

# Atherosclerosis and Liver Function Tests in Coronary Angiography Patients

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## ABSTRACT

**Objective:** Elevated aminotransferase levels indicating liver function, even in the normal range, have attracted great concern as potential novel markers of cardiovascular risk assessment. We hypothesized the possibility that liver function test variations in the normal range might be meaningfully associated to coronary artery disease (CAD).

**Method:** Eighty-eight patients were randomly selected from those who underwent coronary angiography from June 2010 to June 2011 after applying to the outpatient cardiology clinic in Gulhane Military Medical Academy. According to the results of angiographies, patients were classified into three groups as normal, non-critical (< 50% involvement in coronaries), and critical ( $\geq$  50% involvement in coronaries). In addition to angiographic intervention, measurements of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, albumin and the other serum parameters were performed in all patients.

**Results:** The patient groups of CAD were balanced (28 critical cases, 30 non-critical cases and 30 normal cases). Mean age was  $51.93 \pm 9.3$  (range 32–65) years and 19.3 per cent ( $n = 17$ ) were females. Multiple linear regression analysis of all three liver function tests explained a significant portion of the variance, but adjusted r-squares were small (AST = 0.174, ALT = 0.242, albumin = 0.124). Albumin was significantly higher for patients with critical CAD than for patients with no CAD (beta = 3.205,  $p = 0.002$ ). Non-critical CAD was not significantly different from no CAD for any of the dependent variables. Mean AST was significantly higher for patients taking aspirin (beta = 0.218,  $p = 0.049$ ), as was mean ALT (beta = 0.264,  $p = 0.015$ ).

**Conclusion:** Alanine aminotransferase and AST may not be associated with angiographically determined coronary atherosclerosis. Albumin may be more sensitive to demonstrate the burden of atherosclerosis. These results indicate that the association between the liver function tests and coronary atherosclerosis may be more complex than generally appreciated.

**Keywords:** Albumin, aminotransferases, coronary artery disease

## Pruebas de Aterosclerosis y Función Hepática en Pacientes de Angiografía Coronaria

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## RESUMEN

**Objetivo:** Los niveles de la aminotransferasa elevada, que indican la función hepática, incluso en el rango normal, han despertado gran preocupación como posibles marcadores novedosos para la evaluación del riesgo cardiovascular. Sostenemos la hipótesis de que las variaciones en las pruebas de la función hepática en el rango normal, podrían estar significativamente asociadas con la enfermedad de la arteria coronaria (EAC).

**Método:** Ochenta y ocho pacientes fueron seleccionados al azar de aquellos sometidos a angiografía coronaria desde junio de 2010 a junio de 2011, tras su solicitud en la clínica de cardiología ambulatoria de la Academia Médica Militar de Gulhane. Según los resultados de las angiografías, los pacientes fueron clasificados en tres grupos: (i) normal, (ii) no crítico (< 50% compromiso de las coronarias), y (iii) crítico ( $\geq$  50% compromiso de las coronarias). Además de las intervenciones angiográficas, también se

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efectuaron mediciones de aspartato aminotransferasa sérica (AST) y concentraciones de alanina aminotransferasa (ALT), albúmina y otros parámetros del suero, en todos los pacientes.

**Resultados:** Los grupos de pacientes de EAC estuvieron equilibrados (28 casos críticos, 30 casos no críticos, y 30 casos normales). La edad promedio fue  $51.93 \pm 9.3$  años (rango de 32 a 65), y 19.3 por ciento ( $n = 17$ ) eran mujeres. El análisis de regresión lineal múltiple de las tres pruebas de función hepática explica una parte significativa de la varianza, pero los valores de R-cuadrado ajustados fueron pequeños (AST = 0.174, ALT = 0.242, albúmina = 0.124). La albúmina fue significativamente mayor en los pacientes con EAC crítica que en los pacientes sin EAC ( $\beta = 3.205$ ,  $p = 0.002$ ). El grupo EAC no crítico no fue significativamente diferente del grupo sin EAC con respecto a cualquiera de las variables dependientes. La AST promedio fue significativamente mayor en los pacientes que tomaban aspirina ( $\beta = 0.218$ ,  $p = 0.049$ ), al igual que la ALT promedio ( $\beta = 0.264$ ,  $p = 0.015$ ).

**Conclusión:** La alanina aminotransferasa y la AST no pueden asociarse con la aterosclerosis coronaria determinada angiográficamente. La albúmina puede ser más sensible cuando se trata de demostrar la carga de la aterosclerosis. Estos resultados indican que la asociación entre las pruebas de función hepática y la aterosclerosis coronaria puede ser más compleja que lo que generalmente se considera.

**Palabras claves:** Albúmina, aminotransferasas, enfermedad arterial coronaria

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## INTRODUCTION

Variations in the results of liver function tests (LFTs) are of little clinical interest when they remain within normal ranges. Thresholds are established that determine normalcy and no change in therapy is indicated by fluctuations if the LFTs do not exceed those thresholds. However, such variations may not be entirely meaningless.

The most frequent cause of elevated liver enzymes detected was non-alcoholic fatty liver disease (NAFLD) in clinical practice. Non-alcoholic fatty liver disease affects 15–20% of the general population (1) and is associated with cardiovascular risk factors, specifically insulin resistance and metabolic syndrome (2, 3). It is concluded that the development of insulin resistance results in increased hepatic gluconeogenesis and overproduction of triglyceride-rich lipoproteins, and finally causes NAFLD (4, 5). The correlation of aminotransaminases with the predictors of metabolic syndrome including hypertension, dyslipidaemia and blood glucose has been emphasized in several studies. Results have also demonstrated the possible predictive value of hepatic steatosis or its substantial marker, alanine aminotransferase (ALT), and endothelial dysfunction (6, 7), carotid atherosclerosis (8) and coronary events (9) for coronary artery disease [CAD] (1, 2). Recently, elevated liver enzymes, even in the normal range, have attracted great interest as potential novel markers of cardiovascular risk. A Dutch study reported that serum albumin predicted deaths from cardiovascular disease (CVD) in persons aged 55–85 years who were followed in the Longitudinal Aging Study Amsterdam (10). Even within normal ranges, higher serum albumin was associated with lower risk of incident CVD within three years. All-cause mortality was not related. Chronic low serum albumin was not associated with mortality or incident CVD. However, a decline in serum albumin might be an early warning signal for incident CVD even when levels are within the normal range. Serum bilirubin also

appears to be related to CVD events, including myocardial infarction and death, in patients without liver disease (7). Adibi *et al* suggested that the ALT and ALT/aspartate aminotransferase (AST) ratios were associated with coronary atherosclerosis in patients evaluated by coronary angiography. This relation was detected to be independently significant from the effects of predictor in metabolic syndrome and C-reactive protein (CRP) concentration (11).

Liver function tests are measured routinely in primary care and elevated levels may lead to unnecessary and expensive clinical responses. At the same time, some patients present with previously undetected critical liver disease. These concerns indicate a need for a better prognostic model. Liver function tests can be combined with other variables in an algorithm to predict mortality in one year among primary care patients. The model was developed using data from a cohort of 95 977 primary care patients in Tayside, Scotland, who had no apparent liver disease. The validation cohort included 11 653 patients. The LFTs significantly contributed to the accuracy of the algorithm (12).

This study was motivated by the possibility that LFT variations in the normal range might be meaningfully related to CAD. The purpose of this study was to test the association between CAD and LFTs in a sample of hospital patients. The sample was composed of three groups: patients with no CAD, patients with non-critical CAD and patients with critical CAD. Our hypothesis was that LFTs would be related to CAD severity. We adjusted for age, gender and aspirin use, since aspirin is known to affect LFTs.

## SUBJECTS AND METHODS

The methods for collecting this sample and the measures have been previously described (13). Patients ( $n = 88$ ) were randomly selected from those who received coronary angiography from June 2010 to June 2011 after presenting to the

outpatient cardiology clinic in Gulhane Military Medical Academy. Patients were selected if they had stable CAD. Excluded were patients with acute coronary syndrome (within three months), diagnosed liver disease, excessive alcohol intake, cancer, inflammatory bowel disease, metabolic disorders, thyroid disorders, kidney failure and severe co-morbid acute or chronic infection. Participants ( $n = 88$ ) were consented using a procedure approved by the local ethics board.

### Laboratory measurements

Blood samples for biochemical parameters were collected on admission following at least 12 hours of overnight fasting. All blood samples were taken and measured before interventional procedures. Overall, analytes were tested using enzymatic colorimetric method with an Olympus AU2700 auto-analyzer and reagents from Olympus Diagnostics GmbH (Hamburg, Germany).

The results of blood sample analyses including fasting blood glucose, urea, creatinine, sodium, potassium, AST, ALT, total cholesterol, low-density lipoprotein cholesterol, high density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglyceride, sedimentation, uric acid and total blood parameters were recorded before coronary angiography.

The patients were tested with oral glucose tolerance test to exclude the effects of pre-diabetic states (impaired fasting glucose and impaired glucose tolerance) and diabetes mellitus on LFTs. The patients with glomerular filtration rate (GFR) levels  $< 60$  mL/min/1.73m<sup>2</sup> were also excluded in terms of chronic kidney disorder.

Coronary angiographies were implemented through the right femoral artery or the left radial artery of patients by a cardiologist in the angiography laboratory using a Philips Integris 3000 (Philips Medical Systems, Best, The Netherlands). Coronary angiography was performed based on the indications as follows: stable CAD, equivocal treadmill test result, control angiography after percutaneous transluminal coronary angioplasty, or after acute coronary syndrome with a history of at least six months.

### Statistical analysis

Liver function tests were measured as continuous variables. Included in this study were albumin, ALT and AST. Coronary artery disease severity was scored as follows: 50% or more stenosis in at least one vessel was defined as critical, less than 50% was non-critical CAD and no stenosis was defined as normal. Aspirin was scored as taken or not taken. Age was included as a continuous variable. Gender was scored in two categories. SPSS version 15.0 (Chicago, IL, USA) package programme was used for statistical analysis. Multiple linear regression analysis was used to test the hypothesis that CAD was related to LFTs when controlling for covariates. All variables were retained in the models to avoid capitalizing on chance.

## RESULTS

Descriptive statistics are shown in Table 1. Complete data were available for all 88 patients except for ALT (one missing) and albumin (12 missing). Mean LFTs were within normal limits. Distributions were not skewed. The heart disease groups were balanced (28 critical cases, 30 non-critical cases and 30 normal cases). Mean age was  $51.93 \pm 9.3$  (range 32–65) years and 19.3% ( $n = 17$ ) were females.

Table 1: Descriptive statistics ( $n = 88$ )

Liver function tests	
AST: mean (SD)	23.81 (7.4)
ALT: mean (SD)*	24.79 (12.9)
Albumin: mean (SD)**	4.45 (1.87)
Heart disease	
Critical: n (%)	28 (31.8)
Moderate: n (%)	30 (34.1)
Normal: n (%)	30 (34.1)
Aspirin: n (%)	41 (46.6)
Female: n (%)	17 (19.3)
Age: mean (SD)	51.93 (9.3)

\* $n = 87$ ; \*\* $n = 76$

AST: aspartate aminotransferase; ALT: alanine aminotransferase; SD: standard deviation

Reference range: AST: 0–35 U/L; ALT: 0–35 U/L; albumin: 3.5–5.2 g/dL

Multiple linear regression analysis of all three LFTs (Table 2) explained a significant portion of the variance, but adjusted r-squares were small (AST = 0.174, ALT = 0.242, albumin = 0.124). Gender was not significantly associated with any of the dependent variables. Age was positively associated with AST (beta = 0.438,  $p = 0.000$ ) and negatively associated both with ALT (beta = -0.531,  $p = 0.000$ ) and albumin (beta = -2.079,  $p = 0.041$ ). Non-critical CAD was not significantly different from no CAD for any of the dependent variables. Albumin was significantly higher for patients with critical CAD than for patients with no CAD (beta = 3.205,  $p = 0.002$ ). Mean AST was significantly higher for patients taking aspirin (beta

Table 2: Multiple linear regression analysis of AST, ALT and albumin in angiography patients

Variable	AST	ALT	Albumin
	Beta ( $p$ )	Beta ( $p$ )	Beta ( $p$ )
Female (vs male)	-0.192 (0.067)	-0.154 (0.125)	-0.097 (0.402)
Aspirin (vs none)	0.218 (0.049)	0.264 (0.015)	-0.028 (0.820)
Age	0.438 (0.000)	-0.531 (0.000)	-2.079 (0.041)
Critical CAD (vs none)	0.094 (0.492)	0.008 (0.951)	3.205 (0.002)
Non-critical CAD (vs none)	0.151 (0.243)	0.021 (0.865)	1.642 (0.105)
Adjusted r-square	0.174	0.242	0.124
n	88	87	76

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CAD: coronary artery disease

= 0.218,  $p = 0.049$ ), as was mean ALT (beta = 0.264,  $p = 0.015$ ). Triglyceride was the only cholesterol parameter correlated with ALT within all cholesterol panels ( $r = 0.237$ ,  $p = 0.027$ ).

## DISCUSSION

This study is exploratory and our results should be treated with caution for several reasons. The small sample limited the power for detection of effects and also, in a small sample, unusual circumstances in a small number of cases could influence findings. Results from a single-site study may be atypical. Most of the variation in LFTs remained unexplained. Also, the findings only apply to angiography patients with stable CAD and no significant co-morbidities. Nevertheless, we believe the findings are interesting because they show that variation in selected LFTs is significantly related to patient characteristics, but in unexpected ways.

The liver transaminases used in clinical practice, ALT and AST, have been used as predictors of NAFLD. Of these liver transaminases, ALT appears to be the convenient marker for predicting the liver fat accumulation compared with AST. Coronary artery disease was predicted to show an association with LFTs. Few kinds of pathophysiological mechanisms were explained for this association. Initially, strong evidence was reported in studies supporting the relation of elevated ALT with insulin resistance blamed as a major risk factor for atherosclerosis (14, 15). In addition, there can be a systemic inflammatory response related to ALT and CRP levels (16). Also, liver transaminases may be an indicator of lipoprotein metabolism disorders, resulting in the increase of triglyceride-rich lipoproteins in the circulation (17).

In the Hoorn Study, the predictive value of ALT for the 10-year risk of all-cause mortality, incident CVD and coronary heart disease events in a population-based cohort was analysed in 1439 participants. Schindhelm *et al* finally assessed that the predictive value of ALT for coronary events seems separate from the traditional risk factors of CVDs. Alanine aminotransferase could also be the predictor of endothelial dysfunction in these groups of patients (9). Contrary to this study, Saely *et al* concluded that serum ALT and the ALT/AST ratio were significantly related to metabolic syndrome but not to angiographically confirmed coronary atherosclerosis (18). In contrast to the studies showing an association between the increase of ALT and atherosclerosis and cardiovascular events, a follow-up study including 70-year old individuals in Jerusalem proposed that just lower ALT was related to increased mortality in men but not in women (19). Another study that included men over 70 years of age also described a poor survival with the lower ALT (20). Hence, there is variability in the literature about the association with ALT levels in the normal range and cardiovascular pathophysiological factors. However, in our sample, only albumin was related to CAD severity. That association was limited to critical CAD; albumin did not differ between patients with non-critical CAD and patients with normal angiograms. In contrast, age was a strong predictor of all

three LFTs and aspirin was related to two of them: AST and ALT.

Despite the implications of recent findings about the risks associated with LFTs in the normal range (see above), our results offer no support for closer monitoring of LFTs in the normal range. In our sample, variations appear to be driven more by age and aspirin than by CAD. More cohort studies investigating associations between normal LFTs and adverse events are needed. These studies should adjust for the usage of aspirin due to the possible effect on LFTs. These findings demonstrated that the association between ALT and coronary atherosclerosis is more complex than generally appreciated.

## AUTHORS' NOTE

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