available at http://ajws.elsevier.com/tcmj

Tzu Chi Medical Journal

ELSEVIER

Original Article

Association Between Nonalcoholic Fatty Liver Disease and Cardiovascular Risk Factors in a Hospital-Based Study

Hsueh-Chou Lai[1], Tsann Lin[2], Shih-Wei Lai[2], Kuan-Fu Liao[1]*

[1]*Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan*
[2]*Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan*

Article info

Article history:
Received: December 24, 2007
Revised: January 4, 2008
Accepted: January 25, 2008

Keywords:
Cardiovascular risk factors
Hyperuricemia
Nonalcoholic fatty liver disease
Obesity

Abstract

Objective: The objective of this study was to assess the association between nonalcoholic fatty liver disease (NAFLD) and cardiovascular risk factors.

Materials and Methods: This was a hospital-based, cross-sectional study. We retrospectively analyzed the medical records of all the people who received periodic health examinations at one medical center in Taichung, Taiwan from 2001 to 2004. Subjects with alcoholism and those who were positive for hepatitis B surface antigen and hepatitis C virus antibody were excluded. In all, 3488 subjects were included for further analysis. The *t* test, χ^2 test and multivariate logistic regression were used.

Results: There were 1766 men (50.6%) and 1722 women (49.4%). The mean age was 49.4±12.4 years (range, 20–87 years). The overall prevalence of NAFLD was 46.9%, with significantly higher prevalence in men than in women (55.4% *vs.* 38.3%, $p<0.001$). Multivariate logistic regression analysis showed that the factors that were significantly related to NAFLD were male gender (OR, 1.81), generalized obesity (OR, 2.94), central obesity (OR, 2.12), hyperglycemia (OR, 2.05), hypercholesterolemia (OR, 1.32), hypertriglyceridemia (OR, 2.22), high levels of low-density lipoprotein cholesterol (OR, 1.29), low levels of high-density lipoprotein cholesterol (OR, 1.53), and hyperuricemia (OR, 1.63).

Conclusion: We found that NAFLD is significantly related to cardiovascular risk factors and hyperuricemia. (*Tzu Chi Med J* 2008;20(3):213–217)

*Corresponding author. Department of Family Medicine, China Medical University Hospital, 2, Yuh-Der Road, Taichung, Taiwan.
E-mail address: wei@mail.cmuh.org.tw

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a relatively common problem, and is usually incidentally found on abdominal sonography during health examinations (1–5). Although the natural course of NAFLD is still poorly understood, generally speaking, it is considered to be a fairly benign and asymptomatic condition with little progression and no risk of mortality (6). However, there are some reports that NAFLD can progress to

liver cirrhosis and even liver failure [7–9]. Because the liver plays a central role in the metabolism of carbohydrates and lipids [10], the association between NAFLD and metabolic disorders has been widely investigated [1–4,10–15]. Metabolic disorders are a topic of concern that has been debated often and vigorously, and include some of the following: obesity, diabetes mellitus, dyslipidemia, essential hypertension and hyperuricemia [16–23]. The majority of these disorders are considered to be risk factors for the development of cardiovascular disease [16–23]. Modification of certain major risk factors may decrease a patient's risk of developing cardiovascular disease and other serious complications [16,17]. In 2005, cardiovascular disease was the third leading cause of death in Taiwan after neoplasms and cerebrovascular disease [24]. The relationship between NAFLD and cardiovascular risk factors has rarely been studied in Taiwan. Therefore, we conducted a study to explore the following questions. (1) What is the prevalence of NAFLD in Taiwan? (2) What are the related factors for NAFLD?

2. Materials and methods

2.1. Study population

This was a hospital-based, cross-sectional study. We retrospectively analyzed the medical records of all people who received periodic health examinations at one medical center located in Taichung, Taiwan from 2001 to 2004. Subjects who habitually drank alcohol and who were positive for hepatitis B surface antigen and hepatitis C virus antibody were excluded. In all, 3488 subjects were included for further analysis. The institutional review board of the medical center approved this retrospective study.

2.2. Sociodemographic characteristics and other related factors

Subjects who had never smoked or had quit smoking were defined as nonsmokers. Subjects who currently smoked were defined as smokers. Abdominal sonography was performed by gastroenterologists using a high-resolution real-time machine (Toshiba Sonolayer SSA-270A, convex-type 3.5 MHz transducer; Toshiba, Tochigi-Ken, Japan). Fatty liver was diagnosed according to international criteria [15,25,26].

Venous blood samples were obtained in the morning after a 12-hour overnight fast. A number of biochemical markers, such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting glucose and uric acid were measured by a biochemical autoanalyzer (Hitachi 736-15; Hitachi Corp., Tokyo, Japan) in the clinical laboratory of the medical center.

2.3. Diagnostic criteria

Generalized obesity was defined as a body mass index (BMI) $\geq 27\ kg/m^2$ [27]. Central obesity was defined as a waist circumference ≥ 90 cm for men or ≥ 80 cm for women [27]. Hypercholesterolemia was defined as total cholesterol ≥ 200 mg/dL [28]. Hypertriglyceridemia was defined as TG ≥ 150 mg/dL [28]. A low level of HDL-C was defined as <40 mg/dL for men or <50 mg/dL for women [28]. If TG <400 mg/dL, then low-density lipoprotein cholesterol (LDL-C) was calculated by the following formula suggested by Friedewald et al: LDL-C=TC−(HDL-C+TG/5) [29]. A high level of LDL-C was defined as ≥ 130 mg/dL [28]. A ratio of TC/HDL-C >5 was defined as abnormal [30]. If subjects had a fasting glucose level ≥ 110 mg/dL or were receiving drug treatment for elevated glucose, they were considered to have hyperglycemia [31]. Subjects were considered to have hypertension if their average blood pressure on both hand readings exceeded 140 mmHg systolic and/or 90 mmHg diastolic or they were receiving antihypertensive drug treatment [32]. Hyperuricemia was defined as serum uric acid ≥ 7.0 mg/dL for men and ≥ 6.5 mg/dL for women [18].

2.4. Statistical analysis

Statistical analysis was performed using SPSS Taiwan version 10.0 (Sinter Information Corp., Taipei, Taiwan). The *t* test, χ^2 test and multivariate logistic regression were used for statistical analysis. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the study population

Among the subjects, there were 1766 men (50.6%) and 1722 women (49.4%). The mean age was 49.4 ± 12.4 years (range, 20–87 years). The overall prevalence of NAFLD was 46.9%, with a significantly higher prevalence in men than in women (55.4% *vs.* 38.3%, $p<0.001$) (Fig. 1).

3.2. Univariate analysis of cardiovascular risk factors for NAFLD

Using the χ^2 test, factors that were found to be significantly related to NAFLD were generalized obesity,

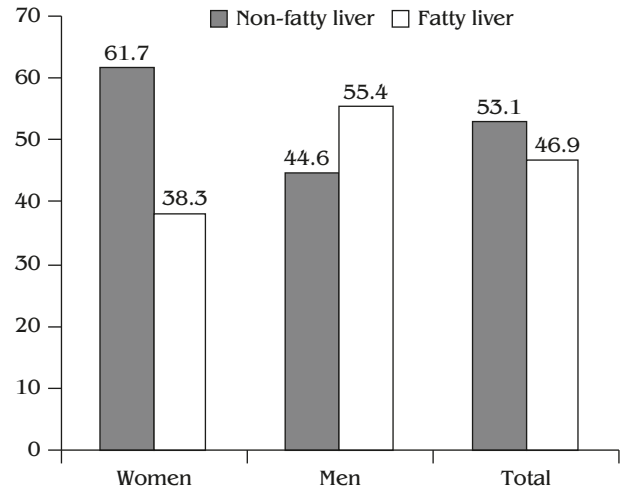

Fig. 1 — Prevalence of nonalcoholic fatty liver disease by gender.

central obesity, hypertension, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, a high level of LDL-C, a low level of HDL-C, a high ratio of TC/HDL-C, and hyperuricemia ($p<0.001$) (Table 1). Subjects with NAFLD were also significantly older as shown by *t* test ($p<0.001$).

3.3. Multivariate logistic regression analysis of related factors for NAFLD

Only the significantly related factors identified in univariate analysis were further analyzed. In the final model, multivariate logistic regression analysis showed that the factors that were significantly related to NAFLD were male gender, generalized obesity, central obesity, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, a high level of LDL-C, a low level of HDL-C, and hyperuricemia (Table 2).

Table 1 — Association between nonalcoholic fatty liver disease and cardiovascular risk factors by univariate analysis*

Variable	Normal	Fatty liver	*p*
Age (yr)	47.5±13.0	51.6±11.3	<0.001
Generalized obesity			<0.001
No	1735 (60.5)	1133 (39.5)	
Yes	116 (18.7)	504 (81.3)	
Central obesity			<0.001
No	1322 (67.5)	636 (32.5)	
Yes	529 (34.6)	1001 (65.4)	
Hypertension			<0.001
No	1505 (58.2)	1080 (41.8)	
Yes	346 (38.3)	557 (61.7)	
Hyperglycemia			<0.001
No	1672 (58.3)	1196 (41.7)	
Yes	179 (28.9)	441 (71.1)	
Hypercholesterolemia			<0.001
No	1071 (61.3)	676 (38.7)	
Yes	780 (44.8)	961 (55.2)	
Hypertriglyceridemia			<0.001
No	1664 (61.1)	1061 (38.9)	
Yes	187 (24.5)	576 (75.5)	
LDL-C ≥130 mg/dL			<0.001
No	1171 (60.2)	773 (39.8)	
Yes	680 (44.0)	864 (56.0)	
Low level of HDL-C			<0.001
No	1138 (62.7)	676 (37.3)	
Yes	713 (42.6)	961 (57.4)	
TC/HDL-C >5			<0.001
No	1482 (64.1)	829 (35.9)	
Yes	369 (31.4)	808 (68.6)	
Hyperuricemia			<0.001
No	1495 (60.7)	966 (39.3)	
Yes	356 (34.7)	671 (65.3)	
Smoker			0.091
No	1500 (53.8)	1289 (46.2)	
Yes	351 (50.2)	348 (49.8)	

*Data presented as mean±standard deviation or *n* (%). LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC/HDL-C = ratio of total cholesterol to high-density lipoprotein cholesterol.

Table 2 — Analysis of multivariate logistic regression for nonalcoholic fatty liver disease

Variable	EP (SE)	OR	95% CI
Intercept	–2.17 (0.19)		
Age (yr)	0.01 (0.00)	1.01	1.00–1.01
Men (women as reference)	0.59 (0.09)	1.81	1.52–2.16*
Generalized obesity (yes *vs.* no)	1.08 (0.13)	2.94	2.28–3.78*
Central obesity (yes *vs.* no)	0.75 (0.09)	2.12	1.77–2.55*
Hypertension (yes *vs.* no)	0.10 (0.10)	1.11	0.91–1.34
Hyperglycemia (yes *vs.* no)	0.72 (0.11)	2.05	1.64–2.55*
Hypercholesterolemia (yes *vs.* no)	0.28 (0.12)	1.32	1.03–1.68†
Hypertriglyceridemia (yes *vs.* no)	0.80 (0.11)	2.22	1.78–2.77*
LDL-C≥130 mg/dL (yes *vs.* no)	0.25 (0.12)	1.29	1.02–1.64†
Low level of HDL-C (yes *vs.* no)	0.42 (0.10)	1.53	1.26–1.85*
TC/HDL-C>5 (yes *vs.* no)	0.20 (0.11)	1.22	0.98–1.52
Hyperuricemia (yes *vs.* no)	0.49 (0.09)	1.63	1.36–1.95*

*$p<0.001$; †$p<0.05$. EP = estimated parameter; SE = standard error; OR = odds ratio; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC/HDL-C = ratio of total cholesterol to high-density lipoprotein cholesterol.

4. Discussion

NAFLD is believed to be one of the most common liver diseases in Western countries and has a notably high potential for reversibility [1–5,12].

The prevalence of NAFLD was 46.9% in our study. Large-scale investigations in Taiwan, India, and Israel indicate that the prevalence of NAFLD is around 11.5–30%, depending on the population studied [33–35]. It is possible that the subjects we studied were more concerned about their health problem, such as fatty liver, and therefore came to the hospital for health examination. That led to a higher prevalence in our study. Another reason may be that we only excluded habitual alcohol drinkers. Thus, some heavy social drinkers might have been included in this study.

As reported in previous studies, metabolic disorders often cluster within the same individual [1–4,10–15]. The liver plays a central role in the metabolism of carbohydrates, lipids and steroids [10]. The real association between NAFLD and metabolic disorders has been explored worldwide, but controversy still exists about the role of NAFLD [1–4,10–15]. In our study, the factors that were significantly related to NAFLD were generalized obesity, central obesity, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, a high level of LDL-C, a low level of HDL-C, and hyperuricemia. Brea and colleagues [36] suggested that if NAFLD is detected by abdominal ultrasound, clinicians should be alert to an increased risk of cardiovascular disease.

The limitations of this study are that it was a retrospective hospital-based study, which could introduce a sampling bias, and because of the inherent limitations of a cross-sectional study, we could not address any substantial causal-effect implications between NAFLD and cardiovascular risk factors or hyperuricemia. Therefore, more research is needed to determine whether NAFLD shares the same pathogenesis as cardiovascular risk factors and hyperuricemia, or whether NAFLD is another component of the metabolic syndrome.

In conclusion, this study illustrates that NAFLD has a significant relationship with cardiovascular risk factors and hyperuricemia.

References

1. 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;29:351–6.
2. Kawai N, Kawai T, Kawai K. Ultrasonic and laboratory studies on fatty liver in white-collar workers. *Nippon Shokakibyo Gakkai Zasshi* 1995;92:1058–65.
3. Ikai E, Ishizaki M, Suzuki Y, Ishida M, Noborizaka Y, Yamada Y. Association between hepatic steatosis, insulin resistance and hyperinsulinaemia as related to hypertension in alcohol consumers and obese people. *J Hum Hypertens* 1995;9:101–5.
4. Tacikowski T, Milewski B, Dzieniszewski J, Rakoczy A, Klosiewicz-Latoszek L. Liver steatosis assessed by ultrasonographic examination in patients with hyperlipoproteinemia. *Wiad Lek* 1994;47:725–30.
5. Al-Quorain A, Satti MB, al-Hamdan AR, et al. Pattern of chronic liver disease in the eastern province of Saudi Arabia. A hospital-based clinicopathological study. *Trop Geogr Med* 1994;46:358–60.
6. O'Connor BJ, Kathamna B, Tavill AS. Nonalcoholic fatty liver (NASH syndrome). *Gastroenterologist* 1997;5:316–29.
7. 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.
8. Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. *Dig Dis Sci* 2000;45:1929–34.
9. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990;12:1106–10.
10. Marceau P, Biron S, Hould FS, et al. Liver pathology and the metabolic syndrome X in severe obesity. *J Clin Endocrinol Metab* 1999;84:1513–7.

11. Takeda T, Fujino A, Mizoue T, Kaji H. Relationship between fatty liver and coronary risk factors. *Sangyo Eiseigaku Zasshi* 2000;42:24–8.
12. Knobler H, Schattner A, Zhornicki T, et al. Fatty liver—an additional and treatable feature of the insulin resistance syndrome. *QJM* 1999;92:73–9.
13. Umeki S, Hisamoto N, Hara Y. Study on background factors associated with impaired glucose tolerance and/or diabetes mellitus. *Acta Endocrinol (Copenh)* 1989;120: 729–34.
14. Cortez-Pinto H, Camilo ME, Baptista A, De Oliveira AG, De Moura MC. Non-alcoholic fatty liver: another feature of the metabolic syndrome? *Clin Nutr* 1999;18:353–8.
15. Lin DY, Sheen IS, Chiu CT. Clinical significance of ultrasonographic fatty liver in asymptomatics: analysis of 1040 check-up subjects. *J Med Ultrasound* 1993;1:165–71.
16. Miccoli R, Ceraudo AM, Manfredi SG, Odoguardi L, Navalesi R. Atherogenic dyslipidemia, metabolic syndrome and cardiovascular risk. *Cardiologia* 1999;44:885–99.
17. Aronow WS. Cardiac risk factors: still important in the elderly. *Geriatrics* 1990;45:71–4,79–80.
18. Saggiani F, Pilati S, Targher G, Branzi P, Muggeo M, Bonora E. Serum uric acid and related factors in 500 hospitalized subjects. *Metabolism* 1996;45:1557–61.
19. Woo J, Swaminathan R, Cockram C, Lau E, Chan A. Association between serum uric acid and some cardiovascular risk factors in a Chinese population. *Postgrad Med J* 1994;70:486–91.
20. Agamah ES, Srinivasan SR, Webber LS, Berenson GS. Serum uric acid and its relation to cardiovascular disease risk factors in children and young adults from a biracial community: the Bogalusa Heart Study. *J Lab Clin Med* 1991;118:241–9.
21. Chen YL, Liao KF, Lai SW, Li TC. Epidemiology of metabolic syndrome—a hospital-based study in Taichung. *Mid Taiwan J Med* 2005;10:196–203.
22. Ho HY, Lai HC, Lai MM, et al. Relationship between non-alcoholic fatty liver and the components of metabolic syndrome—a hospital-based study. *Mid Taiwan J Med* 2006;11:35–41.
23. Lai SW, Tan CC, Ng KC. Hepatic effects in hyperlipidemic patients. *Mid Taiwan J Med* 2002;7:160–4.
24. Department of Health, Taiwan. *Main Causes of Death in 2005.* Taipei, Taiwan: Department of Health, March 18, 2007. Available from: http://www.doh.gov.tw/ufile/doc/causesofdeath.pdf
25. Lin SC, Shih SC, Kao CR, Chou SY. Prevalence of antibodies to hepatitis C virus in patients with nonalcoholic fatty liver. *Zhonghua Yi Xue Za Zhi (Taipei)* 1995;56:80–5.
26. Chang WY, Chen CJ, Lu SN, et al. Relationship between fatty liver, alanine aminotransferase, HBsAg and hepatitis C virus. *J Gastroenterol Hepatol* 1992;7:455–8.
27. Bureau of Health Promotion, Department of Health, Taiwan, January 13, 2008. Available from: http://www.bhp.doh.gov.tw/BHPnet/Portal/Them_Show.aspx?Subject=200712-250023&Class=2&No=200712250120
28. 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). *JAMA* 2001;285:2486–97.
29. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
30. Paccaud F, Schluter-Fasmeyer V, Wietlisbach V, Bovet P. Dyslipidemia and abdominal obesity: an assessment in three general populations. *J Clin Epidemiol* 2000;53:393–400.
31. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2000;23:4–19.
32. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.
33. Chen CH, Huang MH, Yang JC, et al. 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;40:745–52.
34. Amarapurkar D, Kamani P, Patel N, et al. Prevalence of non-alcoholic fatty liver disease: population based study. *Ann Hepatol* 2007;6:161–3.
35. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. *Liver Int* 2006;26:856–63.
36. Brea A, Mosquera D, Martín E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler Thromb Vasc Biol* 2005;25:1045–50.