that the prevalence of fatty liver was positively correlated to several risk factors, including male, aging (>50yr), hyperlipidemia, impaired glucose tolerance/diabetes mellitus, hypertension and overweight/obesity.

CONCLUSION: There is a high prevalence of nonalcoholic fatty liver among certain population in Shanghai, to which overweight and hyperlipidemia are closely relevant.

Shen L, Fan JG, Shao Y, Zeng MD, Wang JR, Luo GH, Li JQ, Chen SY. Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey. *World J Gastroenterol* 2003; 9(5): 1106-1110
http://www.wjgnet.com/1007-9327/9/1106.htm

INTRODUCTION

Fatty liver has increasingly been recognized as an important and common form of chronic liver disease over the past 20 years[1]. Fatty liver consists the intrahepatic accumulation of lipids. It is the commonest liver disease, accounting for abnormal liver function tests in the majority of asymptomatic subjects[2]. Although generally unprogressive, fatty liver is an important precursor to the development of fibrosis in aetiologically diverse conditions such as hepatitis C, and alcoholic and nonalcoholic liver disease[3]. Furthermore, it has the potential to lead to end-stage liver failure[4] via steatohepatitis from lipid peroxidation, even in the nonalcohol drinker, an entity that is being studied with growing interest in the affluent society[5]. Fatty liver is an increasingly common problem worldwide and has been reported in Japan[6,7], Australia[8], America[4,9], Europe[10,11], and the Middle East[12], although geographic variations in prevalence are evident. Along with the steady improvement of living level and wide use of ultrasonography, the number of patients with diagnosis of fatty liver is increasing in China recently. The objective of this study was to determine the prevalence of fatty liver in a specific population in Shanghai by epidemiological survey, and analysis of its risk factors.

MATERIALS AND METHODS

Study participants (demographics)

A total of 4375 administrative officers, who took part in annual regular physical examination from September 1 to November 30 in 1999 (in Renji Hospital and Central Hospital of Putuo District in Shanghai) were recruited. Complete laboratory data were obtained from 4009 participants, who denied regular alcohol drinking and included in this study. 2583 were males and 1426 females. The mean age of participants was 46±14 years with ranged was 20-81 years.

Methods of examination

For each participant, an extensive medical history was obtained that included alcohol intake, history of chronic liver disease in first-degree relatives; a detailed history of viral hepatitis, gallstone disease and drug abuse; previous diagnosis of diabetes, hypertension and coronary heart disease.

Each participant also underwent a detailed physical examination, including of measurement of body weight, height, waist and hip circumferences. The body mass index (BMI) was calculated as: body weight in kg/(height in meter)^2.The waist hip circumferences ratio (WHR) was calculated by dividing waist girth (halfway between the lower costal margin and the iliac crest in the mid expiratory phase of breathing while the subject was standing) by hip girth (maximum circumference around the buttocks) previously measured while the subject was wearing light underwear.

Laboratory tests included routine blood and urine analysis, serum alanine aminotransferase (ALT), total cholesterol (Tch), triglycerine (TG), low-density lipoprotein cholesterol (LDL-Ch), high-density-lipoprotein cholesterol (HDL-Ch), plasma glucose levels, hepatitis B surface antigen (HB_sAg), routine chest fluorography, electrocardiography and optic fundus examination.

Ultrasonographic examination of liver and gallbladder was performed by two experienced ultrasonographers, using the Simens Sonoline-SI450 unit with 3.5MHz probe. Fatty liver was defined as the presence of an ultrasonographic pattern consistent with "bright liver," with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of chronic liver disease[13,14].

Statistical analysis

All statistical analysis was processed by Clinical Epidemiological Network in Zhongshan Hospital, Fudan University with Software SPSS. Statistical analysis was performed by using the SPSS statistical package, version 7.1(SPSS, Inc.). The following tests were applied, unpaired Student' s *t*-test, chi-squared test with Fisher' s exact test, analysis of variance, and logistic regression analysis (LRA). Rejection of the null hypothesis was set at $P<0.05$. Analysis of data was performed through SPSS for Windows statistical package.

RESULTS

Body-mass index (BMI)

The mean BMI was 22.93±2.82. Among them 31.6 % had BMI>24, which were considered as overweight, 53.3 % had BMI between 20-24; and 15.1 % had BMI<20.

Waist-hip-circumference ratio (WHR)

The mean value of WHR was 0.83±0.06. Among them 2.78 % had WHR >0.94, 21.1 % had WHR between 0.88-0.94 and 76.2 % had WHR<0.88.

Blood lipids

The mean TG was 115.9±84.6 mg/dl (1.31±0.95 mmol/L), Tch 189.0±56.7 mg/dl (4.89±1.47 mmol/L). Among them 627 had hypertriglycerinemia only; 282 participants had hypercholestrolemia only and 256 participants had mixed hyperlipidemia. Thus, the prevalence of hyperlipidemia among participants was 28.9 %. Each patient was classified into the following four previously defined hyperlipidemia phenotypes according to 12-hr fasting plasma lipid levels: hypertriglycemia (≥150 mg/dl, 1.7 mmol/L), hypercholesterinamia (≥220 mg/dl, 5.7 mmol/L), mixed hyperlipidemia and normal blood lipids.

Blood glucose, liver function and HB_sAg

Among participants 86 (2.2 %) suffered from impaired glucose tolerance, 93 (2.3 %) had diabetes mellitus (DM); 59 (1.5 %) suffered from increased ALT, and 257 (6.4 %) were HB_sAg positive.

Fatty liver and cholelithiasis

Fatty liver was detected with ultrasound examination in 516 participants (12.9 %); cholesterol crystal in gallbladder was detected in 54 persons (1.3 %), Gallstone or cholecystoectomy was noted in 358 participants (8.9 %).

Influence of sex and aging on parameters

In this study, the mean age of male participants (47.3±14.7 years) was older than the female participants (43.4±23.5 years, $P<0.01$). BMI, WHR, serum level of TG and glucose in male group was significantly higher than those in female group. Levels of serum Tch and LDL -Ch were similar in both groups (Table 1).

As presented in Table 2, there are more participants with increased ALT, positive HB_sAg and arteriosclerosis of optic fudus in male group. Prevalence of DM, coronary artery disease, hypertension and fatty liver are significantly higher in male group than those in female group; but the prevalence of cholelithiasis is similar in both groups.

Table 3 shows sex and age related change of hyperlipidemia. In participants younger than 50 years old, more cases of hypertriglycernemia are detected, whereas participants older than 50 years older, prevalence of hypercholesterolemia increase significantly, especially in females. In whole group the prevalence of three hyperlipidemia types increase significantly with aging.

Among females younger than 50 years old, the prevalence of hyperlipidemia is lower than that among males. After 50 years of age this prevalence was significantly higher than in males.

As in showed the Table 4, the prevalence of fatty liver increased with aging, which is markedly presented in females younger than 50 years. The prevalence of fatty liver in males younger than 50 years is significantly higher (13.3 %) than that in females (2.7 %). In participants older than 50 years, no significant difference of prevalence of fatty liver is noted between males and females (19.1 % *vs* 18.1 %).

Table 1 Obesity indices and lipid parameters in males and females

Parameters	Male	Female	*P* value
BMI	23.5±2.7	21.5±2.6	<0.001
WHR	0.86±0.05	0.79±0.06	<0.001
TG(mg/dl)	126.3±87.7	97.2±75.2	<0.001
TCh(mg/dl)	188.8±56.7	189.3±56.6	>0.05
HDL-Ch(mg/dl)	81.4±75.4	84.4±57.0	>0.05
LDL-Ch(mg/dl)	143.1±166.0	133.5±153.7	>0.05

Table 2 Difference of prevalences of several diseases in males and females

Diseases	Male%	Female%	*P* value
Abnormal ALT	2.1	0.35	<0.001
Positive HB_sAg	7.3	4.8	<0.001
Arteriosclerosis of optic fundus	13.4	6.3	<0.001
Diabetes mellitus	5.1	3.3	<0.001
Coronary artery disease	3.5	2.3	<0.001
Hypertension	15.3	8.2	<0.001
Gallstone	8.9	8.9	>0.05
Fatty liver	15.8	7.5	<0.001

Table 3 Relation between hyperlipidemia and age in males and females

Age (yr)	Sex	*n*	Hypertriglycerinemia %	Hypercholesterolemia%	Mixed hyperlipidemia%	Sum%
<30	Male	314	11.6	1.5	1.2	14.3
	Female	257	1.1	2.7	0.7	4.5
	Total	571	6.9	2.1	1.0	9.0
30-50	Male	1202	17.3	3.9	4.9	26.1
	Female	726	4.5	4.9	1.3	10.7
	Total	1928	12.5	4.3	3.6	20.3
51-64	Male	702	22.6	6.9	9.2	38.7
	Female	324	16.9	18.5	17.5	52.9
	Total	1026	20.8	10.6	11.8	43.2
≥65	Male	365	28.5	12.9	11.3	52.7
	Female	119	24.2	25.0	14.3	63.5
	Total	484	27.4	27.4	12.0	55.4

Table 4 Prevalence of fatty liver in groups of different sex and ages

Age(years)	Sex	Number	Fatty liver *n*%
<30	Males	314	11 (6.4)
	Females	257	2 (1.6)
	Total	571	13 (2.3)
30-50	Males	1202	190 (20.7)
	Females	726	25 (5.4)
	Total	1928	215 (11.2)
51-64	Males	702	125 (17.9)
	Females	324	57 (19.7)
	Total	1026	182 (17.7)
⩾65	Males	365	83 (22.7)
	Females	119	23 (19.3)
	Total	484	106 (21.9)

In this survey 516 patients (12.9 %) with fatty liver were detected by ultrasonography. The age, BMI, WHR, levels of serum TG and Tch of patients with fatty liver were significantly higher than participants without fatty liver (3493 persons). The details were presented in Table 5. The results of monovariant regression analysis of relation between prevalence of fatty liver and other factors was presented in Table 6. Prevalence of fatty liver was associated with several parameters, including sex, BMI, and WHR.

Stepwise logistic multivariant regression analysis of relationship between prevalence of fatty liver and other parameters demonstrated that 9 parameters were closely related with prevalence of fatty liver. As presented in order of importance, these were WHR, increased ALT, BMI, and hypertension, DM and impaired glucose tolerance, hyperlipidemia, male sex and arteriosclerosis of optic fundus.

Table 5 Obesity indices and lipid parameters in groups with and without fatty liver

	Age (years)	BMI (kg/m^2)	WHR	TG (mg/dl)	TCh (mg/dl)
Group without fatty liver	44.6±14.3	22.2±2.4	0.8±0.1	105.0±78.4	186.2±59.5
Group with fatty liver	52.3±13.0	26.0±2.4	0.9±0.1	168.6±93.4	202.2±37.7

Table 6 Results of monovariant regression analysis of fatty liver and various parameters

Parameters	B value	βvalue	T value	*P* value
Sex	0.038	0.063	2.59	0.0000
Age	0.53	0.062	2.79	0.0018
BMI	0.073	0.522	23.89	0.0000
Waist circumference	0.010	0.216	5.87	0.0000
WHR	0.782	0.129	4.96	0.0000
TG	0.000	0.084	3.08	0.0021
TCh	-0.0000	-0.079	-3.12	0.0016
HDL-Ch	-0.000	-0.047	-2.17	0.0300
LDL-Ch	-0.000	0.332	2.61	0.0092
Hyperlipidemia	0.094	0.160	7.27	0.0000
Arteriosclerosis	0.062	0.087	3.59	0.0000
Hypertension	0.068	0.099	4.45	0.0000
Diabetes mellitus	0.149	0.130	3.42	0.0000
Coronary heart disease	0.142	0.067	3.14	0.0018
Abnormal ALT	0.156	0.069	3.24	0.0012
Positive HB_sAg	-0.09	0.063	-3.02	0.0026

Table 7 Results of Logistic multivariant regression analysis

	B	SE	Wald	df	Sig	R	Exp(B)
WHR	2.2	0.19	139.2	1	0.00	0.30	9.1
Abnormal ALT	1.3	0.26	27.0	1	0.00	0.08	3.8
BMI 0.90.15	35.3	1	0.00	0.15	2.4		
Positive HB_sAg	-0.7	0.24	9.3	1	0.00	-0.04	0.05
Hyperlipidemia	0.6	0.06	99.9	1	0.00	0.16	1.8
Diabetes mellitus	0.5	0.11	21.5	1	0.00	0.07	1.7
Hyperlipidemia	0.4	0.05	81.0	1	0.00	0.15	1.5
Sex	0.4	0.05	55.1	1	0.00	0.12	1.5
Arteriosclerosis	0.2	0.09	6.8	1	0.01	0.04	1.3

DISCUSSION

The natural history of fatty liver ranges from asymptomatic indolent to end stage liver disease. Diagnosis of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) may involve ultrasonography, liver biopsy and recognition of related condition[1]. Fatty liver is a common disease of liver without specific clinical features and lack of confirmatory laboratory tests[15-17]. In patients undergoing liver biopsy, the prevalence of NAFL ranges between 15 % and 39 %[18]. This wide range in the prevalence of NAFL is probably related to differences in the study design. Because patients undergoing liver biopsy were highly selected, these data might not reflect the true prevalence of NAFL in the general population. Therefore, current best estimates make the prevalence of NAFL approximately 20 % and of NASH 2-3 % in the general population[18].

While it could be argued that in the absence of histology this figure may not reflect the true prevalence of fatty infiltration, previous studies in which ultrasound findings were compared to histologic results indicate that the overall sensitivity and specificity of ultrasound examinations for the diagnosis of fatty liver are approximately 80-95 % and 90-95 % respectively[13,19-21]. In the present study, the prevalence of NAFL was 15.8 % in males and 7.5 % in females according to ultrasonic criteria of diagnosis for fatty liver.

This study was limited in survey of the administrative officers in two districts of Shanghai. Nevertheless, these participants were representatives of the health status of administrative officers. In comparison with general population, participants of this study had better living condition and less physical exercises. The results of this study showed higher prevalence of hyperlipidemia and fatty liver in participants than those in general population in Shanghai.

Several authors suggested that fatty liver should be included in "metabolic syndrome"[2,14,22]. Evidence for this hypothesis derives, in our opinion, from epidemiology, metabolism, and experimental pathology. The results of this survey showed that overweight was detected in 31.6 % of participants and hyperlipidemia in 28.8 %, and the prevalence of fatty liver was 12.9 %. The prevalence of DM, hypertension and coronary heart disease was 4.5 %, 12.8 % and 3.1 % respectively, suggesting that overweight and associated diseases are becoming common diseases among administrative officers in Shanghai.

Hyperlipidemia is considered as a risk factor for fatty infiltration of the liver[23,24]. The pathogenesis of nonalcoholic steatohepatitis is poorly understood, but lipid peroxidation and oxidative stress are the leading culprits[16, 25]. Diabetes and hypertriglyceridemia were the two states predictive of fatty liver that is consistent with the presence of insulin resistance[23]. NAFL correlates significantly with both anthropometrical data BMI, WHR and with abdominal fat[26]. In clinical practice BMI over

24 used as diagnostic criteria for overweight in China.

In this study, both monovariant and multivariant regression analysis demonstrated a close correlation between BMI and fatty liver. High WHR suggests increased abdominal fatty tissue, which is a strong predictive factor for DM and other metabolism abnormalities[27-30]. Increased WHR is considered as the most important risk factor for fatty liver. The development of fatty liver may be a result of transportation of the abnormal fatty tissue into the liver[23,31,32]. BMI was found to be an independent predictor of fatty liver in either sex[33]. Both monovariant and multi variant regression analysis revealed that hypertension is correlated with fatty liver. The relation between fatty liver and impaired glucose tolerance, DM and hyperlipidemia has been well established[34-43], and was confirmed again in this study. Fatty liver could be gender-related[33]. The results of this study showed that in male participants younger than 50 years old, the prevalence of three types of hyperlipidemia and fatty liver were markedly higher than those in females. In participants older than 50 years old the prevalence were similar in males and females. This result suggested that female hormones might have favorable effects on lipid metabolism in liver. Monovariant analysis showed that many factors were correlated with prevalence of fatty liver. However, logistic multivariant regression analysis demonstrated that only nine parameters were closely correlated with fatty liver.

In majority of patients with fatty liver, the hepatic function is normal, therefore determination of ALT can not reflect the content of fat retention in liver[7,44]. Results of this study showed negative correlation between positive HB_sAg and fatty liver, which might explain that chronic hepatitis B infection would not induce the development of fatty liver. The sensibility by liver function tests to detect fatty liver was inferior to that of BMI[7]. But hepatitis C may be linked to hepatic steatosis[45-47].

This epidemiological survey demonstrated that fatty liver is a common disease among administrative officers in Shanghai. Overweight, hyperlipidemia, and DM are high risk factors for fatty liver. It is clear that NAFL is a chronic liver disease with the potential for progression to cirrhosis and to cause liver-related death[48,50]. Although ultrasonography provides the prevalence of NAFL, it can not delineate the different histologic form of NAFL[18]. If it is clinically indicated, a liver biopsy to assess the degree of inflammation and fibrosis should be performed during follow-up[10]. To reduce the incidence of fatty liver, comprehensive measures are necessary [32,51-53].

REFERENCES

1 **Brunt EM**. Nonalcoholic steatohepatitis: definition and pathology. *Semin Liver Dis* 2001; **21**: 3-16

2 **Lonardo A**. Fatty liver and nonalcoholic steatohepatitis. Where do we stand and where are we going? *Dig Dis Sci* 1999; **17**: 80-89

3 **McCullough AJ**, Falck-Ytter Y. Body composition and hepatic steatosis as precursors for fibrotic liver disease. *Hepatology* 1999; **29**: 1328-1330

4 **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**: 1413-1419

5 **James O**, Day C. Non-alcoholic steatohepatitis: another disease of affluence. *Lancet* 1999; **353**: 1634-1636

6 **Tominaga K**, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, Kusano Y. Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological ultrasonographic survey. *Dig Dis Sci* 1995; **40**: 2002-2009

7 **Yano E**, Tagawa K, Yamaoka K, Mori M. Test validity of periodic liver function tests in a population of Japanese male bank employees. *J Clin Epidemiol* 2001; **54**: 945-951

8 **Powell EE**, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990; **11**: 74-80

9 **Araujo LM**, De Oliveira DA, Nunes DS. Liver and biliary ultrasonography in diabetic and non-diabetic obese women. *Diabetes Metab* 1998; **24**: 458-462

10 **Bellentani S**, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F, Cristanini G, Tiribelli C. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med* 2000; **132**: 112-117

11 **Mathiesen UL**, Franzen LE, Fryden A, Foberg U, Bodemar G. The clinical significance of slightly to moderately increased liver transaminase values in asymptomatic patients. *Scand J Gastroenterol* 1999; **34**: 85-91

12 **el-Hassan AY**, Ibrahim EM, al-Mulhim FA, Nabhan AA, Chammas MY. Fatty infiltration of the liver: analysis of prevalence, radiological and clinical features and influence on patient management. *Br J Radiol* 1992; **65**: 774-778

13 **Joseph AE**, Saverymuttu SH, al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol* 1991; **43**: 26-31

14 **Lonardo A**, Bellini M, Tartoni P, Tondelli E. The bright liver syndrome. Prevalence and determinants of a "bright" liver echopattern. *Ital J Gastroenterol Hepatol* 1997; **29**: 351-356

15 **Skelly MM**, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. *J Hepatol* 2001; **35**: 195-199

16 **Reid AE**. Nonalcoholic steatohepatitis. *Gastroenterology* 2001; **121**: 710-723

17 **Angulo P**, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999; **30**: 1356-1362

18 **Falck-Ytter Y**, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis* 2001; **21**: 17-26

19 **Hultcrantz R**, Gabrielsson N. Patients with persistent elevation of aminotransferases:Investigation with ultrasonography, radionuclide imaging and liver biopsy. *J Intern Med* 1993; **233**: 7-12

20 **Layer G**, Zuna I, Lorenz A, Zerban H, Haberkorn U, Bannasch P, van Kaick G, Rath U. Computerized ultrasound B-scan texture analysis of experimental diffuse parenchymal liver disease: Correlation with histopathology and tissue composition. *J Clin Ultrasound* 1999; **19**: 193-201

21 **Mendler MH**, Bouillet P, LeSidaner A, Lavoine E, Labrousse F, Sautereau D, Pillegand B. Dual-energy CT in the diagnosis and quantification of fatty liver: Limited clinical value in comparison to ultrasound scan and single-energy CT, with special reference to iron overload. *J Hepatol* 1998; **28**: 785-794

22 **Marceau P**, Biron S, Hould FS, Marceau S, Simard S, Thung SN, Kral JG. Liver pathology and the metabolic syndrome X in severe obesity. *J Clin Endocrinol Metab* 1999; **84**: 1513-1517

23 **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

24 **Ludwig J**, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434-438

25 **Fan JG**, Zeng MD, Wang GL. Pathogenesis of fatty liver. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 75-76

26 **Sabir N**, Sermez Y, Kazil S, Zencir M. Correlation of abdominal fat accumulation and liver steatosis: importance of ultrasonographic and anthropometric measurements. *Eur J Ultrasound* 2001; **14**: 121-128

27 **Mensenkamp AR**, Havekes LM, Romijn JA, Kuipers F. Hepatic steatosis and very low density lipoprotein secretion: the involvement of apolipoprotein E. *J Hepatol* 2001; **35**: 816-822

28 **Nehra V**, Angulo P, Buchman AL, Lindor KD. Nutritional and metabolic considerations in the etiology of nonalcoholic steatohepatitis. *Dig Dis Sci* 2001; **46**: 2347-2352

29 **Sharabi Y**, Eldad A. Nonalcoholic fatty liver disease is associated with hyperlipidemia and obesity. *Am J Med* 2000; **109**: 171

30 **Fong DG**, Nehra V, Lindor KD, Buchman AL. Metabolic and nutritional considerations in nonalcoholic fatty liver. *Hepatology* 2000; **32**: 3-10

31 **Loguercio C**, De Girolamo V, de Sio I, Tuccillo C, Ascione A, Baldi F, Budillon G, Cimino L, Di Carlo A, Di Marino MP, Morisco

F, Picciotto F, Terracciano L, Vecchione R, Verde V, Del Vecchio Blanco C. Non-alcoholic fatty liver disease in an area of southern Italy: main clinical, histological, and pathophysiological aspects. *J Hepatol* 2001; **35**: 568-574

32 **Fan JG**. Steatohepatitis studies in China. *Shijie Huaren Xiaohua Zazhi* 2001; **9**: 6-10

33 **Lonardo A**, Trande P. Are there any sex differences in fatty liver? A study of glucose metabolism and body fat distribution. *J Gastroenterol Hepatol* 2000; **15**: 775-782

34 **Sonsuz A**, Basaranoglu M, Bilir M, Senturk H, Akin P. Hyperinsulinemia in nondiabetic, both obese and nonobese patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2002; **97**: 495

35 **Urso R**, Visco-Comandini U. Metformin in non-alcoholic steatohepatitis. *Lancet* 2002; **359**: 355-356

36 **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

37 **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

38 **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

39 **Paradis V**, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, Conti M, Huet S, Ba N, Buffet C, Bedossa P. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology* 2001; **34**: 738-744

40 **Marchesini G**, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 2001; **50**: 1844-1850

41 **Sanyal AJ**. Insulin resistance and nonalcoholic steatohepatitis: fat or fiction? *Am J Gastroenterol* 2001; **96**: 274-276

42 **Luyckx FH**, Lefebvre PJ, Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. *Diabetes Metab* 2000; **26**: 98-106

43 **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

44 **Sonsuz A**, Basaranoglu M, Ozbay G. Relationship between aminotransferase levels and histopathological findings in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2000; **95**: 1370-1371

45 **Lai MM**. Hepatitis C virus proteins: direct link to hepatic oxidative stress, steatosis, carcinogenesis and more. *Gastroenterology* 2002; **122**: 568-571

46 **Giannini E**, Ceppa P, Testa R. Steatosis in chronic hepatitis C: can weight reduction improve therapeutic efficacy? *J Hepatol* 2001; **35**: 432-433

47 **Ong JP**, Younossi ZM, Speer C, Olano A, Gramlich T, Boparai N. Chronic hepatitis C and superimposed nonalcoholic fatty liver disease. *Liver* 2001; **21**: 266-271

48 **Bacon BR**, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994; **107**: 1103-1109

49 **Kumar KS**, Malet PF. Nonalcoholic steatohepatitis. *Mayo Clin Proc* 2000; **75**: 733-739

50 **Xu ZJ**, Fan JG, Wang GL, Ding XD, Tian LY, Zheng XY. Rat model of nonalcoholic stestohepatitis with firosis by a fat –rich diet. *Shijie Huaren Xiaohua Zazhi* 2002; **10**: 392-396

51 **Angulo P**, Lindor KD. Treatment of nonalcoholic fatty liver: present and emerging therapies. *Semin Liver Dis* 2001; **21**: 81-88

52 **Chitturi S**, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. *Semin Liver Dis* 2001; **21**: 27-41

53 **Cortez-Pinto H**, Chatham J, Chacko VP, Arnold C, Rashid A, Diehl AM. Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study. *JAMA* 1999; **282**: 1659-1664

Edited by Zhang JZ