Association Between Elevated Liver Enzymes and C-Reactive Protein

Possible Hepatic Contribution to Systemic Inflammation in the Metabolic Syndrome

Arthur Kerner, Ophir Avizohar, Ron Sella, Peter Bartha, Oren Zinder, Walter Markiewicz, Yishai Levy, Gerald J. Brook, Doron Aronson

Objective—The objective of this study was to test whether the frequent association between liver enzyme elevations and various components of the metabolic syndrome is associated with higher C-reactive protein (CRP) levels.

Methods and Results—Alanine aminotransferase (ALT), alkaline phosphatase (Alk-P), and high-sensitivity CRP were measured in 1740 subjects. Adjusted geometric mean CRP was calculated for subjects with normal and elevated ALT and for subjects with normal and elevated Alk-P, adjusting for age, sex, smoking, physical activity, body mass index, fasting glucose, triglycerides, the presence of hypertension and low HDL cholesterol, and use of aspirin or hormone replacement therapy. Adjusted CRP levels were higher in subjects with elevated ALT (2.21 versus 1.94 mg/L, $P=0.028$) or elevated Alk-P (2.58 versus 1.66 mg/L, $P<0.0001$). Logistic regression showed that compared with subjects with normal liver function tests, the adjusted odds for high-risk CRP (>3 mg/L) were significantly higher in subjects with elevated ALT (OR, 1.5; 95% CI, 1.2 to 1.9, $P=0.002$) or elevated Alk-P (OR, 2.1; 95% CI, 1.7 to 2.6, $P<0.0001$).

Conclusions—Elevations of liver enzymes are associated with higher CRP concentrations. Hepatic inflammation secondary to liver steatosis is a potential contributor to the low-grade inflammation associated with the metabolic syndrome. **(*Arterioscler Thromb Vasc Biol*. 2005;25:193-197.)**

Key Words: C-reactive protein ■ inflammation ■ liver steatosis ■ metabolic syndrome ■ nonalcoholic fatty liver ■ obesity

Arterial inflammation has emerged as central to the initiation and progression of atherosclerosis. Of the markers of inflammation, C-reactive protein (CRP) has been shown in multiple prospective studies to predict incident myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death.[1,2]

Obesity and the metabolic syndrome are associated with chronic inflammatory response, characterized by abnormal cytokine production, increased acute phase reactants, and activation of inflammatory signaling pathways.[3] Recent studies have shown that elevated CRP is strongly associated with various characteristics of the metabolic syndrome.[4–6] A growing body of evidence implicates adipose tissue as a major regulator of chronic low-grade inflammation in patients with the metabolic syndrome. Adipose tissue produces proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6,[3,5,7,8] and is considered an important source of basal production of interleukin-6, the chief stimulator of the production of CRP in the liver.[9]

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are highly prevalent diseases that accompany the epidemic of obesity and the metabolic syndrome.[10–13] It is estimated that 25% of the American adult population has NAFLD.[14] Many studies have shown a strong association between components of the metabolic syndrome and both NAFLD and NASH.[10,12,13,15,16]

Current understanding of the progression of NAFLD and NASH involves a "2-hit" hypothesis in which the initial metabolic disturbance causes steatosis and a second pathogenic stimulus causes oxidative stress, reactive oxygen species formation, and cytokine production.[10,11,17,18] Thus it has been suggested that inflammatory processes that occur in the liver contribute to the systemic inflammation that characterizes the metabolic syndrome.[19]

Elevated serum alanine aminotransferase (ALT) levels is the most common liver abnormality in NAFLD and NASH, whereas alkaline phosphatase (Alk-P) and γ-glutamyltransferase are less frequently elevated.[20] NAFLD is a common explanation for abnormal liver tests results and accounts for asymptomatic elevation of aminotransferase levels in up to 90% of cases.[21]

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Although subjects with characteristics of the metabolic syndrome frequently have abnormal liver function tests,[10,12,13,15,16] there are no data on the association between elevated liver function tests (a crude marker of NAFLD) and metabolic abnormalities in relation to markers of inflammation. The aim of this study was to examine the relationship between abnormal liver function tests and CRP levels in middle-aged subjects with characteristics of the metabolic syndrome.

Methods

Subjects

We studied middle-aged subjects who reported to the Rambam Center for Preventive Medicine for investigation of cardiovascular risk factors. A complete medical history was taken by a physician. Subjects with known inflammatory disease and coronary disease and subjects using stains or with alcohol consumption ≥40 g per week were excluded. The investigational review committee on human research approved the study. All subjects enrolled in the study signed a statement agreeing to the use of their medical information for research purposes.

Definitions

Diagnosis of the metabolic syndrome was based on the recent Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Criteria.[22] The following cutoff limits were used: (1) systolic blood pressure≥130 mm Hg, diastolic blood pressure≥85 mm Hg , or on antihypertensive medication; (2) triglyceride≥1.7 mmol/L (150 mg/dL); (3) low HDL cholesterol≤1.0 mmol/L (40 mg/dL) for men and ≤1.3 mmol/L (50 mg/dL) for women; and (4) fasting glucose≥6.1 mmol/L (110 mg/dL). Because waist circumference was not measured in all subjects, we used a body mass index (BMI) cut point ≥30 kg/m^2 for obesity, as suggested by the recent World Health Organization criteria for diagnosis of the metabolic syndrome.[23] Subjects with ≥3 of the above criteria were diagnosed as having the metabolic syndrome.

Cigarette smoking was trichotomized into "never," "past," or "current" by use of standard questionnaire. For leisure time physical activity, we considered 3 categories (never or rarely, mild, and intensive or competitive).

Elevated ALT values were defined as >500 nkat/L (30 U/L) for men and >317 nkat/L (19 U/L) in women, based on the cutoff values provided by Prati et al.[24] These cutoff values increase the sensitivity for detection of patients with liver injury (primarily patients with hepatic steatosis).[24] Using these cutoff values corresponded approximately to the upper quartile in the study population (22% of men and 28% of women were classified as having elevated ALT values). Because cutoffs for elevated Alk-P have not been clearly defined, elevated Alk-P levels were defined as the upper quartile of Alk-P in the study population.

Laboratory Measurements

Venous blood samples were collected from each subject after a 12-hour fast and used for assay of glucose, total and HDL cholesterol, triglycerides, ALT, and Alk-P using Hitachi 911 automate and Boehringer Mannheim reagents. The intra-assay coefficients of variation for ALT and Alk-P were 4.4% and 5.0%, respectively.

CRP was measured with latex-enhanced immunonephelometry on a Behring BN II Nephelometer (Dade Behring). In this assay, polystyrene beads coated with mouse monoclonal antibodies bind CRP present in the serum sample and form aggregates. The intensity of the scattered light is proportional to the size of the aggregates and thus reflects concentration of CRP present in the sample. The intra-assay and interassay coefficients of variation for CRP were 3.3% and 3.2%, respectively. The lower detection limit of the assay was 0.15 mg/L.

Statistical Methods

The distribution of CRP levels was highly skewed. Therefore, logarithmically transformed values of CRP (ln CRP) were used in all analyses, with results expressed as geometric means.

Geometric means of CRP were adjusted for age, sex, level of physical activity, smoking status, components of the metabolic syndrome (presence of obesity, glucose intolerance, hypertension, low HDL-cholesterol, and elevated triglycerides), and use of hormone replacement therapy (HRT) and aspirin, using ANCOVA, under a general linear model. In additional models, geometric means of CRP were calculated using metabolic risk factors as continuous variables (BMI, fasting glucose, systolic blood pressure, HDL-cholesterol, and triglycerides).

In addition, geometric means of CRP were calculated using 2-way ANCOVA under a general linear model with ln CRP as the dependent variable, liver function tests (normal or elevated) as 1 factor, and the severity of metabolic abnormalities as the other (0 characteristics of the metabolic syndrome, 1 or 2 characteristics, and ≥3 characteristics). Similar models were fitted with liver function tests as 1 factor and levels of adiposity as the other (normal weight, overweight, and obese). The *P*-value for the main effect in these models is reported.

Multivariate logistic regression models were used to examine the association between the metabolic syndrome and high-risk CRP, defined as CRP >3.0 mg/L based on the recent American Heart Association/Centers for Disease Control and Prevention consensus recommendations,[25] in relation to liver function test status. These logistic regression models were used to calculate the probability of a high-risk CRP for each patient, and receiver operating characteristic (ROC) curves were constructed for each of these models. The discriminant accuracy of each logistic model was quantified in terms of the area under these curves.[26,27] Differences were considered significant at the 2-sided $P<0.05$ level. All statistical analyses were performed using the SPSS statistical software (Version 11.5).

Results

The study population included 1740 subjects (mean age 49±10 years, 61% males). The majority of subjects (65.5%) were overweight or obese (BMI≥25 kg/m^2), and 258 (14.8%) had the metabolic syndrome. The clinical characteristics of the study participants, according to the number of elevated liver function tests, are presented in Table 1. The prevalence of positive criteria for all components of the metabolic syndrome was higher in subjects with elevated ALT and in subjects with elevated Alk-P (Table 2).

Adjusted geometric mean CRP levels were significantly higher in subjects with elevated ALT or elevated Alk-P (Figure 1). The analyses were repeated using continuous rather than dichotomous variables for all components of the metabolic syndrome (BMI, systolic blood pressure, triglycerides, HDL cholesterol, and fasting glucose). In the continuous variable models, the adjusted geometric mean CRP was also higher in patients with elevated ALT (2.21 versus 1.94 mg/L, $P=0.028$) or elevated Alk-P (2.58 versus 1.66 mg/L, $P<0.0001$).

Using the same models, we tested the significance of trends for increasing CRP levels across increasing quartiles of liver function tests. CRP levels increased with increasing quartiles of both ALT (*P* for trend=0.005) and Alk-P (*P* for trend <0.0001).

There was a significant increase in CRP levels with increasing number of abnormal liver function tests. The adjusted geometric mean CRP was 1.78 mg/L (95% CI, 1.68 to 1.89) in subjects with normal ALT and Alk-P; 2.29 mg/L (95% CI, 2.12 to 2.48) in subjects with elevated ALT or

TABLE 1. Clinical and Biochemical Characteristics of the Study Participants

Variable	All Cases (n=1740)
Age, years	49±10
Female, %	683 (39)
Physical Activity	
Mild	739 (42)
Intensive	246 (14)
Smoking, %	
Current	353 (20)
Past	203 (12)
Obesity, %	363 (20)
Glucose intolerance or diabetes, %	211 (12)
Hypertension, %	314 (18)
Hypertriglyceridemia, %	616 (35)
Low HDL, %	596 (34)
Metabolic syndrome	258 (15)
HRT	101 (6)
Aspirin use	81 (5)
Alanine aminotransferase	19 (14, 25)
Alkaline phosphatase	63 (53, 76)

Data are mean±SD, percentages, or median (interquartile range) for variables with skewed distribution. HRT indicates hormone replacement therapy.

Alk-P; and 2.75 mg/L (95% CI, 2.29 to 3.25) in subjects with both elevated ALT and Alk-P (P for trend <0.0001).

Adjusted geometric mean CRP levels were also computed in analyses in which study participants were stratified into 6 groups according to liver function tests status (normal or elevated) and 3 categories of adiposity. Two-way ANCOVA main effects indicated that elevated ALT (P=0.01) and the level of adiposity (P<0.0001) were significantly associated with increased CRP levels. There were no significant interactions (P=0.80), indicating that the effects were additive. Figure 2A shows adjusted geometric mean CRP levels obtained from the 2-way ANCOVA model using the main effects of Alk-P status (P<0.0001) and the level of adiposity (P<0.0001). For each level of adiposity, the adjusted geometric mean CRP level was lowest among subjects with normal alkaline phosphates and highest among subjects with elevated Alk-P.

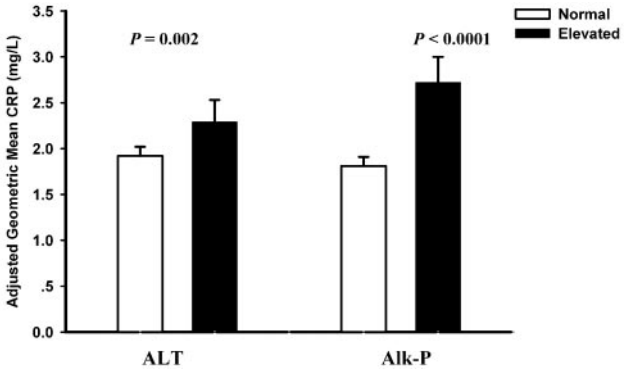

Figure 1. Adjusted geometric mean CRP levels and 95% CIs according to liver function tests status. CRP levels were adjusted for age, sex, smoking status, physical activity, components of the metabolic syndrome (obesity, glucose intolerance, hypertension, low HDL-cholesterol, and high triglycerides), and use of HRT and aspirin using ANCOVA under a general linear model. Alk-P indicates alkaline phosphatase.

Similar results were obtained when subjects were classified according to ALT status and the severity of metabolic abnormalities (elevated ALT main effect P<0.0001; metabolic abnormalities main effect P<0.0001). Figure 2B shows adjusted geometric mean CRP levels obtained from the 2-way ANCOVA model using the main effects of Alk-P status (P<0.0001) and the number of metabolic abnormalities (P<0.0001).

Multivariate logistic regression models were developed to determine the ability of elevated liver function tests to predict high-risk CRP (>3 mg/L). Compared with subjects with normal liver function tests, the adjusted odds for high-risk CRP level were significantly higher in subjects with either elevated ALT (OR, 1.5; 95% CI, 1.2 to 1.9, P=0.002) or elevated Alk-P (OR, 2.1; 95% CI, 1.7 to 2.6, P<0.0001). The area under the ROC curve of the logistic model for high-risk CRP using the presence of the metabolic syndrome data alone was 0.57±0.07. The area under the ROC curve increased with the addition of ALT data (0.61±0.07) and with the addition of Alk-P data (0.69±0.06).

TABLE 2. Positive Criteria for Components of the Metabolic Syndrome According to Liver Function Tests Category

Variable	Normal ALT (n=1347)	Elevated ALT (n=393)	Normal AlkP (n=1298)	Elevated AlkP (n=435)
Obesity (BMI>30 Kg/m^2)	221 (16)	142 (36)*	248 (19)	114 (26)†
Fasting glucose≥110 mg/dL	133 (10)	78 (20)*	145 (11)	65 (15)§
Arterial pressure≥130/85 mm Hg or pharmacologically treated	219 (16)	95 (24)*	220 (17)	94 (22)§
Triglycerides≥150 mg/dL	428 (32)	188 (48)*	407 (31)	208 (22)*
HDL<40 mg/dL for men or <50 mg/dL for women	421 (31)	175 (45)*	423 (32)	172 (40)§
Metabolic syndrome	150 (11)	108 (28)*	175 (13)	83 (19)‡

Data are the No. of positive cases and prevalence.
*P<0.0001; †P<0.005; ‡P<0.01; §P<0.05.

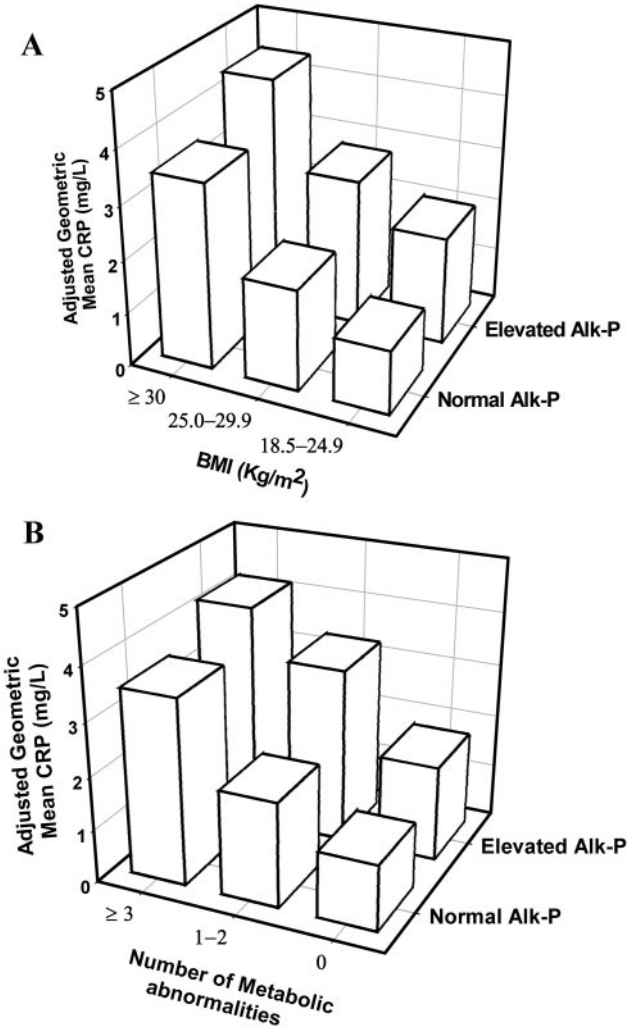

Figure 2. Adjusted geometric mean CRP levels according to Alk-P levels and categories of adiposity (normal weight, overweight, and obese; A) or number of components of the metabolic syndrome (0 components, 1 or 2 components, and ≥3 components; B). Alk-P indicates alkaline phosphatase.

Discussion

The results of this study show a direct association between elevated liver function tests (defined as liver enzyme levels in the upper quartile of the study population) and serum CRP concentrations. Elevation of liver function tests was associated with increasing number of all components of the metabolic syndrome, indicating that they mainly represent NAFLD. However, the association between elevated liver function tests and CRP was independent of the presence of metabolic abnormalities and other factors known to influence CRP levels, such as smoking, level of physical activity, and HRT. The association between liver enzyme abnormalities and increased CRP concentrations raises the possibility that inflammatory processes that accompany NAFLD contribute to the systemic inflammation observed in subjects with obesity and other characteristics of the metabolic syndrome.

Our study has several important limitations. We assume that most cases of elevated liver enzymes are secondary to NAFLD. There are several reasons for this hypothesis. First, biopsy and ultasonographic studies of patients referred for unexplained aminotransferase elevations indicate that these cases are caused by fatty infiltration of the liver in 90% of cases.[24,28,29] Second, in our study population, there was a strong relationship between elevated liver enzymes and all components of the metabolic syndrome (Table 2). Notwithstanding, tissue samples for histology were not collected and, therefore, the true cause of liver enzyme elevations in the study participants cannot be determined with certainty. In addition, the Adult Treatment Panel III definition of the metabolic syndrome used in our study is weakly correlated with direct measurements of insulin resistance.[30]

The association between NAFLD and obesity, diabetes mellitus, hypertriglyceridemia, and hypertension is well established,[10,12,13,15,16] and the simultaneous presence of several metabolic abnormalities increases the risk of more advanced stages of liver disease.[13] CRP levels are elevated in metabolic disorders such as obesity, glucose intolerance, and hypertriglyceridemia.[4,31,32] There is no consensus regarding the mechanism for the association between metabolic disorders and chronic subclinical inflammation,[19] and several possible explanations have been suggested. These include release of proinflammatory cytokines from adipose tissue[5,8,33]; metabolic abnormalities associated with insulin resistance, including hyperglycemia,[34] elevated free fatty acids, and endothelial dysfunction; and primary insulin resistance independent of its associated metabolic abnormalities.[35]

Although the liver is recognized as a major source of inflammatory mediators, it is generally assumed that hepatic production of CRP in subjects exhibiting metabolic abnormalities that characterize insulin resistance occurs under the influence of cytokines produced in other tissues.[33,36] However, inflammatory processes occur in the liver in response to fatty infiltration independent of extra hepatic stimulation.[18,37,38]

The liver has one of the largest resident population of macrophages (Kupffer cells), which are key components of the innate immune systems. Hepatic macrophages generate various inflammatory mediators and cytokines that modulate the phenotype of neighboring hepatocytes and other immune cells that travel through the liver.[38] Similar to infiltration of lipoprotein particles into the arterial wall, fat accumulation in the liver stimulates hepatic cytokine production, which could further contribute to the increased CRP levels. For example, the production of tumor necrosis factor-α is one of the earliest events in NAFLD, triggering the production of other cytokines that together recruit inflammatory cells, promote hepatocyte injury, and initiate a healing response.[18] Histological evidence of mononuclear or polymorphonuclear cell infiltration (or both) is characteristic of the progression of simple steatosis to NASH,[11] and the presence of greater number of characteristics of the metabolic syndrome is associated with more severe necroinflammatory activity in liver biopsies.[13] Animal studies suggest that hepatic macrophages might be responsible in part for the obesity-associated cytokine production in peripheral tissues.[37]

The results of this study suggest that liver inflammation secondary to NAFLD contributes to the subclinical systemic inflammation in individuals with features of the metabolic syndrome. Previous studies indicate that mild increases in liver enzyme levels should not be interpreted as nonspecific biochemical interference, especially in the presence of features of the

metabolic syndrome,[24] because they correspond to typical histopathologic lesions.[28,39,40] Given that CRP levels provide additional prognostic information regarding subsequent cardiovascular events in people with the metabolic syndrome,[6,32,41] the results of this study suggest that these minor liver abnormalities are also relevant in the context of cardiovascular risk.

Conclusion

Mild elevations in liver enzymes are associated with higher plasma CRP concentrations. Hepatic inflammation secondary to NAFLD is a potential contributor to the chronic low-grade inflammation associated with metabolic risk factors and the metabolic syndrome.

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