Inverse relationship of hepatic steatosis and alanine aminotransferase with sex hormone-binding globulin in men

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Inverse relationship of hepatic steatosis and alanine aminotransferase with sex hormone-binding globulin in men.

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ABSTRACT

Inverse relationship of hepatic steatosis and alanine aminotransferase with sex hormone-binding globulin in men.

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Objective: Sex hormone-binding globulin (SHBG) is a serum glycoprotein produced predominantly in hepatocytes. As such, the synthesis of SHBG could be associated with liver function and metabolic syndrome. ALT levels could reflect hepatocellular injury and insulin resistance; however, the relationship between hepatic steatosis and ALT with SHBG has not been investigateded in human. The objective of this study was to investigate the association between SHBG and hepatocyte damage among Korean male patients with hepatic steatosis enrolled in a health examination program.

Methods: We performed a retrospective cross-sectional study with 883 participants who underwent routine health examination. A total of 883 men with or without hepatic steatosis were divided into three groups. We analyzed the risk of lower serum SHBG levels with or without elevated serum ALT levels using odds ratios with 95% confidence intervals.

Results: A significantly increased risk of lower serum SHBG level was observed in the group with hepatic steatosis with ALT elevation (95% CI 1.197 - 3.053).

Conclusions: In men with hepatic steatosis, we found that elevated serum ALT levels were associated with lower serum SHBG levels. This finding suggested that subjects with both hepatic steatosis and increased ALT should be considered to have a low level of SHBG.

Key words : sex hormone-binding globulin, alanine aminotransferase, and hepatic steatosis.

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I. INTRODUCTION

Sex hormone-binding globulin (SHBG) is a serum glycoprotein produced predominantly in hepatocytes.[1, 2] It controls the transport of sex steroid hormones in the blood circulation to their target tissues.[1, 3] Many previous studies have revealed that low levels of serum SHBG are associated with metabolic syndrome, type II diabetes, and cardiovascular disease.[4, 5] Nonalcoholic fatty liver disease (NAFLD) grade is also known to be inversely related to serum SHBG levels:[6, 7] As the grade of hepatic steatosis increases, serum SHBG level decreases.[2, 7] Hepatocyte is the primary site of SHBG synthesis, and therefore the synthesis of SHBG could be associated with liver function.[1] Various studies have investigated the relationship between SHBG and biomarkers of liver function.[8] However, despite several epidemiological studies, it is still controversial whether serum ATL is associated with SBHG. M. Flechtner-Mors et al. found no relationship between ALT and SHBG, while Mariana Ayala et al. found that SHBG and ALT were inversely related with each other.[1, 9] Whereas ALT level is known to reflect hepatocellular injury or death, it is still unclear whether ALT, liver function marker, modulates the relationship between SHBG and hepatic steatosis.[10] Furthermore, ALT is a predictive marker of insulin resistance[11, 12] and several studies have suggested that hyperinsulinemia is associated with the decreased expression of SHBG.[13]

This study was aimed to investigate the association between SHBG and

hepatocyte damage represented by ALT among Korean male patients with hepatic steatosis, enrolled in a health examination program.

II. MATERIALS AND METHODS

1. Study population

This retrospective study included 1719 men aged >19 years old who visited the Health Promotion Center of Gangnam Severance Hospital, Yonsei University College of Medicine in Seoul, Korea. Subjects underwent routine health examination between January 2007 and July 2010. Of them, 478 subjects were excluded because of missing values. Subjects who were positive for hepatitis B surface antigen or hepatitis C antibody were also excluded. In addition, we excluded 143 subjects with a history of hepatocellular carcinoma and 155 subjects with alcohol consumption ≥ 140 g/week. Ultimately, a total of 883 men were included in this study.

2. Measurements

Examinations were performed by medical staff according to a standard protocol. Demographic, anthropometric, and laboratory data were gathered for each participant The participants were asked whether they were undergoing or had recently undergone treatment for any disease. If the patient were under treatment, they were questioned for the date of diagnosis and a list of current medications. Trained staff reviewed the completed questionnaires and entered the responses into the database. Participants were classified as non-smokers, ex-smokers or current smokers. Subjects were categorized by alcohol intake as a heavy drinker (alcohol ingestion ≥ 140 g/week) or light drinker (alcohol ingestion < 140 g/week). Body weight and height were measured in light indoor clothing and no shoes to the nearest 0.1kg and 0.1cm, respectively. BMI was calculated as the ratio of weight (kg)/height (m2). Blood pressure measurement was obtained with the participant in the sitting position, after 5 min of rest using an automated device (TM-2665P, A&D Co., LTD., Tokyo, Japan).

The diagnosis of fatty liver was based on abdominal ultrasonography with a 3.5-MHz transducer (HDI 5000, Philips, Bothell, USA).[14] Ultrasonography was performed by an experienced radiologist. Participants were diagnosed with fatty liver if at least two of the following three findings were present: increased liver echogenicity, deep attenuation, and vascular blurring.

Venous blood sampling was performed after a fasting period of 12h. White blood cell (WBC) counts were quantified by an automated blood cell counter (ADVIA 120, Bayer, NY, USA). Fasting plasma glucose, total cholesterol, HDL cholesterol, triglycerides, and alanine aminotransferase were measured using a Hitachi7600-110 chemistry autoanalyzer (Hitachi, Tokyo, Japan). T3, free T4 (fT4), and SHBG were measured via electrochemiluminescent methods using Modular E170 (Roche Diagnostics, Mannheim, Germany).

3. Statistical analysis

The distribution of SHBG was markedly skewed and log-transformed in the analyses where normality was required. ALT elevation was defined as ALT ≥ 30 U/L.[15, 16] We divided the study participants into tertiles of SHBG levels with cut-points of 28.60 and 48.90nmol/L, and defined the lowest tertile of SHBG as low SHBG.[17]

Multivariable logistic regression was used to assess the association of ALT elevation with the risk of low SHBG. We adjusted for age, BMI, SBP, DBP, WBC, glucose, T3, total cholesterol, HDL, and TG. To investigate the interrelationships among hepatic steatosis, elevated ALT level and the risk of low SHBG, we divided our participants into the following three groups: the reference group, hepatic steatosis group without ALT elevation, and hepatic steatosis with ALT elevation group. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were performed using SPSS statistical software (version 18.0, Chicago, IL). All statistical tests were two-sided and significance was determined at a p-value < 0.05.

III. RESULTS

1. Baseline characteristics of each group were described in Table 1. In hepatic steatosis with ALT ≥ 30 group, the log transformed SHBG was 1.51 (1.35 ~ 1.62), which was significantly lower than that of the reference group ($p < 0.0001$). The subjects in hepatic steatosis with ALT ≥ 30 group had a higher BMI, SBP, DBP, glucose, and TG. They were more likely to have a history of diabetes. The subjects in hepatic steatosis with ALT ≥ 30 group were also younger and had a lower HDL cholesterol level.

2. Table 2 shows the correlation analysis between SHBG and several factors that were known to be associated with SHBG in previous studies. BMI, DBP, WBC, glucose, cholesterol and TG were negatively correlated with SHBG, while age, T3 and HDL were positively associated with SHBG.

3. Multivariate logistic regression models were used to evaluate the relationship between hepatic steatosis and elevated ALT levels with the risk of low SHBG levels (Table 3). In multivariable regression analysis model 1 adjusting wih age and BMI, the OR for lower SHBG was 2.370 (1.539 ~ 3.650) in hepatic steatosis group with ALT ≥ 30 compared with the reference group. Even after progressive adjustment for several factors that were previously found to be associated with SHBG, the subjects in hepatic steatosis group with ALT ≥ 30 were still more likely to have a lower SHBG level (OR: 1.912; 95% CI 1.197 ~ 3.053).

Table 1. Characteristics of the study participants

	Reference group	Hepatic steatosis and ALT < 30	Hepatic steatosis and ALT ≥ 30	p-value
N	349	315	219	
Age (years)	53.9 ± 10.0	55.4 ± 9.9	53.3 ± 9.0	0.001
BMI (kg/m^2)	23.4 ± 2.5	25.4 ± 2.9	25.9 ± 2.6	0.000
SBP (mmHg)	125.2 ± 16.1	127.5 ± 16.0	130.9 ± 17.2	0.001
DBP (mmHg)	77.5 ± 9.1	79.9 ± 9.7	81.6 ± 9.7	0.000
WBC (10^3/μL)	5.8 ± 1.7	6.3 ± 1.8	6.5 ± 1.7	0.000
Glucose (mg/dL)	97.3 ± 19.3	100.1 ± 16.3	107.6 ± 25.9	0.000
T3 (ng/mL)	109.8 ± 22.6	109.4 ± 15.8	114.8 ± 24.9	0.000
Cholesterol (mg/dL)	187.2 ± 33.4	192.3 ± 34.9	193.5 ± 36.5	0.058
HDL (mg/dL)	48.6 ± 10.9	44.1 ± 9.6	42.2 ± 9.3	0.000
TG† (mg/dL)	92.0 (67.0 ~ 122.5)	122.0 (93.0 ~ 164.0)	143.0 (94.0 ~ 202.0)	0.000
HTN(%),(n)	23.6 (86)	33.7 (106)	33.3 (73)	0.034
DM(%), (n)	9.2 (32)	13.0 (41)	21.9 (48)	0.000

BMI: body mass index; SBP: systolic pressure; DBP: diastolic pressure; HDL: high density lipoprotein; TG: triglyceride; HTN: hypertension; DM: diabetes mellitus.

†Data are expressed as the median (25~75%).

Table 2. Correlation between SHBG and various parameters

	γ	p-value
Age	0.247	0.000
BMI	-0.309	0.000
SBP	-0.029	0.368
DBP	-0.085	0.009
WBC	-0.117	0.000
Glucose	-0.090	0.006
T3	0.327	0.000
Cholesterol	-0.084	0.010
HDL	0.155	0.000
TG	-0.314	0.000
HTN	-0.014	0.591
DM	-0.052	0.052

Table 3. Odds ratio and 95% confidence interval for low SHBG levels according to hepatic steatosis and ALT elevation

	Study groups		
	Reference group	Hepatic steatosis and ALT < 30	Hepatic steatosis and ALT ≥ 30
Model I†	1.00	1.754 (1.165 ~ 2.641)	2.370 (1.539 ~ 3.650)
Model II‡	1.00	1.549 (1.011 ~ 2.375)	1.912 (1.197 ~ 3.053)

†Model I: adjusted for age and BMI

‡ Model II: adjusted for age, BMI, SBP, DBP, WBC, glucose, T3, cholesterol, HDL, and TG levels

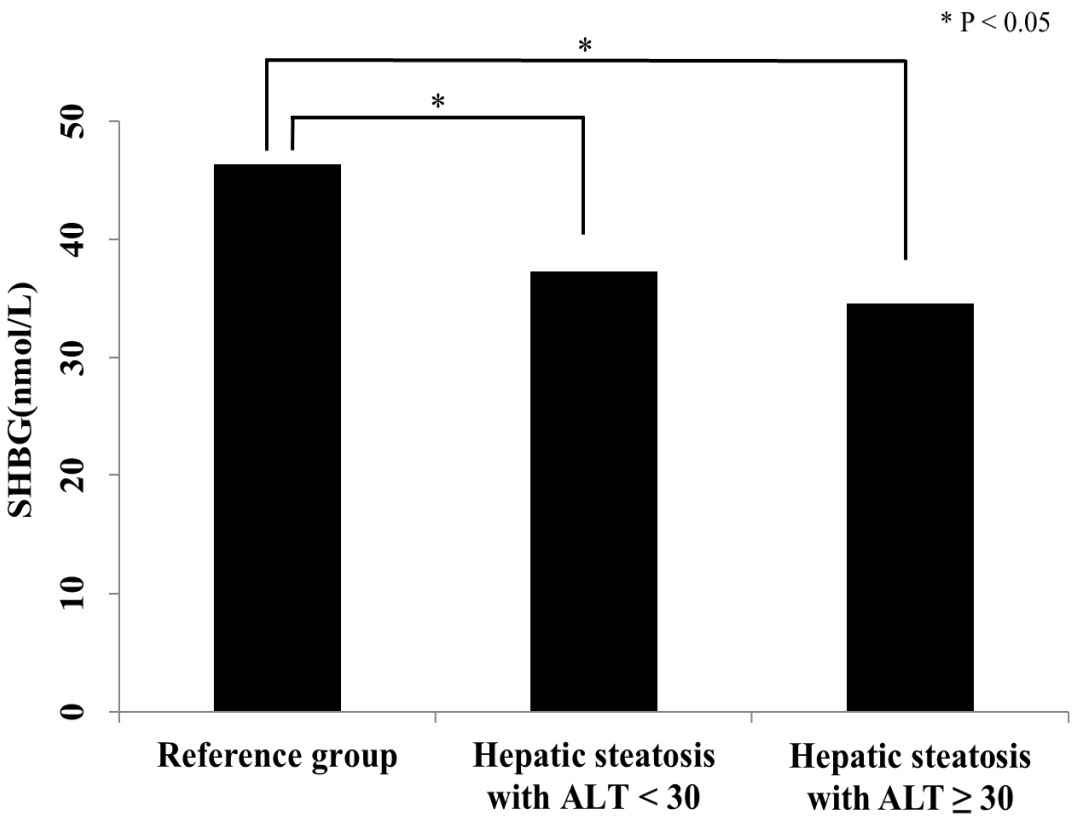

Figure 1. Mean value of SHBG for the study population between reference group, ALT < 30 with hepatic steatosis group, and ALT ≥30 with hepatic steatosis group. * p < 0.05 by multiple co-variant ANOVA controlling for age, BMI, and T3.

IV. DISCUSSION

In this cross-sectional study, we examined the joint effect of hepatic steatosis and ALT on SHBG concentration. A previous observational study showed that hepatic steatosis was independently related with a low SHBG level.[1] In addition , the severity of hepatic steatosis was proportionally correlated with the risk of a low SHBG level.[2] Another previous study also reported that serum ALT level was inversely associated with SHBG level.[3] Taken together, hepatic steatosis and serum ALT may be associated with a high risk of a low SHBG concentration. However, the joint effect of hepatic steatosis and ALT on serum SHBG level has not been investigated. In multivariate logistic regression analysis, we observed that the hepatic metabolic disturbance jointly affected a low SHBG concentration independent of body mass index (BMI) and metabolic profiles. This is the first report showing that an increased ALT could be a good marker of low SHBG in patients with hepatic steatosis. Non-alcoholic fatty liver comprises a spectrum of liver condition ranging from simple steatosis to steatohepatitis and cirrhosis. Although liver biopsy is regarded as the gold standard for the assessment of the severity of fatty liver, it has limited applicability in clinical setting because of the risk related to the technique and uncertainty of the distribution of fatty infiltration. Previous studies reported the association between serum ALT and the grade of hepatic steatosis confirmed by liver biopsy,[18] suggesting that patients with fatty liver and a higher ALT level might have the increased risk for a lower SHBG level compared to patients with hepatic steatosis but a lower ALT level. Regarding these results, severity of hepatic steatosis can be closely associated with a lower SHBG concentration. Mariana Ayala et al. also showed that serum SHBG levels were inversely associated with ALT serum level.[9]

There are some potential mechanisms by which elevated ALT levels affect serum SHBG levels. First, hepatocyte is the primary synthesis site of SHBG even though SHBG is also expressed in testicular germ cells.Thyroid hormone, insulin, and cytokines regulate the expression SHBG in the hepatocyte.[1, 19] These hormones interacts with their receptors and activate various signal cascades

resulting in alterations of hepatocyte nuclear factor 4 alpha (HNF-4a) protein levels which regulates SHBG expression.[1] Also, metabolic syndrome, sex hormone, dietary, and liver fat influence serum SHBG levels. Xiaomin Hua et al reported that serum SHBG level was inversely associated with NAFLD, and correlated with lipid profile.[20] They observed a negative relationship between serum SHBG and TG, and positive relationship between HDL. In a study of S. A. Paul Chubb et al, lower SHBG was also associated with increased serum level of smaller, denser low density lipoproteins.[21] The relationship between serum SHBG and lipid profiles was discussed in the study of A. Desmeules et al, about post-heparin hepatic lipase, and lipoprotein lipase activity.[22] Previous studies have showed that participants with elevated LPL activity had a lowed TG and highed HDL level, whereas participants with highed hepatic lipase activity had a lowed HDL level. A. Desmeules et al observed a negative relationship between serum SHBG and hepatic lipase activity, where as a positive relationship was found between serum SHBG and lipoprotein lipase activity.[22] This implied that correlation between lipid profile and activity of hepatic lipase and lipoprotein lipase could affect serum SHBG levels. In the study of V. Miksztowicz et al, hepatic lipase activity was significantly increased in patients with hepatic steatosis grade 3 compared with grade 1.[23] Serum SHBG levels were associated with the high-grade NAFLD in the study Shin et al.[7] Correlations of lipid profile, hepatic lipase, lipoprotein lipase, NAFLD, and SHBG were associated with NAFLD and elevated liver enzymes. In the study of Mattias Ekstedt et al, a serum ALT levels were elevated in follow-up of NAFLD patients with progressive fibrosis.[24] Second, almost all ALT is found in the cytosol of hepatocytes. ALT activity in the liver is about 3000 times greater than that in the serum. Thus, in the cases of hepatocellular injury or death, release of ALT from damaged liver cells increases serum ALT levels.[15] Therefore, elevated ALT levels could reflect hepatocellular injury or death, and thus could also be associated with a decrease of serum SHBG level. Third, insulin resistance could be another possible mechanism explaining this association between ALT and SHBG. Previous study suggested that an increased ALT level is associated with

insulin resistance.[20, 25] A recent study proposed that glucose-induced lipogenesis may affect hepatic production of SHBG, and glucose also could directly decrease the expression of SHBG.[26] In the present study, we observed an inverse relationship between serum glucose and SHBG concentration. Therefore, this finding suggested that there could be an interaction between ALT, glucose and SHBG.

Our study has several limitations. First, it followed a retrospective cross-sectional method, which is hard to conclude a causal relationships. Therefore, a cause-and-effect relationship among ALT and SHBG cannot be inferred. Second, although a liver biopsy is the gold standard for the diagnosis of a hepatic steatosis, a biopsy-proven NAFLD was not assessed in the present study. Despite some limitations, ultrasonography is a non-invasive and preferred modality for mass screening for hepatic steatosis with a reasonable sensitivity and specificity. Third, our study did not include sex hormone levels, which is another factor that influences SHBG synthesis. However, although with these limitation, the present study includes other meaningful factors, particularly T3 level which could influences SHBG levels. Fourth, exclusion criteria of this study did not comprise autoimmune hepatitis. However, in Korea, the prevalence of autoimmune hepatitis seems to be lower than that in western countries.[27] Therefore, limitation due to incomplete exclusion criteria might be little in this study.

In male patients with hepatic steatosis, elevated serum ALT levels were associated with lower serum SHBG levels. Further investigation about the association between SHBG and ALT has to be pursued in future longitudinal studies.

V. CONCLUSION

In men with hepatic steatosis, we found that elevated serum ALT levels are associated with lower serum SHBG levels. This finding suggested that subjects with both hepatic steatosis and increased ALT should be considered for a low SHBG.

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ABSTRACT(IN KOREAN)

지방간이 있는 남성에서 성호르몬결합글로불린과 알라닌닌아미노기전달효소와의 관련성

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서인호

목적: 성호르몬결합글로불린(SHBG)은 주로 간에서 합성된 뒤 혈청에 존재하는 당단백질이다. 이런 성호르몬결합글로불린은 간기능 및 대사증후군과 연관이 있는 것으로 알려져 있다. 알라닌아미노기전달효소(ALT)는 간세포의 손상과 인슐린 저항성을 반영한다. 하지만, 지방간을 가진 환자에서 알라닌아미노기전달효소와 성호르몬결합글로불린 사이의 관계는 아직 연구되지 않았다. 이 연구의 목적은 한국 남성 중 지방간을 가진 환자에서 간손상과 성호르몬결합글로불린 사이의 관계를 보는 것 이다.

방법: 정기 건강검진을 시행받은 사람 중 883명에 대해서 후향적 연구를 시행하였다. 이들은 총 3개의 그룹으로 분류하였다. 알라닌아미노기전달효소의 상승 여부에 따른 성호르몬결합글로불린이 낮은 그룹에 속할 승산비를 분석하였다.

결과: 지방간이 있는 환자에서 알라닌아미노기전달효소가 상승한 군이 낮은 성호르몬결합글로불린을 가질 위험도가 통계적으로 유의미하게 높았다.

결론: 지방간을 가진 남성에서 알라닌아미노기전달효소의 상승과 낮은 성호르몬결합글로불린 사이에 관련이 있었다. 이는 지방간 환자에서 간손상을 보인다면 성호르몬결합글로불린이 낮을 수 있음을 보여준다.

핵심되는 말 : 지방간, 성호르몬결합글로불린, 알라닌아미노기전달효소

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