J Med Sci 2015;35(5):182-189
DOI: 10.4103/1011-4564.167708

ORIGINAL ARTICLE

Correlation between Liver Function Tests and Metabolic Syndrome in Hepatitis-free Elderly

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Background: We aimed to investigate the relationship between liver function tests (LFTs) and metabolic syndrome (MetS) as several studies have shown positive correlations between some of the LFTs, including alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (γ-GT), and MetS but have not fully explored the same in the elderly. Owing to the progress in public health, the aging of the general population becomes a major issue. **Design:** We enrolled subjects aged over 60 years who underwent routine health checkups in a Health Screening Center after excluding subjects with a history of hepatitis B or C infection, excessive alcohol consumption, liver fibrosis, cirrhosis, acute hepatitis, diabetes, hypertension, dyslipidemia, cardiovascular disease, or receiving medications for these diseases. Finally, 9,282 participants were eligible for analysis. **Statistical Analysis:** All data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with the Levene's test. A *t*-test was used to evaluate the differences between the two groups. Univariate and multivariate regressions were used to observe correlations between different parameters. Receiver operating characteristic curves of each LFT were used to predict MetS. Areas under curves and 95% confidence interval were also estimated and compared. **Results:** With the exception of aspartate aminotransferase and α-fetal protein, the results of LFTs, including total and direct bilirubin, alkaline phosphatase (ALP), ALT, and γ-GT, were altered in the group with MetS. Furthermore, the levels of γ-GT in men and ALP in women were independently associated with all MetS components and had the highest areas under receiver operating characteristic curves. **Conclusion:** Abnormal LFTs are highly correlated with MetS in the hepatitis-free elderly, with levels of γ-GT in men and ALP in women being the most important factors. LFTs may represent an auxiliary tool for the detection of MetS.

Key words: Liver function tests, metabolic syndrome, elderly

INTRODUCTION

The combination of impaired glucose tolerance, central obesity, hypertension, and dyslipidemia is termed metabolic syndrome (MetS).[1,2] However, elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) are also associated with MetS.[4-12]

Many abnormal liver function test (LFT) cases are due to nonalcoholic fatty liver disease (NAFLD).[13] To avoid bias, we enrolled 9,282 subjects over 60 years old without liver disease. Thus, the relationship between levels of AST, ALT, ALP, γ-glutamyl transpeptidase (γ-GT), total bilirubin (T-Bil), direct bilirubin (D-Bil), and α-fetoprotein (AFP), and MetS components was evaluated to enable early MetS detection.

Received: June 17, 2015; Revised: July 16, 2015; Accepted: August 12, 2015
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METHODS

Patients

We enrolled subjects aged over 60 years who underwent routine health checkups between 1999 and 2007 at an MJ Health Screening Center. MJ Health Screening Centers are private clinics located throughout Taiwan that provide regular health examinations to their members. Originally, 27,679 subjects were randomly selected. The following exclusion steps were performed to recruit individuals who fit our study purposes:

1. 1,121 subjects were excluded because of missing data on MetS components, LFTs, hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C virus antibody tests.

2. 7,639 subjects with a history of diabetes, hypertension, dyslipidemia, cardiovascular disease, or receiving medications for these diseases or other medications known to affect components of MetS were excluded including estrogen.
3. 4,785 subjects were excluded because of chronic hepatitis B or C infection.
4. 4,852 subjects with a history of excessive alcohol consumption (>20 g/day for men and >10 g/day for women), liver fibrosis, cirrhosis, hepatobiliary operation, or acute hepatitis were also excluded from this study.

The remaining 9,282 subjects were eligible for analysis. All subjects were delinked. To avoid data of the same subject but from different years were analyzed repeatedly; data with the same sequential number were only selected once. The study protocol was approved by the institutional review board of MJ Health Screening Centers, and informed consent was obtained from all the participants.

Data collection

Participants visited the clinic at 8 AM after at least a 10-h fast. Information about medical history, lifestyle, alcohol intake, smoking, and physical exercise was obtained through an interview with senior nursing staff. A complete physical examination was conducted, and waist circumference was taken at the midway point between the inferior margin of the last rib and the crest of the ilium, in a horizontal plane. After resting for 5 min in a sitting position, systolic and diastolic blood pressures were measured on the right arm using a computerized automatic mercury sphygmomanometer. A venous blood sample was collected for biochemical study. For the analysis of fasting plasma glucose (FPG) and lipid profiles, plasma was separated from blood within 1 h and stored at −30°C. FPG was assessed using the glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Springs Instruments, Yellow Springs, OH, USA). Total cholesterol and triglycerides were measured with a Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan) using the dry multilayer analytical slide method. Serum high-density lipoprotein cholesterol concentration was analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation. AST and ALT levels were measured by the ultraviolet method with P5P (ARCHITECT c System, Abbott Diagnostics, Lake Forest, IL, USA). Hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody were detected by using chemiluminescent microparticle immunoassays (ARCHITECT i System, Abbott Diagnostics). LFTs including γ-GT, D-Bil, T-Bil, ALT, AST, AFP, and ALP were performed using a CX7 biochemistry analyzer (Beckman, Fullerton, CA, USA).

Definition of metabolic syndrome

The harmonized criteria of 2009[14] were used for the detection of MetS. Waist circumference was adjusted to ≥90 and ≥80 cm for Taiwanese men and women, respectively.[15] The other 4 criteria remained the same: Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, triglycerides ≥150 mg/dL, FPG ≥100 mg/dL, high-density lipoprotein cholesterol ≤40 and ≤50 mg/dL for men and women, respectively, or intake of related medications. Subjects had to satisfy at least 3 criteria to be diagnosed with MetS. Based on these criteria, patients were assigned to the group with or without MetS.

Liver sonography

An abdominal sonogram was recorded for every participant using a high-resolution B-mode scanner (SSA-240A, Toshiba Corporation, Tokyo, Japan), and the results were interpreted by 2 highly experienced radiologists. The radiologists participated in regular conferences to discuss all the radiologic results with the aim to reduce expert bias. Normal liver echogenicity was assigned a score of 0, whereas increased echogenicity was assigned a score of 1 based on liver-kidney echo discrepancy and loss of echoes from the walls of the portal veins.[16] Liver cyst, mass, and cirrhosis were all excluded by the radiologist.

Statistical analysis

The data were analyzed with SPSS version 18.0 (SPSS, Chicago, IL, USA). All data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with the Levene's test. Continuous variables were expressed as mean ± standard error of the mean. The *t*-test was used to evaluate the differences between the two groups. Univariate and multivariate regressions were used to observe correlations between different parameters. Receiver operating characteristic curves of each LFT were used to predict MetS. Areas under curves (AUCs) and 95% confidence interval were also estimated and compared. All statistical tests were two-sided and considered statistically significant when $P < 0.05$.

RESULTS

Table 1 summarizes the demographic data of the 9,282 subjects with and without MetS. Among all the LFTs, only the differences in the levels of AST and AFP between the groups with and without MetS did not reach statistical significance for both sexes. In addition, D-Bil in men also showed a borderline *P*-value of 0.051. The results of Pearson's correlation analysis between all the biochemical parameters of the liver and the MetS components are shown in Table 2. It can be noted that, although the relationships are not exactly the same in men and

Table 1: Demographic data of study subjects with and without metabolic syndrome

	MetS (−)	MetS (+)	*P*
Men			
n	3752	504	
Age (years)	66.1±5.8	66.6±6.1	0.049
Body mass index (kg/m^2)	22.00±2.47	24.12±2.46	<0.001
Waist circumference (cm)	79.0±7.2	86.7±7.4	<0.001
Systolic blood pressure (mmHg)	125.4±18.2	138.8±17.6	<0.001
Diastolic blood pressure (mmHg)	73.4±10.5	80.0±10.8	<0.001
FPG (mg/dL)	99.1±14.6	107.9±20.7	<0.001
High-density lipoprotein (mg/dL)	54.9±14.1	41.2±10.9	<0.001
Triglycerides (mg/dL)	96.3±42.6	164.2±66.3	<0.001
T-Bil (mg/dL)	0.92±0.49	0.85±0.36	0.003
D-Bil (mg/dL)	0.24±0.24	0.21±0.12	0.051
ALP (U/L)	132.6±59.6	140.6±65.4	0.005
AST (U/L)	24.8±12.5	24.9±13.5	0.859
ALT (U/L)	22.6±17.8	25.4±23.1	0.001
γ-GT (U/L)	21.8±21.0	28.5±32.7	<0.001
AFP (ng/mL)	3.8±18.0	3.6±1.7	0.813
Women			
n	4206	820	
Age (years)	64.4±4.9	66.8±6.2	<0.001
Body mass index (kg/m^2)	22.07±2.60	23.91±2.80	<0.001
Waist circumference (cm)	72.8±6.2	79.8±7.4	<0.001
Systolic blood pressure (mmHg)	127.0±18.5	141.9±18.2	<0.001
Diastolic blood pressure (mmHg)	71.7±10.6	78.2±10.4	<0.001
FPG (mg/dL)	97.5±12.1	105.0±18.4	<0.001
High-density lipoprotein (mg/dL)	66.0±15.6	49.5±12.4	<0.001
Triglycerides (mg/dL)	97.3±41.3	158.1±66.6	<0.001
T-Bil (mg/dL)	0.80±0.30	0.74±0.28	<0.001
D-Bil (mg/dL)	0.18±0.08	0.17±0.08	<0.001
ALP (U/L)	131.6±62.5	153.7±70.5	<0.001
AST (U/L)	24.0±9.6	24.0±11.3	0.982
ALT (U/L)	20.1±13.3	21.2±16.8	<0.001
γ-GT (U/L)	18.0±18.1	21.2±27.1	<0.001
AFP (ng/mL)	3.3±3.1	3.2±1.7	0.592

†Data are shown as mean ± SEM; *MetS (−) = Without metabolic syndrome; MetS (+) = With metabolic syndrome; SEM = Standard error of mean; γ-GT = γ-glutamyl transpeptidase; AFP = α-fetal protein; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ALP = Alkaline phosphatase; D-Bil = Direct bilirubin; T-Bil = Total bilirubin; FPG = Fasting plasma glucose

women, T-Bil and D-Bil, as well as ALP were related mainly to triglycerides and high-density lipoprotein cholesterol. In men, γ-GT and ALT were strongly correlated with MetS, but in women such relationships could only be found for waist circumference, FPG, and triglycerides. In contrast to γ-GT and ALT, AFP had no positive correlations, except with FPG in women. The relationships revealed with multiple regression analysis were generally similar to those found with the Pearson's correlation analysis [Table 3].

In receiver operating characteristic curve analysis, only AST in both sexes and AFP in women failed to show significant associations with MetS. The highest values of AUC were found for γ-GT (0.597 ± 0.014) in men and ALP (0.601 ± 0.011) in women. Although these values were not high enough to have predictive power, it should be pointed out that the study participants were healthier than a typical study population. Therefore, the extreme end of the data distribution was lost, which affected the capability to predict MetS from AUC. The second highest AUC values were found for D-Bil in men and T-Bil in women. However, these values were significantly lower than the highest AUCs in both genders.

DISCUSSION

Although several studies reported on the relationships between LFTs and MetS, it has not been clarified which LFTs exhibit the strongest associations, especially in the elderly. In the current study, we found that γ-GT in men and ALP in women have the highest correlations with MetS. Moreover, the extents of these correlations are different in men and women. Our results indicate intriguing roles of abnormal LFTs, which warrants further investigation.

The positive relationship between γ-GT and MetS in hepatitis-free subjects has been verified in numerous studies.[17-23] For example, a meta-analysis was conducted of 9 prospective cohort studies including 47,499 participants and 5,009 cases of MetS. These studies examined the risks of developing MetS in subjects with the highest and lowest γ-GT levels. The pooled relative risk was 1.63 for the group with high γ-GT.[17] Another 4-year cohort study had similar findings. It was noted that, in 3,698 Korean male workers, γ-GT had a positive correlation with the risk of MetS incidence.[23] Furthermore, Kang *et al*. found that, as the quartile of serum γ-GT level increased in 3,246 adults (age: 20-70 years old; 1,622 men and 1,624 women) who visited Center for Health Promotion in Pusan National University Hospital for a medical checkup, the number of components of MetS and the prevalence of MetS also increased.[21] In addition to its relationship with MetS, γ-GT has also been shown to be associated with dyslipidemia and abnormal glucose tolerance. This suggests that serum γ-GT probably interacts with MetS through its effects on hepatic insulin resistance, which is not related to NAFLD.[21] γ-GT

Table 2: Pearson's correlation coefficients between metabolic syndrome components and each liver function test

	T-Bil	D-Bil	ALP	AST	ALT	γ-GT	AFP
Men							
Waist circumference							
r	0.027	0.011	−0.010	−0.020	0.067	0.119	0.006
P	0.074	0.465	0.525	0.185	0.000	0.000	0.716
Systolic blood pressure							
r	−0.021	−0.023	0.025	−0.011	−0.003	0.031	0.011
P	0.171	0.140	0.101	0.471	0.854	0.042	0.455
Diastolic blood pressure							
r	0.003	−0.014	0.007	−0.008	0.022	0.045	0.008
P	0.868	0.345	0.628	0.587	0.145	0.003	0.582
FPG							
r	−0.002	−0.022	−0.013	−0.036	0.032	0.048	−0.002
P	0.912	0.154	0.406	0.020	0.038	0.002	0.873
Triglycerides							
r	−0.067	−0.057	0.066	−0.023	0.035	0.155	0.000
P	0.000	0.000	0.000	0.137	0.024	0.000	0.995
High-density lipoprotein							
r	0.060	−0.033	−0.133	−0.009	−0.057	−0.037	−0.019
P	0.000	0.029	0.000	0.541	0.000	0.015	0.226
Women							
Waist circumference							
r	−0.034	0.018	0.127	0.012	0.058	0.030	0.010
P	0.017	0.196	0.000	0.382	0.000	0.034	0.484
Systolic blood pressure							
r	−0.018	0.000	0.096	0.011	−0.002	0.011	−0.015
P	0.200	0.994	0.000	0.451	0.862	0.428	0.284
Diastolic blood pressure							
r	−0.001	0.022	0.100	0.005	0.017	0.008	−0.008
P	0.929	0.127	0.000	0.722	0.241	0.595	0.563
FPG							
r	0.032	0.002	0.047	−0.017	0.039	0.032	0.091
P	0.023	0.892	0.001	0.230	0.006	0.022	0.000
Triglycerides							
r	−0.113	−0.166	0.161	−0.023	0.014	0.068	0.014
P	0.000	0.000	0.000	0.096	0.331	0.000	0.328
High-density lipoprotein							
r	0.094	−0.024	−0.148	0.001	−0.021	−0.013	0.008
P	0.000	0.093	0.000	0.961	0.146	0.350	0.556

*T-Bil = Total bilirubin; D-Bil = Direct bilirubin; ALP = Alkaline phosphatase; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; γ-GT = γ-glutamyl transpeptidase; AFP = α-fetal protein; FPG = Fasting plasma glucose

level, even when in the normal range, was also found to be significantly associated with anti-oxidative stress activity, accumulation of oxidative stress, MetS, and atherosclerosis. Measuring the γ-GT level is easy and inexpensive, and it can be used as a sensitive marker of oxidative stress and MetS.[24] Overall, our results are consistent with those of the

Table 3: Multivariate regression analysis of correlations between metabolic syndrome components and liver function tests used as independent variables

	T-Bil	D-Bil	ALP	AST	ALT	γ-GT	AFP
Men							
Waist circumference							
β	—	—	—	—	0.337	0.117	—
P	—	—	—	—	0.000	0.000	—
Systolic blood pressure							
β	—	—	—	—	—	0.031	—
P	—	—	—	—	—	0.042	—
Diastolic blood pressure							
β	—	—	—	—	—	0.045	—
P	—	—	—	—	—	0.003	—
FPG							
β	—	—	—	−0.267	0.245	0.053	—
P	—	—	—	0.000	0.000	0.002	—
Triglycerides							
β	−0.041	−0.037	0.067	—	0.132	0.177	—
P	0.220	0.296	0.000	—	0.000	0.000	—
High-density lipoprotein							
β	0.422	−0.436	−0.106	—	−0.277	0.021	—
P	0.000	0.000	0.000	—	0.000	0.201	—
Women							
Waist circumference							
β	−0.101	—	0.094	—	0.244	−0.023	—
P	0.000	—	0.000	—	0.000	0.139	—
Systolic blood pressure							
β	—	—	0.096	—	—	—	—
P	—	—	0.000	—	—	—	—
Diastolic blood pressure							
β	—	—	0.100	—	—	—	—
P	—	—	0.000	—	—	—	—
FPG							
β	0.125	—	0.057	—	0.211	−0.003	0.100
P	0.000	—	0.000	—	0.000	0.849	0.000
Triglycerides							
β	0.152	−0.306	0.181	—	—	0.044	—
P	0.000	0.000	0.000	—	—	0.005	—
High-density lipoprotein							
β	0.311	—	−0.107	—	—	—	—
P	0.000	—	0.000	—	—	—	—

†Data were adjusted for age; *T-Bil = Total bilirubin; D-Bil = Direct bilirubin; ALP = Alkaline phosphatase; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; γ-GT = γ-glutamyl transpeptidase; AFP = α-fetal protein; FPG = Fasting plasma glucose

main studies in this field. However, we observed a stronger correlation between the γ-GT level and MetS in the elderly men. The reason for this sex-related difference is currently unknown.

Some studies have suggested that there is a link between increased ALP and a greater likelihood of having MetS and its components.[25-30] For example, Kim *et al*. examined the relationship between the serum ALP level and the development of MetS in 14,224 middle-aged Korean men during a 4-year period. The results showed that higher serum ALP level correlated positively with body fat mass and visceral fat mass. At the baseline, none of the participants had MetS. However, after 4 years, 1,179 developed MetS and, at the same time, serum ALP levels also increased.[26] Another cross-sectional study conducted in Croatia revealed similar finding in a group of independently living elderly persons aged 70-90 years. Men with MetS had higher levels of ALP.[27] Our results are in line with these studies. Furthermore, we also showed that ALP was most tightly associated with MetS in elderly women.

In agreement with published studies, our results suggest a negative correlation between bilirubin levels and the prevalence of MetS and its components.[11,12,31-34] For instance, a cross-sectional study including 12,342 Korean adults showed that high bilirubin was associated with significantly lower odds ratio of developing MetS.[33] Another large-scale cross-sectional study, also performed in Korea, demonstrated that T-Bil level was inversely associated with the prevalence of MetS, even after the adjustment for other risk factors of MetS.[34]

The main strength of this study is that it is the first to explore the correlations between the results of different LFTs and MetS in the elderly. In addition, we also provide new information regarding sex-related differences in these correlations. However, the study has several limitations. First, the subjects were recruited from a single private health screening center. Thus, they had better than average economic status and likely received more medical support. However, we believe that the relationships that we observed are not affected by these confounding factors. Second, it is generally accepted that the core defect in MetS is insulin resistance, which was not evaluated in our study. Third, since subjects receiving medications for the treatment of MetS components were excluded from this study, we could not analyze the subpopulation with more severe MetS. Although this precluded the complete evaluation of the relationship between LFTs and MetS, it would be difficult and unethical to recruit subjects with severe MetS who did not receive any treatment. Furthermore, the strict exclusion criteria that we employed facilitated a precise assessment of the association between LFTs and MetS. Finally, although there are some important markers that are highly related to MetS, we still cannot analyze them in the present study. This is mainly due to the fact that our data were derived from the health examination. If any markers that were not measured or collected in the beginning, it would not be possible to do further evaluation.

CONCLUSION

Abnormal LFTs are associated with MetS in the elderly in a sex-dependent manner. In particular, γ-GT in men and ALP in women showed the highest associations with MetS. Abnormal LFT values could serve as a sensitive indicator for the early detection of MetS in the elderly.

ACKNOWLEDGMENTS

The authors thank the personnel of the MJ Health Screening Center for providing the data.

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