Relationship of hepatic steatosis and alanine aminotransferase with coronary calcification

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Dong Hyuk Jung

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ABSTRACT

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Background: It has been observed that hepatic steatosis is related to an increased risk of cardiovascular disease (CVD), and alanine aminotransferase (ALT), an indicator for severity of hepatic steatosis, is also associated with CVD. This study focused on the relationship of hepatic steatosis and ALT with coronary calcification.

Methods: We performed a cross-sectional study to examine the association of hepatic steatosis and serum ALT with coronary calcification in 621 subjects (385 men, 236 women; age 30-75 year). We evaluated hepatic steatosis and ALT as categorical variables and constructed four groups (reference group; only with hepatic steatosis; only with ALT > 30 U/L; with both hepatic steatosis and ALT > 30 U/L), which were non-overlapping. Multi-detected row computed tomography (MDCT) was used to measure coronary calcium score (CCS).

Results: The adjusted ORs (95% CIs) for coronary calcification of the four groups were 1.00 (reference), 1.54 (0.62-3.83), 2.45 (0.73-8.16), and 2.89 (1.08-7.72) after adjusting for confounding variables.

Conclusions: In summary, patients with both hepatic steatosis and ALT elevation are associated with coronary calcification as a marker of coronary atherosclerosis determined by MDCT. This finding suggested that the subject with both hepatic steatosis and elevated ALT should be considered for further evaluation of coronary atherosclerosis.

Key words: hepatic steatosis, alanine aminotransferase, and coronary atherosclerosis

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I. INTRODUCTION

Hepatic steatosis is the most common liver disease in developed countries,[1] and its prevalence increased to 70-90 % in patients with obesity and type 2diabetes.[2] For a long time, hepatic steatosis was considered a benign manifestation. Recently, hepatic steatosis has attracted growing interest as a potentially novel risk factor for insulin resistance,[3] type 2 diabetes,[4] and metabolic syndrome.[5] Several epidemiologic studies have also shown that hepatic steatosis is associated with mortality and cardiovascular diseases.[6,7] In the majority of cases, patients with hepatic steatosis tend to show asymptomatic elevation of liver enzymes.[8] Of the enzymes, alanine aminotransferase (ALT) is strongly associated with hepatic triglyceride accumulation.[9] In addition, recent studies reported that the ALT level was related with insulin resistance and atherosclerosis.[10,11] In routine cardiology practice, coronary calcification is a marker of atherosclerotic plaque burden [12] that can be quantified by multi-detected row computed tomography (MDCT).

The coronary calcium score (CCS) is proportionally associated with the severity of atherosclerotic disease.[13] In addition, CCS is a strong predictor of future cardiac event, independent of the conventional risk factors.[14] However, little is known about the joint effect of hepatic steatosis and serum ALT on coronary artery calcification. Therefore, we examined the relationship of hepatic steatosis and serum ALT with coronary calcification as a marker of coronary atherosclerosis in Korean adults.

II. MATERIALS AND METHODS

1. Study population

A total of 1,402 subjects were enrolled from the health promotion center of Gangnam Severance Hospital from January 2007 to October 2008. They visited a health promotion center to check the risk factors for cardiovascular disease and other diseases. The subjects completed a questionnaire including items such as age, gender, exercise, smoking, alcohol habits, and medical and medication history. Demographic, anthropometric, and laboratory data of each subject were investigated. Subjects meeting any of the following criteria were excluded: subjects with missing data on any covariate information; subjects taking alcohol intake of 20g/day;[15] a positive test for hepatitis B antigen and hepatitis C antibody; and a history of cancer or cardiovascular disease. After these exclusions, 621 subjects (385 men, 236 women; age 30-75 year) were included in the final analysis. The elevation of serum ALT was defined as ALT > 30 U/L. [16] The study was approved by the Institutional Review Board at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea and was carried out in accordance with the principles of Declaration of Helsinki.Only subjects that agreed with written consent were included in this study.

2. Laboratory measurements

Venous blood was collected from an antecubital vein after a 12-hour fast. Fasting plasma glucose, total cholesterol, triglyceride, ALT, γ-glutamyltransferase (GGT), uric acid, and high density lipoprotein (HDL) cholesterol levels were measured by enzymatic methods using a Hitachi 7600-110 automated chemistry analyzer (Hitachi, Tokyo, Japan).

3. Ultrasound examination

The diagnosis of hepatic steatosis was based on abdominal ultrasonography with a 3.5-MHz transducer (HDI 5000, Philips, Bothell, U.S.). The ultrasonography was performed by experienced radiologists who were unaware of the aims of the study. Of three known findings (increased liver echogenicity, deep attenuation, and vascular blurring), the subjects were diagnosed with hepatic steatosis if at least two of the three findings were present.[17]

4. Multi-detected row Computed Tomography (MDCT)

Computed tomography coronary angiography (CTCA) was performed using a 64-MDCT scanner (Philips Brilliance 64, Philips Medical System, Best, Netherlands). A ß-blocker (40-80 mg propranolol hydrochloride; Pranol, Dae Woong, Seoul, Korea) was administered orally one hour before the examination to reduce the heart rate in patients who had a heart rate of more than 65 beats per minute (bpm). We used a prospective ECG-gating protocol, one with a step-and-shot technique and additional padding of the tube-on time. In the

supine position, CTCA was performed in the craniocaudal direction within a single breath-hold at the end-inspiratory suspension. A 1.0 ml/kg of iodinated contrast medium (Optiray 350; Tyco healthcare, Kantata, Canada) was administered intravenously at a rate of 5 mL/s followed by 50 mL of normal saline at a rate of 5mL/s using a power injector (Nemoto; Nemoto Kyorindo, Tokyo, Japan). Imaging was performed by using a real time bolus tracking technique in which a region of interest was located at the ascending aorta. The scans were started 7 seconds after reaching a trigger threshold of 110 Hounsfield Units (HU). All patients held their breath during the imaging process. The scanning parameters were as follows: step-and-shoot axial scanning direction, 420-ms gantry rotation time, 120 kV, 210 mAs, 64 x 0.625-mm slice collimation, and 4-cm table feed per rotation.

The image reconstruction was performed on the scanner's workstation using commercially available software (Extended Brilliance Workstation, Philips Medical System, Best, Netherlands). Original axial images and multiplanar reformatted reconstructions rendered orthogonal and perpendicular to the vessel course of each respective segment were used for assessment. Curved multiplannar reformation (MPR) images were generated.

5. Statistical Analysis

We defined the 30 U/L value as the cut-off point of elevated ALT.[16] To assess the joint effects of hepatic steatosis and serum ALT on coronary calcification,

we divided the study subjects into four groups as follows: reference group; hepatic steatosis; ALT > 30 U/L; with both hepatic steatosis and ALT > 30 U/L. The basic characteristics of the study population of each group were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. All continuous variables are presented as means (SD) or medians (IQR), and the categorical variables are summarized as percentages in each group. Multivariate regression analysis was used to measure the strength of relation between the cardiovascular risk factor and serum ALT levels. The odds ratio for CCS>100 was calculated using a multivariate logistic regression analysis after adjusting for confounding variables across the groups. All analyses were conducted using SPSS statistical software (version 15.0, Chicago, IL). All statistical tests were two-sided and significance was determined at a p value < 0.05.

III. RESULTS

A total of 621 subjects (men/women: 385/236; age: 30-75yrs) were enrolled for final analysis. The average of ages of all subjects was 52.3 ± 9.2 (not shown in table). Table 1 shows the demographic, clinical, and laboratory data of the study population. Of subjects who underwent US, hepatic steatosis was found in 251 (40.4%), elevated ALT > 30 U/L were found in 152 (24.4%), and CCS > 100 with moderate – high risk of CVD was found in 62 (10%). Subjects with both hepatic steatosis and ALT >30 U/L had a higher body mass index (BMI), waist/ hip ratios, γ-glutamyltransferase, uric acid, fasting glucose, triglyceride, systolic blood pressure, diastolic blood pressure, and show a higher percentage of hypertension, diabetes, and statin therapy than the other three groups. Table 2 shows the results of multivariate analysis of factors related with CCS >100. Older age (OR; 1.12(1.08-1.17)) and smoking (OR; 4.00(1.67-9.51)) were significantly associated with CCS > 100.

To assess the joint effect of hepatic steatosis and serum ALT on coronary artery calcification, we divided the study population into four groups by hepatic steatosis and serum ALT level: hepatic steatosis with normal ALT levels in 152 and only elevated ALT levels in 54. The reference group included 317 subjects without hepatic steatosis and with normal ALT levels. A ninety-eight patients had both hepatic manifestations of metabolic disturbance. The results of the logistic regression analysis for CCS > 100 are presented in Table 3. After adjusting for age, sex, BMI, waist/ hip ratios, uric acid, systolic, and diastolic

blood pressure, cigarette smoking, γ-glutamyltransferase, triglyceride, HDL cholesterol, diabetes and hypertention, the adjusted OR (95% CIs) for the presence of CCS > 100 for the group with both hepatic steatosis and ALT elevation was 2.89 (1.08-7.72) compared to the referent group.

Table 1. Baseline characteristics of the study population according to hepatic steatosis and alanine aminotransferase in the study population [a]

		Reference group	ALT < 30 U/L hepatic steatosis	ALT > 30 U/L hepatic steatosis	ALT > 30 U/L hepatic steatosis
n [b]		317	152	54	98
Age ,years		51.4 ± 9.1	54.2 ± 9.0	51.9 ± 10.0	52.3 ± 8.6
Sex, %, female		51.7	29.6	20.6	16.0
BMI, kg/m^2		22.4 ± 2.5	24.9 ± 2.8	23.4 ± 2.7	25.7 ± 2.1
CRP		1.5 (0.4-1.8)	2.2 (0.6-2.9)	1.2 (0.3-1.4)	2.0 (0.7-2.6)
ALT, U/L		18.0 (15-21)	20.7 (17-25)	42.1 (32-47)	45.5 (34-53)
GGT, U/L		26.9 (13-31)	33.4 (20-36)	59.7 (20-75)	61.9 (34-68)
Uric acid, mg/dl		4.9 ± 1.2	5.7 ± 1.3	5.3 ± 1.2	6.4 ± 1.1
Fasting glucose, mg/dl		91.8 ±19.4	100.2 ± 28.0	93.6 ± 19.6	102.2± 17.3
Total-chole, mg/dl		188.2 ± 32.5	196.6± 36.3	189.0 ± 32.7	209.2 ± 42.4
HDL-cholesterol, mg/dl		57.3 ± 14.3	48.1± 10.6	51.4 ± 12.5	46.0 ± 8.9
Smoking status,%	Never	60.4	39.3	40.3	33.3
	Current	16.5	24.0	33.9	34.3
	Ex	23.2	36.7	25.8	32.3
Systolic BP, mmHg		119.7 ± 15.7	126.0 ± 15.4	122.1 ± 13.8	126.7 ± 15.1
Diastolic BP, mmHg		74.1 ± 9.3	78.3 ± 9.6	76.9 ± 9.2	79.4 ± 9.5
Hypertension, % [c]		24.2	36.2	25.4	41.0
Diabetes, % [d]		3.0	9.9	11.1	16.0

[a] Data are mean ± SD, proportions, or medians (interquartile ranges) for skewed variables.

[b] P-value was calculated for continuous variables by using one-way ANOVA test or by chi-square test for categorical variables. All P-values are < 0.001 for overall differences across the categories for continuous and categorical variables except gender (p =0.02) and CRP (p =0.01).

[c] Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or a history of the disorder.

[d] Diabetes was defined as fasting plasma glucose level ≥ 126 mg/dl or a history of the disorder.

CRP, C-reactive protein; Total-chole, total cholesterol; ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma glutamyl transferase; BP, blood pressure.

Table2. Multivariate analysis of factors associated with coronary calcium score > 100 in study population

Variables	OR	(95% CI)
Age, years	1.12 [a]	(1.08-1.17)
Fasting glucose, mg/dl	1.01	(0.99-1.03)
Smoking (Never vs. Current)	4.00 [a]	(1.67-9.51)
Hypertension	1.18	(0.61-2.29)
ALT (every 10, U/L increment)	1.19	(0.88-1.60)

[a] $p < 0.001$

ALT, alanine aminotransferase; CI, confidence interval; OR, odds ratio

Table3. Combined effects of hepatic steatosis and ALT on coronary calcium score >100

Odds Ratio (95% CI)			
Reference group	ALT < 30 U/L hepatic steatosis	ALT > 30 U/L S hepatic steatosis	ALT > 30 U/L C hepatic steatosis
[a] Model 1			
1.00	1.43 (0.88-2.29)	1.81 (0.84-4.30)	2.39 (1.28-5.09) [c]
[b] Model 2			
1.00	1.54(0.62-3.83)	2.45 (0.73-8.16)	2.89 (1.08-7.72) [c]

[a] Model 1; Adjusted for age, sex, fasting glucose, smoking, and hypertension.

[b] Model 2; Adjusted for age, sex, body mass index, waist/hip ratios, uric acid, systolic blood pressure, diastolic blood pressure, γ - glutamyltransferse, triglyceride, HDL-cholesterol, fasting glucose ,CRP, smoking, diabetes and hypertension.

[c] $p < 0.05$

IV. DISCUSSION

In this study, we examined the joint effect of hepatic steatosis and ALT levels on CCS. A previous cross-sectional study has shown that hepatic steatosis was independently associated with coronary artery calcification, regardless of classical risk factors such as DM and smoking.[18] In addition, the severity of hepatic steatosis was proportionally correlated with the degree of atherosclerotic change.[19] A prospective study also reported that ALT at baseline was associated with coronary heart disease events independent of metabolic measures.[20] Taken together, hepatic steatosis and serum ALT levels may be associated with a higher risk of coronary artery calcification. However, the joint effect of hepatic steatosis and ALT levels on coronary artery calcification has not been investigated. In this study, we examined the joint effect of hepatic steatosis and ALT levels on CCS. In multivariate logistic regression analysis, we found that hepatic manifestations of metabolic disturbance jointly affect coronary artery calcification. This is the first report that an elevated level ALT could be a good predictor for coronary artery calcification in patients with hepatic steatosis; thus, these patients with both hepatic steatosis and a high level of ALT should be recommended for the assessment and improvement of the CVD risk profile.

NAFLD comprises a spectrum of liver condition ranging from simple steatosis to steatohepatitis and cirrhosis.[21] Although liver biopsies are regarded as the gold standard for the assessment of fatty liver severity, it has limited

applicability in clinical studies because of the risk related to the technique and uncertainty of distribution of fatty infiltration. Proton magnetic resonance spectroscopy (H-MRS) is a non-invasive technique and has been validated against the direct assessment of steatosis.[22] However, its high cost is a limitation for applicability of epidemiological studies. Regarding this, serum ALT levels deserve particular attention, because a previous study has prospectively shown the association between serum ALT levels and hepatic steatosis grade assessed by liver biopsies.[23] In addition, Westerbacka et al. reported the correlation of ALT levels and hepatic fat accumulation measured by H-MRS.[9]

In this view, hepatic steatosis patients with elevated serum ALT levels might have a greater risk for coronary artery calcification compared to subjects with or without only one hepatic abnormal finding, because the severity of hepatic steatosis is closely associated with atherosclerosis.[24] Wang et al. has also shown that serum ALT levels are related with the risk of carotid intima thickness in patient with hepatic steatosis, regardless of risk factors for atherosclerosis and metabolic syndrome.[19]

Some mechanisms could explain the significant relationship between serum ALT levels and coronary atherosclerosis. One possible explanation is that elevated ALT and coronary calcification may be represented by increased oxidative stress and inflammation. A recent report demonstrated that ALT was related with markers for oxidative stress and inflammation.[25] Decreased adiponectin levels, a cytokine with anti-atherogenic properties, might be another

possible mechanism explaining this association. Aygun et al. has shown that the adiponectin concentration was lower in patients with both hepatic steatosis and elevated ALT levels compared to patients with only hepatic steatosis.[26] Yokoyama et al. also reported an inverse relation between serum ALT levels and adiponectin in Japanese subjects.[27]

A recent study demonstrated that elevated ALT levels correlate with insulin resistance in women.[28] Anthony et al. has shown that serum ALT levels were associated with insulin resistance directly measured in the Insulin Resistance Atherosclerosis Study.[29] Taken together, insulin resistance might be the reason why the serum ALT level is related with coronary artery atherosclerosis. Some studies found that the serum ALT level was associated not only with insulin resistance but with endothelial dysfunction assessed by brachial artery flow-mediated dilation in type 2 diabetes patients. Although there may be variance each laboratories, serum levels of 10-45 U/L are accepted as the normal range.[30] However, Kim et al. has shown that 30 U/L was the best cut off value for the prediction of liver disease in a large prospective Korean cohort. As a result, we defined 30 U/L as the cut off value for ALT elevation.[16]

There are several studies showing the association between hepatic steatosis and metabolic syndrome. Fan at al. showed a relationship between fatty liver and metabolic parameters, such as blood pressure, waist hip ratio, plasma glucose, and triglyceride in a general population.[31] Li et al. also reported the association between hepatic steatosis and metabolic syndrome components.[32] Lee et al.

recently demonstrated that hepatic steatosis assessed by ultrasonography was positively related with uric acid.[33] In accordance with previous reports, the group with both hepatic steatosis and elevated ALT was associated with an increased risk of metabolic disturbance, such as elevated triglyceride, BMI, blood pressure, fasting blood sugar, and decreased HDL-cholesterol, compared with the reference group. However, these metabolic parameters did not change the association between hepatic manifestation and the coronary calcium score.

The prevalence of hepatic steatosis and elevated ALT is higher in men than women in our study. Our findings are in accordance with previous studies that have also shown that being male is one of the risk factors for hepatic steatosis and elevated liver enzyme. Lee et al. demonstrated that fatty liver by ultrasonography has been found to be more frequent in men.[34] George et al. reported that men had independently a 1.5 fold higher probability of having elevated liver enzymes.[35] The possible reasons for gender differences may be associated with fat distribution, because the visceral fat is considered more important than subcutaneous fat to the development of hepatic steatosis.[34] In addition, although, alcohol consumption was adjusted, a difference in drinking might not have been completely controlled in these analyses.

The CCS represents the atherosclerotic plaque burden and quantification coronary calcium, a marker of atherosclerosis.[12] The extent of coronary atherosclerosis is more significantly correlated with death due to acute myocardiac infarction and sudden cardiac event than the severity of stenosis.[36]

Furthermore, the majority of cardiac attacks that occurred at the site of non-obstructive plaque is as high as 83%.[37] Goodman et al. have shown that subjects with a calcium score ≥ 100 have more than nine times greater risk for coronary death events, compared to subjects with a calcium score < 100.[38]

Our study has several limitations. It is a cross-sectional study, suggesting that caution should be taken in causal interpretations. Therefore, our observations remain to be confirmed in prospective studies. Second, the most common cause of elevated liver enzymes besides hepatic steatosis are chronic hepatitis B and C, autoimmune hepatitis, and hemochromatosis.[39] Unfortunately, we did not check autoimmune hepatitis and hemochromatosis. However, hereditary hemochromatosis is less common in the Asia-Pacific region, compared to Caucasian communities,[40] and we excluded subjects with viral hepatitis such as type B and type C common in Asian populations. Third, hepatic steatosis diagnosis was not confirmed by liver biopsy, which is the best diagnostic tool for confirming steatosis. Finally, although one study reported a day-by-day variation up to 30% and diurnal variation,[41] we evaluated the serum ALT levels only once. However, we excluded subjects with a history of alcohol intake of more than 20g a day as it may interfere with ALT levels, and we collected blood samples in the morning.

V. CONCLUSION

In conclusion, hepatic steatosis and elevation ALT levels jointly affect coronary artery calcification. Serum ALT levels may be a surrogate marker for coronary artery calcification in patients with hepatic steatosis. In addition, this finding suggested that subjects with both hepatic steatosis and elevated ALT should be considered for further evaluation of coronary atherosclerosis.

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ABSTRACT (IN KOREAN)

지방간 및 alanine aminotransferase 와 관상 동맥 석회화 수치와의 관련성

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배경: 지방간은 심혈관계 질환의 위험성을 증가와 관련이 있다는 연구 결과가 최근에 발표되고 있다. 또한, alanine aminotransferase (ALT)가 지방간의 정도를 나타낼 뿐 아니라 심혈관계 질환의 위험성과도 관련이 있다는 알려져 있다. 이번 연구에서는 지방간과 alanine aminotransferase (ALT)과 심혈관계 질환의 위험 인자 중 하나인 관상 동맥 석회화 수치와의 관련성에 관하여 살펴 보고자 한다.

방법: 강남 세브란스 병원 건강증진 센터를 방문한 621명 (남자: 385명, 여자: 236명)을 대상으로 한 관찰 연구이다.

혈중 ALT 수치를 범주화하여, 30 U/L 이하이며, 초음파상 지방간이 없는 환자군과, 초음파상 지방간만 있는 군, ALT 수치만 30 U/L 이상인 군, ALT수치가 30 U/L 이상이며 동시에 지방간이 있는 군, 총

4군으로 인구 집단을 나누었다. Multi-detected row computed tomography (MDCT)를 통해서 관상 동맥 석회화 수치를 구하였다.

결과: 관상 동맥 석회화 수치 100 이상을 관상 동맥의 동맥 경화성 변화의 중등도 위험군으로 정의하였고, 각군의 위험도를 로짓 분석으로, 심혈관계 위험인자를 보정한 후 확인해본 결과 1.00, 1.54 (0.62-3.83), 2.45 (0.73-8.16), 2.89 (1.08-7.72) 이었다.

결론: 지방간과, 동시에 ALT 수치가 30 U/L 이상인 경우 그렇지 않은 경우에 비교하여, 심혈관계에 위험 인자인 관상 동맥 석회화 수치의 상승의 위험도가 높다. 이러한 사실은 임상적으로 지방간이 있으면서, ALT 가 상승된 환자에서 적극적인 심혈관계에 대한 검사가 필요할 수 있다는 것을 제시한다.

핵심되는 말: 지방간, alanine aminotransferase, 관상 동맥 동맥경화증