Synergistic effect of fatty liver and smoking on metabolic syndrome

Po-Hsin Chiang, Tsui-Yen Chang, Jong-Dar Chen

Po-Hsin Chiang, Tsui-Yen Chang, Jong-Dar Chen, Department of Family Medicine, Shin Kong Wu Ho-Su Memorial Hospital, #95 Wen Chang Road, Shih Lin, Taipei 111, Taiwan, China
Jong-Dar Chen, School of Medicine, Fu Jen Catholic University, #510 Chung Cheng Road, Hsinchuang, Taipei 242, Taiwan, China

Author contributions: Chiang PH, Chang TY and Chen JD designed the research; Chiang PH and Chang TY performed the research; Chiang PH and Chen JD analyzed the data; Chiang PH wrote the paper.

Correspondence to: Dr. Jong-Dar Chen, Department of Family Medicine, Shin Kong Wu Ho-Su Memorial Hospital, #95 Wen Chang Road, Shih Lin, Taipei 111, Taiwan, China. m006671@ms.skh.org.tw
Telephone: +886-2-28332211-2626 Fax: +886-2-28389420
Received: August 20, 2009 Revised: October 2, 2009 Accepted: October 9, 2009 Published online: November 14, 2009

Abstract

AIM: To investigate the association of fatty liver and smoking on metabolic syndrome and its components.

METHODS: This cross-sectional study enrolled participants who attended annual health screening at Shin Kong Wu Ho-Su Memorial Hospital from January to December 2005. A total of 3455 (1981 men and 1474 women) subjects were included in final analyses. Fatty liver was diagnosed using abdominal ultrasonography by trained gastroenterologists. The modified National Cholesterol Education Program Adult Treatment Panel III was used to define metabolic syndrome. The associations between smoking, fatty liver and metabolic syndrome were analyzed using multiple logistic regression.

RESULTS: Subjects with fatty liver, and who smoked tobacco, had the highest odds ratios (ORs) for high waist circumference [OR, 4.5 (95% CI: 3.3-6.1), P < 0.05], hypertriglyceridemia [OR, 8.1 (95% CI: 6.0-10.9), P < 0.05], low serum high-density lipoprotein cholesterol (HDL-C) [OR, 8.3 (95% CI: 6.1-11.3), P < 0.05], and metabolic syndrome [OR, 9.5 (95% CI: 6.7-13.4), P < 0.05] compared to subjects without fatty liver who did not smoke tobacco. We also found that the ORs for hypertriglyceridemia, low serum HDL-C, and metabolic syndrome for subjects with fatty liver who smoked tobacco had greater than the sum of the ORs for subjects with fatty liver who did not smoke plus those who did not have fatty liver and who did smoke.

CONCLUSION: Fatty liver and smoking had a synergistic effect on metabolic syndrome and its components, especially for hypertriglyceridemia and low serum HDL-C.

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Key words: Smoking; Fatty liver; Synergistic effect; Metabolic syndrome

INTRODUCTION

Fatty liver is an increasingly recognized condition with growing prevalence in the modern world and is strongly associated with insulin resistance. The association between fatty liver and metabolic syndrome was broadly discussed in previous studies[1-9]. Fatty liver and metabolic syndrome are becoming important public health issues worldwide.

Smoking is a major risk factor for cardiovascular disease[10]. Previous studies have shown that smoking reduces insulin sensitivity or induces insulin resistance[11].
and enhances cardiovascular risk factors such as elevated plasma triglycerides (TG)\[16-19\], decreased high-density lipoprotein cholesterol (HDL-C)\[20,28\] and hyperglycemia\[21\]. Furthermore, several studies show that smoking is associated with metabolic abnormalities and increases the risk of metabolic syndrome\[21-24\]. Nakanishi et al\[21\] reported that subjects who habitually smoked tobacco had a 1.07- to 1.66-fold risk of developing metabolic syndrome compared to subjects who did not smoke, and the quantity of tobacco smoked had a dose-dependent relationship with the severity of metabolic syndrome.

Habitual smoking is a modifiable risk factor for metabolic syndrome and cardiovascular disease\[20,25\]. The most effective way for smokers to decrease the risk of metabolic syndrome and cardiovascular disease is to stop smoking.\[20\]. However, Nakanishi et al\[21\] found that smoking cessation was also associated with a 1.3-fold risk of metabolic syndrome due to subsequent body weight gain. Wada et al\[22\] proposed that the effect of smoking on metabolic syndrome would remain over 20 years after smoking cessation.

The effects of fatty liver and habitually smoking tobacco on metabolic syndrome have not been previously addressed. The purpose of the present study was to investigate the possible interactive effects of fatty liver and smoking on metabolic syndrome and its components.

**MATERIALS AND METHODS**

This retrospective cross-sectional study enrolled participants who voluntarily attended annual health screenings at the health center of the Shin Kong Wu Ho-Su Memorial Hospital from January to December 2005. Demographic data, medical histories, family histories regarding risk factors for metabolic syndrome, smoking habits, exercise habits, and alcohol consumption habits were collected through a self-administered questionnaire. This study was approved by the Shin Kong Wu Ho-Su Memorial Hospital Institutional Review Board, and written informed consent was obtained from all participants. Hepatitis C (n = 109), alcohol consumption more than three times per week (n = 77), and subjects whose abdominal ultrasonographic findings revealed cirrhosis or other chronic liver parenchymal disease (n = 88) were excluded from this study. Thus, a total of 3455 (1981 men and 1474 women) subjects were included in the final analyses.

At the time of examination, sitting blood pressure (mmHg) was measured by an automated oscillometric BP recorder Dinamap DPC 100X-EN (GE Medical Systems, Milwaukee, Wisconsin, USA) applied to the patient’s left arm following a sufficiently long period of rest. Height and body weight were determined with a foot-to-foot bioelectric impedance analyzer (BF-220, Tanita Corp., Tokyo, Japan); these measurements were made to the nearest 0.1 cm and 0.1 kg, respectively, with subjects wearing light clothing. Body mass index (BMI, kg/m\(^2\)) was calculated as body weight divided by the square of the individual’s height. Waist circumference (WC, cm) was measured midway between the lowest border of the ribs and the iliac crest in the horizontal plane, and to the nearest 0.5 cm, by trained nurses using an anthropometric non-stretchable tape after normal expiration.

Fasting blood samples were collected from all subjects after at least an 8-h fast. Serum levels of total cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), HDL-C (mg/dL), serum triglycerides (TG, mg/dL), and fasting blood glucose (FPG, mg/dL) were measured by an automated Hitachi 7600 clinical analyzer (Hitachi, Ltd., Tokyo, Japan).

Abdominal ultrasonographic examinations were performed by trained gastroenterologists using a Philips EnVisor M2540R (Philips, Andover, Minnesota, USA) without reference to the participants’ history of liver disease, biochemical data, or other clinical findings. Using sonography, fatty liver was diagnosed on the basis of abnormally intense, high-level echoes arising from the hepatic parenchyma, liver-kidney difference in echo amplitude, echo penetration into the deep portion of the liver, and clarity of liver blood-vessel structure.

Subjects were classified as current smokers or non-smokers. Alcohol consumption was quantified as the number of drinking times per week, and subjects who drank more than three times per week were excluded before analysis.

**Definition of metabolic syndrome**

Metabolic syndrome was defined as three or more risk factors as defined by the National Cholesterol Education Program Adult Treatment Panel III Guideline criteria and modified by the International Diabetes Federation specifically for the Chinese population, including (1) fasting glucose level ≥ 100 mg/dL, (2) serum triglyceride level ≥ 150 mg/dL, (3) HDL-C level (men < 40 mg/dL, women < 50 mg/dL), (4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, and (5) WC (men ≥ 90 cm, women ≥ 80 cm). The participants were allocated to one of four study groups according to their smoking status and ultrasonographic liver findings. Group 1 was defined as subjects who did not smoke and did not have fatty liver [fatty liver (-)/smoking (-)]. Group 2 was defined as subjects who did not have fatty liver, but currently smoked [fatty liver (-)/smoking (+)]. Group 3 was defined as subjects who showed ultrasonographic evidence of fatty liver but did not smoke [fatty liver (+)/smoking (-)]. Group 4 was defined as subjects who had ultrasonographic evidence of fatty liver and smoked concurrently [fatty liver (+)/smoking (+)].

**Statistical analysis**

ANOVA was used for comparison of continuous variables. The \( \chi^2 \) test was used for comparison of categorical variables. The association between smoking, fatty liver and metabolic syndrome components were analyzed using multiple logistic regression. We controlled confounding factors such as age, gender, drinking habit, and physical activity. A P-value less than 0.05 was defined as statistically significant. All statistical analyses
were performed using SAS statistical software, (SAS for Windows, version 8.02; SAS Institute Inc, Cary, NC, USA).

RESULTS

Table 1 summarized the demographic data and lifestyle factors among the study subjects stratified by fatty liver and smoking habit. The fatty liver group had more men, higher BMI, and more alcohol drinkers compared to subjects without fatty liver. The frequency of regular exercise was similar for subjects with and without fatty liver. Furthermore, subjects who smoked tobacco also drank alcohol with greater frequency and exercised more regularly compared to subjects who did not smoke.

Table 2 summarized the clinical and biochemical characteristics of the study subjects. Participants with fatty liver had a significantly greater WC, FPG, blood pressure and TG, and lower serum HDL-C compared to participants without fatty liver. Higher TG levels and lower HDL-C levels were found in the smoking group compared to subjects who did not smoke. Participants with fatty liver who smoked had the highest triglyceride levels (225.9 mg/dL) and the lowest HDL-C levels (44.3 mg/dL) among the four study groups.

The prevalence of metabolic syndrome abnormalities was significantly higher in the fatty liver group compared to subjects without fatty liver (Table 3). Subjects with fatty liver also had a higher prevalence of metabolic syndrome compared to those without fatty liver. Subjects who smoked had a higher prevalence of metabolic syndrome and more metabolic syndrome abnormalities, especially for higher TGs and lower HDL-C compared to subjects who did not smoke.

Table 4 showed the associations among fatty liver, smoking, and metabolic syndrome using multiple

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**Table 1** Demographic data and lifestyle factors among study subjects (n = 3455), stratified by fatty liver and smoking habit (mean ± SD) a (%)

|                | Fatty liver (-) | Fatty liver (+) | P-value  |
|----------------|-----------------|-----------------|----------|
|                | Non-smoker (n = 1702) | Smoker (n = 365) | Non-smoker (n = 1057) | Smoker (n = 331) |        |
| Age (yr)       | 45.9 ± 11.9     | 42.6 ± 10.8     | 49.9 ± 11.0 | 44.9 ± 9.4      | < 0.0001 |
| BMI (kg/m²)    | 22.0 ± 2.6      | 22.3 ± 2.7      | 25.7 ± 3.2  | 25.9 ± 3.0      | < 0.0001 |
| Male           |                |                | 691 (40)    | 290 (79.5)      | 695 (68.5) | 315 (95.2) | < 0.0001 |
| Drinking a     | 127 (7.5)       | 99 (27.1)       | 122 (11.5)  | 93 (28.1)       | < 0.0001 |
| Physical activity a | 944 (55.5) | 242 (66.5) | 568 (53.8) | 223 (67.4) | < 0.0001 |

1 Alcohol consumption ≥ 1 time and ≤ 3 times per week (subjects who drank more than 3 times per week were excluded before analysis);
2 Exercise ≥ 1 time per week. BMI: Body mass index.

**Table 2** Clinical and biochemical characteristics of study subjects (n = 3455) classified by fatty liver and smoking habit (mean ± SD)

|                | Fatty liver (-) | Fatty liver (+) | P-value  |
|----------------|-----------------|-----------------|----------|
|                | Non-smoker (n = 1702) | Smoker (n = 365) | Non-smoker (n = 1057) | Smoker (n = 331) |        |
| WC (cm)        | 79.9 ± 8.3      | 80.8 ± 7.4      | 88.1 ± 6.5  | 88.8 ± 7.4      | < 0.0001 |
| FPG (mg/dL)    | 89.2 ± 19.3     | 89.8 ± 21.4     | 101.9 ± 33.4 | 99.7 ± 33.4      | < 0.0001 |
| SBP (mmHg)     | 113.9 ± 19.8    | 111.8 ± 16.8    | 125.9 ± 20.1 | 122.4 ± 18.8      | < 0.0001 |
| DBP (mmHg)     | 68.6 ± 11.3     | 69.7 ± 10.9     | 76.5 ± 11.4  | 78.1 ± 10.6      | < 0.0001 |
| TG (mg/dL)     | 97.7 ± 49.5     | 130.1 ± 74.3    | 170.6 ± 129.3 | 225.9 ± 298.5    | < 0.0001 |
| HDL-C (mg/dL)  | 60.1 ± 14.9     | 52.6 ± 13.8     | 48.9 ± 11.4  | 44.3 ± 12.6      | < 0.0001 |

WC: Waist circumference; FPG: Fasting plasma glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol.

**Table 3** Prevalence of metabolic risk factors and metabolic syndrome among study subjects (n = 3455) classified by fatty liver and smoking habit (a %)

|                | Fatty liver (-) | Fatty liver (+) | P-value  |
|----------------|-----------------|-----------------|----------|
|                | Non-smoker | Smoker | Non-smoker | Smoker |        |
| Central obesity a | 497 (29.2) | 51 (14.0) | 501 (47.4) | 137 (41.4) | < 0.0001 |
| FPG ≥ 100 mg/dL | 164 (9.6) | 40 (11.0) | 317 (30.0) | 76 (23.0)    | < 0.0001 |
| High blood pressure a | 356 (20.9) | 63 (17.3) | 477 (45.1) | 119 (36.0) | < 0.0001 |
| TG ≥ 150 mg/dL | 207 (12.2) | 103 (28.2) | 478 (45.2) | 197 (59.3) | < 0.0001 |
| Low HDL-C a | 223 (13.1) | 71 (19.5) | 320 (30.6) | 147 (44.4) | < 0.0001 |
| Metabolic syndrome | 123 (7.2) | 33 (9.0) | 364 (34.4) | 121 (36.6) | < 0.0001 |

1 Waist circumference in men ≥ 90 cm or in women ≥ 80 cm; 2 Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; 3 High-density lipoprotein cholesterol in men < 40 mg/dL or in women < 50 mg/dL.
Table 4 ORs for metabolic risk factors and metabolic syndrome among subgroups of subjects, analyzed by multiple logistic regression, adjusted for age, gender, drinking alcohol, and physical activity (n = 3455)

|                     | Fatty liver (-) | Fatty liver (+) |
|---------------------|-----------------|-----------------|
|                     | Non-smoker (n = 1702) | Smoker (n = 365) | OR     | 95% CI | OR     | 95% CI |
| Central obesity     | 1 (reference)    | 0.7             | 0.5-1.1 | 3.5     | 2.9-4.2 | 4.5      | 3.3-6.1 |
| FPG ≥ 100 mg/dL     | 1 (reference)    | 1.3             | 0.8-1.9 | 3.6     | 2.9-4.6 | 2.8      | 2.0-4.1 |
| High blood pressure | 1 (reference)    | 0.7             | 0.5-1.0 | 2.7     | 2.3-3.2 | 1.7      | 1.3-2.3 |
| TG ≥ 150 mg/dL      | 1 (reference)    | 2.4             | 1.8-3.2 | 5.3     | 4.4-6.5 | 8.1      | 6.0-10.9 |
| Low HDL-C           | 1 (reference)    | 2.0             | 1.4-2.7 | 3.4     | 2.7-4.1 | 8.9      | 6.1-11.3 |
| Metabolic syndrome  | 1 (reference)    | 1.4             | 0.9-2.2 | 6.6     | 5.2-8.4 | 9.5      | 6.7-13.4 |

*OR = 0.05. P < 0.05. *Waist circumference in men ≥ 90 cm or in women ≥ 80 cm; *Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; *High-density lipoprotein cholesterol in men < 40 mg/dL or in women < 50 mg/dL; OR: Odds ratio; CI: Confidence interval.

Table 5 ORs for metabolic risk factors and metabolic syndrome among fatty liver groups, analyzed by multiple logistic regression, adjusted for age, gender, drinking alcohol, and physical activity (n = 1388)

|                     | Fatty liver (+) |
|---------------------|----------------|
|                     | Non-smoker (n = 1057) | Smoker (n = 331) |
|                     | OR     | 95% CI | OR     | 95% CI |
| Central obesity     | 1 (reference) | 1.2   | 0.9-1.6 |          |
| FPG ≥ 100 mg/dL     | 1 (reference) | 0.7   | 0.5-1.1 |          |
| High blood pressure | 1 (reference) | 0.6   | 0.5-0.9 |          |
| TG ≥ 150 mg/dL      | 1 (reference) | 1.5   | 1.2-2.0 |          |
| Low HDL-C           | 1 (reference) | 2.7   | 2.0-3.7 |          |
| Metabolic syndrome  | 1 (reference) | 1.3   | 1.0-1.8 |          |

*P < 0.05. *Waist circumference in men ≥ 90 cm or in women ≥ 80 cm; *Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; *High-density lipoprotein cholesterol in men < 40 mg/dL or in women < 50 mg/dL.

logistic regression. We found that subjects with fatty liver had significantly increased odds ratios (ORs) for developing metabolic syndrome and its components. Subjects who smoked had higher ORs for developing hypertriglyceridemia and low serum HDL-C, whether they had fatty liver or not. In addition, subjects with fatty liver who smoked had the highest ORs of high WC, hypertriglyceridemia, low HDL-C, and metabolic syndrome. We also found the ORs of hypertriglyceridemia, low HDL-C, and metabolic syndrome for subjects in group 4 [fatty liver (+)/smoking (+)] were greater than the sum of the ORs for subjects in group 3 [fatty liver (+)/smoking (-)] plus group 2 [fatty liver (-)/smoking (+)].

Table 5 showed the ORs for metabolic syndrome components among fatty liver groups. In comparison with subjects with fatty liver who did not smoke, subjects with fatty liver who smoked had significantly increased ORs for hypertriglyceridemia [OR, 1.5 (95% CI: 1.2-2.0), P < 0.05], low HDL-C [OR, 2.7 (95% CI: 2.0-3.7), P < 0.05] and metabolic syndrome [OR, 1.3 (95% CI: 1.0-1.8), P < 0.05].

DISCUSSION

In this study, we found that fatty liver was associated with an increasing OR for metabolic syndrome. The OR for developing metabolic syndrome increased significantly among subjects with fatty liver compared to those without fatty liver. We also found that smoking was associated with high TG levels and low HDL-C levels. Subjects who smoked had increased ORs for hypertriglyceridemia and low HDL-C, whether they had fatty liver or not. Moreover, fatty liver and smoking seemed to have a synergistic effect on metabolic syndrome. The ORs for hypertriglyceridemia, low HDL-C, and metabolic syndrome for subjects in group 4 [fatty liver (+)/smoking (+)] had greater than the sum of the ORs for subjects in group 3 [fatty liver (+)/smoking (-)] group plus group 2 [fatty liver (-)/smoking (+)]. In fatty liver groups, subjects who smoked had a significantly increased OR for hypertriglyceridemia, low HDL-C, and metabolic syndrome compared to subjects who did not smoke.

Metabolic syndrome and fatty liver were well discussed in previous studies. Insulin resistance played a pivotal role in the pathophysiology of both fatty liver and metabolic syndrome[13,20]. Furthermore, several studies showed that smoking induced insulin resistance or hyperinsulinemia and led to metabolic syndrome[11,13,23,24]. The associations between fatty liver, smoking, and metabolic syndrome were discussed in many studies individually, but the effect of interaction of fatty liver and smoking on metabolic syndrome was not investigated. In our study, subjects with fatty liver who smoked had a significantly increased risk of metabolic syndrome.

The effects of cigarette smoking inducing high plasma TGs and low HDL-C levels were shown in several studies[14,16-20,23,24,29,30]. While these studies provided evidence that smoking increased plasma TG and decreased HDL-C levels, most of these studies did not control potential confounding factors. Fatty liver also increased the risk of dyslipidemia such as hypertriglyceridemia and decreased HDL-C[13]. In our study, after controlling for confounding factors such as age, gender, drinking habit, and physical activity, the ORs for hypertriglyceridemia in subjects remained high: group 2 [fatty liver (-)/smoking (+)] 2.4 (95% CI: 1.8-3.2), group 3 [fatty liver (+)/smoking (-)] 5.3 (95% CI: 4.4-6.5), and group 4 [fatty liver (+)/smoking (+)] 8.1 (95% CI: 6.0-10.9) compared to subjects without fatty liver who did not smoke. Additionally, the ORs for low HDL-C were 2.0 (95% CI: 1.4-2.7) for group 2 [fatty liver (-)/smoking (+)], 3.4 (95% CI: 2.7-4.1) for group 3 [fatty liver (+)/smoking (-)], and 8.3
Fatty liver is a clinicopathologic condition characterized by significant lipid deposition in the liver parenchyma. Fatty liver: Metabolic syndrome is a cluster of metabolic abnormalities and is associated with waist circumference, serum triglycerides level, serum HDL-C level, blood pressure and fasting blood glucose (FPG) level. Fatty liver: Metabolic syndrome is a frequent metabolic abnormality affecting approximately 20% of the non-diabetic population worldwide and increasing risks of cardiovascular diseases and mortality. Fatty liver and smoking increase the risk of developing metabolic syndrome through the pathogenic factor of insulin resistance and were well discussed in previous studies separately. We aimed to investigate possible interactive effects of fatty liver and smoking on metabolic syndrome.

Research frontiers
It was recognized that fatty liver, smoking and metabolic syndrome associated with insulin resistance would increase the risks of serious complications such as cirrhosis, hepatocellular carcinoma and cardiovascular diseases. We want to identify the interactive effect of fatty liver and smoking on metabolic syndrome and provide evidence for lifestyle modification and appropriate management.

Innovations and breakthroughs
The authors provided evidence that fatty liver and smoking had a synergistic effect on metabolic syndrome and its components, especially for triglyceride and HDL-C levels. We suggested that smoking cessation would have the great benefit of reducing the risk of metabolic syndrome, especially for subjects with fatty liver.

COMMENTS
Background
Metabolic syndrome is a frequent metabolic abnormality affecting approximately 20% of the non-diabetic population worldwide and increasing risks of cardiovascular diseases and mortality. Fatty liver and smoking increase the risk of developing metabolic syndrome through the pathogenic factor of insulin resistance and were well discussed in previous studies separately. We aimed to investigate possible interactive effects of fatty liver and smoking on metabolic syndrome.

Research frontiers
It was recognized that fatty liver, smoking and metabolic syndrome associated with insulin resistance would increase the risks of serious complications such as cirrhosis, hepatocellular carcinoma and cardiovascular diseases. We want to identify the interactive effect of fatty liver and smoking on metabolic syndrome and provide evidence for lifestyle modification and appropriate management.

Innovations and breakthroughs
The authors provided evidence that fatty liver and smoking had a synergistic effect on metabolic syndrome and its components, especially for triglyceride and high-density lipoprotein cholesterol (HDL-C) levels.

Applications
After identifying the synergistic effect of fatty liver and smoking on metabolic syndrome, the authors suggested that smoking cessation would have the great benefit of reducing the risk of metabolic syndrome, especially for subjects with fatty liver.

Terminology
Metabolic syndrome: Metabolic syndrome is a cluster of metabolic abnormalities and is associated with waist circumference, serum triglycerides level, serum HDL-C level, blood pressure and fasting blood glucose (FBG) level. Fatty liver: Fatty liver is a clinicopathologic condition characterized by significant lipid deposition in the liver parenchyma.

Peer review
This retrospective study investigated the possible interactive effect of fatty liver and smoking on metabolic syndrome. This study was based on a large scale population base (n = 3455) and the results are interesting. Study results
suggested that smoking cessation would reduce the risk of metabolic syndrome, especially for people with fatty liver.

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S-Editor Tian L  L-Editor O’Neill M  E-Editor Zheng XM