Original article

Association between Abnormal Liver Function and Risk Factors for Metabolic Syndrome among Freshmen

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Abstract

Purpose: The aim of this study was to investigate the prevalence of obesity and metabolic syndrome among freshmen and to find the association between abnormal liver function and risk factors for metabolic syndrome in Taiwan.

Methods: A total of 515 freshmen who were less than 22 years of age and negative for hepatitis B surface antigen marker from one general university in North Taiwan participated in this study during their school entry health examination in September 2004. Demographic characteristics, body height, body weight, biochemistry values such as alanine aminotransferase, and risk factors for metabolic syndrome such as blood pressure, fasting blood sugar, high-density lipoprotein cholesterol, triglycerides, and waist circumference were recorded for statistical analysis. Subjects with elevated serum alanine aminotransferase levels were considered to have abnormal liver function.

Results: The prevalence of overweight, obesity, and metabolic syndrome among freshmen in Taiwan was 18.5%, 6.0% and 1.4%, respectively. The prevalence of abnormal liver function test was 6.2%. In multivariate logistic regression analyses, patients of metabolic syndrome were 94.5 times more likely (95% confidence interval [CI] = 10.5–852.5) to be associated with abnormal liver function after adjusting for gender and age. Among the risk factors for metabolic syndrome, enlarged waist circumference (adjusted odds ratio [OR] = 10.1, 95% CI = 4.3–23.8), and elevated triglyceride (adjusted OR = 6.1, 95% CI = 1.6–23.5) were found to be statistically significantly associated with abnormal liver function.

Conclusions: Central obesity and elevated triglyceride level were the two risk factors for metabolic syndrome associated with abnormal liver function among freshmen in Taiwan. © 2007 Society for Adolescent Medicine. All rights reserved.

Keywords:

Metabolic syndrome; Nonalcoholic fatty liver disease; Freshmen; Abnormal liver function

Obesity and metabolic syndrome are well-known major predisposing conditions to nonalcoholic fatty liver disease (NAFLD) [1,2]. NAFLD is being increasingly recognized as a common liver disorder that represents the hepatic manifestation of the metabolic syndrome, a variably defined aggregate of disorders related to obesity, insulin resistance,

type 2 diabetes, hypertension, and hyperlipidemia [3]. NAFLD encompasses the entire spectrum of liver disease, which includes simple hepatic steatosis without inflammation, nonalcoholic steatohepatitis (NASH), and the resulting cirrhosis and end-stage liver disease [4]. Hepatocellular carcinoma is a documented complication in an as yet unknown percentage of cases of NASH-related cirrhosis [3].

Excluding viral hepatitis, alcoholic liver disease, hematochromatosis, and metabolic liver disease, NAFLD is the most common liver disease in developed countries [2,5]. Unexplained aminotransferase elevation was found to be

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strongly associated with adiposity and other features of the metabolic syndrome, and thus may represent NAFLD [6]. In the early 1980s, the positive rate of hepatitis B surface antigen (HBsAg) in the general population of Taiwan was as high as 15–20%. [7]. Since universal hepatitis B vaccination was launched in 1984, the carrier rate of hepatitis B has declined [8]. However, the prevalence of metabolic syndrome is increasing because of the rising prevalence of childhood and adolescent obesity. The prevalence of metabolic syndrome for adults in Taiwan is about 10–15% [9,10]. Therefore, NAFLD may become the most common liver disease among children and adolescents in the future, after hepatitis B infection has been controlled with mass vaccination.

The majority of college freshmen are in the late adolescent stage and are commonly considered as young adults. Despite the copious studies published on metabolic syndrome in recent years, few have focused on individuals in this transitional period. Therefore, the aim of our study is to investigate the prevalence of obesity and metabolic syndrome in freshmen and to delineate the association between abnormal liver function and variable risk factors for metabolic syndrome.

Subjects and Methods

Study design

We conducted a cross-sectional study to see the association between risk factors for metabolic syndrome and abnormal liver function among freshmen who were less than 22 years of age and negative for hepatitis B surface antigen marker.

Data sources

The majority of the freshmen attending the selected university received routine school entrance health examination during an 8-day scheduled period. We randomly sampled 1 day's attendants as the study subjects. Those who were more than 22 years of age or positive for hepatitis B surface antigen marker were excluded; thus 515 persons were randomly selected from 4,013 freshmen in one university in Taipei city, Taiwan in 2004. All of the study subjects signed informed consent proved by school health committee and the ClinicalTrials.gov identifier was NCT00173940. Questionnaires, physical examination, and blood tests were performed by medical staffs from the university hospital and health center.

Definitions

The metabolic syndrome was defined using the modified diagnostic criteria of the 2005 International Diabetes Federation consensus in Asian populations [11]. With a lower waist circumference cut-off, the prevalence of the metabolic syndrome was comparable to that in Western populations

[12]. Risk factors for metabolic syndrome included central obesity (defined as waist circumference ≥ 90 cm for men and ≥ 80 cm for women, according to ethnicity-specific values for Chinese individuals [13]) plus any two of the following four variables: elevated blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension); raised serum triglyceride level (≥ 150 mg/dL, or specific treatment for this lipid abnormality); reduced high-density lipoprotein cholesterol (HDL-C; < 40 mg/dL in males and < 50 mg/dL in females, or specific treatment for this lipid abnormality); and raised fasting glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes. Body mass index (BMI) cutoffs were adopted as suggested by the Department of Health in Taiwan including normal (BMI ≥ 18.5 kg/m² but < 24 kg/m²), overweight (BMI ≥ 24 kg/m² but < 27 kg/m²), and obese (BMI ≥ 27 kg/m²) categories. Subjects with elevated serum alanine aminotransferase (ALT) levels (ALT ≥ 41 U/L in men and ≥ 31 U/L in women, according to the University Hospital laboratory reference) were considered to have abnormal liver function test (LFT).

Serum viral markers and biochemistry

HBsAg was detected using radioimmunoassay kits by DADE Behring, Rosys Beh III, and Abbott. Fasting plasma glucose, serum triglyceride, and HDL levels were measured using standard laboratory tests at the university hospital.

Statistical analysis

SAS version 9.1 software (SAS Institute, Cary, NC) was used for statistical analysis. χ^2 Analysis and Fisher's exact test were used to identify factors influencing the differences in liver function in persons with metabolic risk factors. Multivariate logistic regression analysis was performed to see the association between metabolic syndrome and abnormal liver function after adjusting for age and gender taken metabolic syndrome as an independent variable. Furthermore, stepwise multivariate logistic regression analyses were done to identify the odds ratios of abnormal LFT with regard to the different risk factors for metabolic syndrome after adjusting for age and gender. Odds ratios (OR) and 95% confidence intervals (95% CI) were also calculated. Statistical significance throughout was set at 5%.

Results

After exclusion of 40 individuals who were more than 22 years of age or positive for hepatitis B surface antigen marker, 515 freshmen were included in the final analysis. Among them, 271 were male (52.6%). Their mean age was 18.9 ± 0.8 years, and their mean BMI was 21.4 ± 3.5 kg/m². The data distribution for age, BMI, risk factors for metabolic syndrome, and ALT among the study subjects by gender is shown on Table 1. The prevalence of overweight, obesity, and metabolic syndrome was 18.5%, 6.0% and

Table 1

Data distribution of age, body mass index, risk factors for metabolic syndrome, and alanine aminotransferase among the study subjects (n = 515)

Item	No. (%) (n = 515)	Males (n = 271)	Females (n = 244)	p
Age (years)	18.9 ± 0.8	18.9 ± 0.8	18.8 ± 0.8	.15
Body mass index (kg/m ²)	21.4 ± 3.5	22.3 ± 3.5	20.4 ± 2.6	<.0001
Waist circumference (cm)	72.5 ± 10.1	77.1 ± 10.6	67.3 ± 6.4	<.0001
Blood pressure (mm Hg)				
Systolic (mm Hg)	116.2 ± 15.8	122.5 ± 14.4	109.2 ± 14.2	<.0001
Diastolic (mm Hg)	66.6 ± 10.4	68.9 ± 10.0	64.1 ± 10.3	<.0001
Triglyceride (mg/dL)	66.5 ± 48.9	70.2 ± 41.7	62.5 ± 55.6	.59
HDL-cholesterol (mg/dL)	46.4 ± 9.4	46.4 ± 9.7	46.4 ± 9.1	.85
LDL-cholesterol (mg/dL)	106.8 ± 29.8	107.7 ± 30.1	105.7 ± 29.5	.38
Total cholesterol (mg/dL)	163.9 ± 26.8	162.6 ± 26.3	165.2 ± 27.3	.30
Fasting glucose (mg/dL)	92.9 ± 8.4	94.5 ± 9.2	92.9 ± 8.4	<.0001
Alanine aminotransferase (U/L)	17.3 ± 18.4	21.5 ± 22.3	17.3 ± 18.4	<.0001

Data are mean ± SD.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

1.4%, respectively. We identified 32 persons with abnormal LFT (6.2%) and 483 persons with normal LFT, set as the control group (93.8%). The results of persons with metabolic risk factors in abnormal LFT subgroup compared with those with normal LFT are shown in Table 2. Waist circumference, blood pressure, triglycerides, HDL-C, and metabolic syndrome disclosed significant differences in the two subgroups. The mean ALT value was 74.7 ± 40.5 U/L for those who had metabolic syndrome, and 16.6 ± 16.7 U/L for those who did not have metabolic syndrome ($p < .05$). In univariate logistic regression analysis, factors which were related to abnormal LFT were enlarged

waist circumference, elevated triglyceride, elevated blood pressure, and reduced HDL-C. The ORs and 95% CIs are shown in Table 3. The multivariate logistic regression analyses revealed that individuals with metabolic syndrome were 94.5 times more likely (95% CI = 10.5–852.5) to have abnormal LFT after adjusting for gender, and age (Table 4). Among the risk factors for metabolic syndrome, enlarged waist circumference (adjusted OR = 10.1, 95% CI = 4.3–23.8) and elevated triglyceride (adjusted OR = 6.1, 95% CI = 1.6–23.5) were statistically significantly associated with abnormal LFT after adjusting for gender and age (Table 5).

Table 2

Comparison of risk factors for metabolic syndrome in abnormal liver function subgroup compared with normal liver function subgroup

Variable	No. (%) (n = 515)	Abnormal liver function (n = 32)	Normal liver function (n = 483)	p
Waist circumference				
≥90 cm in males, ≥80 cm in females	39 (7.6)	14 (43.8)	25 (5.2)	<.0001 ^a
<90 cm in males, <80 cm in females	476 (92.4)	18 (56.3)	458 (94.8)	
Blood pressure				
Systolic ≥130 or diastolic ≥85 mm Hg	93 (18.1)	12 (37.5)	81 (16.8)	.003 ^a
Systolic <130 and diastolic <85 mm Hg	422 (81.9)	20 (62.5)	402 (83.2)	
Triglycerides				
≥150 mg/dL	13 (2.5)	6 (18.8)	7 (1.5)	<.0001 ^a
<150 mg/dL	502 (97.5)	26 (81.3)	476 (98.6)	
High-density lipoprotein cholesterol				
<40 mg/dL in males, <50 mg/dL in females	238 (46.2)	8 (25.0)	230 (47.6)	.013 ^b
≥40 mg/dL in male, ≥50 mg/dL in females	277 (53.8)	24 (75.0)	253 (52.4)	
Fasting glucose				
≥100 mg/dL	78 (15.2)	6 (23.7)	72 (14.9)	.557
<100 mg/dL	437 (84.9)	26 (76.3)	411 (85.1)	
Metabolic syndrome				
Yes	7 (1.4)	6 (18.8)	1 (0.2)	<.0001 ^{a,c}
No	508 (98.6)	26 (81.3)	482 (99.8)	

^a $p < .01$.

^b $p < .05$.

^c Fisher's exact test.

Table 3

Univariate logistic regression analysis to evaluate the association between risk factors for metabolic syndrome and abnormal liver function

Variables	OR	95% CI	<i>p</i>
Waist circumference			
≥90 cm in males, ≥80 cm in females	14.2	6.4–31.9	<.0001 ^a
<90 cm in males, <80 cm in females	1		
Blood pressure			
Systolic ≥130 or diastolic ≥85 mm Hg	3.0	1.4–6.3	.005 ^a
Systolic <130 and diastolic <85 mm Hg	1		
Triglycerides			
≥150 mg/dL	15.7	4.9–50.0	<.0001 ^a
<150 mg/dL	1		
High-density lipoprotein cholesterol			
<40 mg/dL in males, <50 mg/dL in females	0.37	0.2–0.8	.017 ^b
≥40 mg/dL in males, ≥50 mg/dL in females	1		
Fasting glucose			
≥100 mg/dL	1.3	0.5–3.3	.558
<100 mg/dL	1		
Metabolic syndrome			
Yes	111.2	12.9–958.1	<.0001 ^a
No	1		

^a *p* < .01.^b *p* < .05.

Discussion

Tissue biopsy is the gold standard for the confirmation of steatohepatitis, NASH, or NAFLD; however the feasibility of liver biopsy as a mass screening method is low, and therefore abnormal ALT levels have been used as surrogate marker of steatohepatitis in previous studies [3,6,14]. We also used elevated serum ALT levels to imply possible NAFLD after the exclusion of individuals with hepatitis B infection, since liver diseases such as hepatitis caused by mononucleosis syndrome from Epstein-Barr virus or cytomegalovirus infections in our study population were rare [15].

Our data showed that the prevalence of metabolic syndrome among freshmen is 1.4%, which is much lower than adults in Taiwan (15%). There are two important findings

from this study; First, individuals with metabolic syndrome is noted to have 94.5 times higher (95% CI = 10.5–852.5) risk of abnormal liver function test as compared to those without. Second, enlarged waist circumference and elevated triglyceride levels were the two metabolic factors associated with abnormal LFT even after adjusting for age and gender.

Our findings in freshmen were in agreement with previous studies, which disclosed that metabolic syndrome is a strong predictor of NAFLD in adults [16–20]. A study by Shen et al showed that the presence of bright liver and elevated ALT level was independently associated with in-

Table 4

Multivariate logistic regression analysis to evaluate association between metabolic syndrome and abnormal liver function test results

Variables	OR	95% CI	<i>p</i>
Age			
Continuous variable	0.9	0.6–1.5	.74
1			
Sex			
Male	3.0	1.2–7.5	.016 ^a
Female	1		
Metabolic syndrome			
Yes	94.5	10.5–852.5	<.0001 ^b
No	1		

CI = confidence interval; OR = odds ratio.

^a *p* < .05.^b *p* < .01.

Table 5

Multivariate logistic regression analysis to evaluate the association between risk factors for metabolic syndrome and abnormal liver function

Variable	OR	95% CI	<i>p</i>
Age			
Continuous variable	0.9	0.6–1.5	.76
1			
Sex			
Male	2.5	1.0–6.3	.046 ^a
Female	1		
Waist circumference			
≥90 cm in males, ≥80 cm in females	10.1	4.3–23.8	<.0001 ^b
<90 cm in males, <80 cm in females	1		
Triglycerides			
≥150 mg/dL	6.1	1.6–23.5	.009 ^b
<150 mg/dL	1		

CI = confidence interval; OR = odds ratio.

^a *p* < .05.^b *p* < .01.

creased risk of metabolic syndrome in adults [16]. With regard to adolescents or young adults, in a study in Korean adolescents, metabolic syndrome was strongly associated with elevated ALT level, and the risk for elevated ALT level increases with the number of components of metabolic syndrome [20]. However, the Dionysos nutrition and liver study conducted in Italy revealed that NAFLD is associated with numerous features of the metabolic syndrome instead of elevated ALT level only [21].

With regard to individual components of the metabolic syndrome, enlarged waist circumference was much more likely to have abnormal LFT in our study, which was also comparable to results of previous studies in adults and children [17,20,22,23–26]. Increasing evidence shows that abdominal adiposity has a direct influence on health, and waist circumference is a reliable indicator of visceral fat and central adiposity, which correlates with health risks to a greater extent than does adipose tissue in other regions of the body because of high association between the visceral fat and insulin resistance [27–29].

NAFLD is the resultant disequilibrium in lipid homeostasis, which causes triglycerides to accumulate in the liver. An increase in oxidative stress, caused by the generation of reactive oxygen species as a result of mitochondrial abnormalities and induction of the cytochrome P-450 system, could be one mechanism by which NAFLD develops into NASH [30]. In addition to central obesity, elevated triglyceride level was also noted to have high association with elevated ALT level in our subjects. It has also been found to be associated with hepatic steatosis or NAFLD in adults [6,17,20] and in children [24,26]. Because enlarged waist circumference and elevated triglycerides had been identified as components of a syndrome of lipid overaccumulation associated with metabolic risk and accelerated mortality after middle age [31], our study likewise showed similar trends thus indicating that clinicians should provide closer follow-up of adolescents or young adult patients with central obesity or hypertriglyceridemia.

In regard to the association of HDL-C and abnormal LFT, the result of univariate logistic regression analysis in our study showed that lower HDL-C was associated with 63% lowered risk (95% CI = 17–84%) of abnormal LFT. Its negative association remained after adjustment for age and gender, although this was not statistically significant. The result was quite different from other studies, which disclosed low HDL-C associated with elevated ALT level in adults or obese adolescents with suspected fatty liver [6,17,20,32]. It is known that lipid composition varies by puberty stage in youth. Total cholesterol drops in mid-puberty and begins rising toward adult levels at the end of puberty [33,34]. These lipid changes throughout puberty complicate the definition of cut-off points for dyslipidemia in young persons. Therefore, the appropriateness of the HDL-C cutoff value for the metabolic syndrome in young adults is questionable. On the other hand, racial/ethnic dif-

ferences may be the cause of this discrepancy. Further research is needed to explore this issue.

Apart from central obesity and elevated triglyceride level, there were no obvious association between HDL-C, high blood pressure or impaired fasting glucose and abnormal LFT after adjusting for age and gender. Hypertension has been recognized as an important component of the metabolic syndrome in adults, but its role in children and adolescents is still not clear [35]. Few studies of youth have examined the relationship of blood pressure and insulin values, and their results are conflicting. Some investigators found a positive association between insulin levels and blood pressure [36,37], whereas others did not [38,39].

There are several limitations to our study. First, the sample size of abnormal LFT subgroup was relatively small (32 cases). However, we could still find a significant association between central obesity, elevated triglyceride, and elevated ALT levels among freshmen. Second, we were not sure whether the definition of adult metabolic syndrome is applicable to adolescents and young adults. A commonly encountered problem with the use of ALT as a population-based screening test is related to the cutoff value used to detect normality [6]. Third, the sensitivity and specificity of ALT values in discerning hepatic steatosis and steatohepatitis are variable [40]. Fourth, we did not perform further diagnostic tests to prove NAFLD, such as abdominal ultrasonography or biopsy study. Fifth, we could not completely exclude other types of hepatitis among the study subjects but we could omit this because these other types are rare.

In conclusion, we suggest that aggressive lifestyle modification in young adults is very important for reducing the morbidity associated with the metabolic syndrome, not only cardiovascular disease but also fatty liver disease. Childhood manifestation of metabolic syndrome is likely to continue into adulthood, and early identification may help target interventions to prevent future morbidities. We further emphasize that measurement of waist circumference is a simple, inexpensive, and reliable tool that should be included as part of physical examinations in the routine school-entry health examination. We are looking forward to more prospective study for metabolic syndrome and NAFLD in adolescents and young adults.

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