A Constellation of Cardiovascular Risk Factors Is Associated With Hepatic Enzyme Elevation in Hyperlipidemic Patients

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Abnormal circulating levels of hepatic enzymes are frequently found in subjects displaying hyperlipidemia or obesity or both. At present, there is a paucity of information on the principal cardiovascular risk factors that are associated with elevated plasma levels of hepatic enzyme activity in hyperlipidemic patients. We analyzed the potential relationships between serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) and cardiovascular and metabolic risk factors in a cohort of 8,501 men and women referred to our outpatient clinic for hyperlipidemia by their general practitioner. In this cohort, 27.6% of patients displayed serum levels of ALT above the upper limit of normal values. Both men and women who exhibited ALT levels superior to the upper limit of the normal range had elevated systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), alcohol intake, and serum levels of blood glucose, uric acid, total cholesterol, and triglycerides ($P < .0035$ for all parameters). In a multivariate analysis, BMI, uric acid, and blood glucose remained significantly associated with ALT levels in men and women. We conclude that cardiovascular and metabolic features characterizing the plurimetabolic syndrome, including serum uric acid levels, are associated with significant elevation of hepatic enzyme activities. Because these abnormalities may not only be reversible but also associated with a poor prognosis, further studies are needed to identify those dyslipidemic patients who are at risk for the development of severe hepatic tissue damage.

ELEVATED LEVELS of alanine aminotransferase (ALT) activity are intimately associated with liver tissue damage and are considered to represent a nonspecific marker of a spectrum of hepatic diseases. Such elevation is frequently encountered in subjects displaying hyperlipidemia in the presence or absence of obesity.[1-3] In addition, both obesity and hyperlipidemia are frequent in patients with abnormal serum activities of liver enzymes.[4] When other causes of hepatic enzyme elevation have been excluded, the combination of characteristic histologic findings and hepatic enzyme elevation is referred to as nonalcoholic steatohepatitis (NASH), a distinct clinical entity typical of obese patients associated with diabetes, hyperlipidemia, or both.[5,6] Although previously considered as benign, recent studies have established that a significant proportion of moderately obese patients with hyperlipidemia may develop extensive fibrosis and even cirrhosis,[7-10] with a subsequent marked increase in liver-related mortality.[7] The importance of overweight as a potential cause of serious liver injury was further demonstrated in patients with cryptogenic cirrhosis, in whom obesity was found in 47% of cases and represented the most commonly identified risk factor.[8]

In addition to obesity, serum hepatic enzyme levels are related to other characteristic features of the plurimetabolic syndrome, such as circulating levels of cholesterol, triglycerides, and blood glucose, insulin resistance, and systolic (SBP) and diastolic blood pressure (DBP).[11-13] More recently, we detected a significant correlation between hepatic enzyme levels and both hemostatic and fibrinolytic parameters, and more specifically plasminogen activator inhibitor type 1 (PAI-1); indeed, the latter was frequently increased in patients displaying features of the plurimetabolic syndrome.[14-16] Our hypothesis that steatosis might be associated with some of these features was further demonstrated by liver ultrasonography in a group of 64 apparently healthy males[17] and by evidence that adipose tissue does not contribute significantly to circulating levels of PAI-1.[18,19]

Despite the well-established role of obesity and diabetes mellitus in NASH, there is a paucity of data on the frequency of hepatic enzyme elevation and of the associated cardiovascular risk factors in patients referred for hyperlipidemia. Therefore, we evaluated the potential relationship between hepatic enzyme activities and major cardiovascular risk factors in a large cohort of hyperlipidemic patients.

MATERIALS AND METHODS

Population

Data obtained from a large cohort of 8,501 patients who had been referred to our outpatient clinic (Endocrinology Department, Cardiovascular Prevention Center, Hôpital Pitié-Salpétrière, Paris) and who displayed hyperlipidemia were analyzed. Patients were referred by their general practitioner when they presented either plasma low-denisty lipoprotein (LDL)-cholesterol levels above 160 mg/dL or triglyceride levels above 150 mg/dL. Patients with hyperlipidemia secondary to renal disease or hypothyroidism were excluded; these hyperlipidemias were detected by clinical and biological evaluation (measurement of thyroid-stimulating hormone [TSH], serum creatinine, and urine test for protein). We also excluded those patients who had clinical liver disease, a known hepatitis, or who were drug addicts. All patients were questioned as to their current treatment, medical history, smoking status, and alcohol intake. Alcohol intake was calculated on the basis of the number and the type of drinks taken by each patient and then expressed in grams of absolute alcohol per day. Routine medical examination included measurements of weight, height (body mass index [BMI] was calculated as weight/height^2), and DBP and SBP taken in a supine position after 10-minute rest. Patients were classified as overweight and obese when the BMI was above 25 and 30 kg/m^2,

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respectively.[20,21] Patients were considered as presenting diabetes mellitus when they were treated with oral antidiabetic drugs, insulin and/or when the blood glucose level was above 7.0 mmol/L.[22]

Analytical Methods

Venous blood samples were taken between 7:30 and 9:30 AM after a 12-hour overnight fast. Lipid analyses were performed within 3 hours of blood sampling. Total plasma levels of cholesterol and triglyceride were determined by enzymatic methods (Kone Lab, Thermoclinical Labsystems, Cergy Pontoise, France; and Biomerieux, Marcy L'Etoile, France, respectively), and high-density lipoprotein (HDL)-cholesterol by an enzymatic procedure after phosphotungstic acid/magnesium chloride precipitation; the latter method was approved by the French Society of Clinical Biology.[23] ALT, aspartate aminotransferase (AST) and gamma glutamyl transpeptidase (GGT) activities were determined at 37°C according to Klauke et al.[24] In a large group of healthy blood donors,[25] upper normal values for men were established as 35, 32, and 49 U/L for ALT, AST, and GGT, respectively, and for women as 26, 27, and 49 U/L, respectively. Blood glucose and uric acid levels were determined by routine clinical analyses.

Statistical Analysis

Mean values ± SD were calculated for all continuous variables. Comparison of means between the categories was performed using *t* tests. Pearson correlation coefficients were calculated for hepatic enzymes in relation to the other continuous variables. Multiple regression analysis was undertaken to analyze whether the relation between ALT activity and the other variables was independent. For the multivariate analysis, we selected all of the parameters that were correlated in the univariate analysis; standard coefficients and *P* values are given. For variables that were colinear (SBP and DBP), we tested the model with both parameters. Since none of the results differed significantly when one or the other parameters were selected, we arbitrarily chose the model that included DBP. We undertook a logistic regression analysis to analyze parameters independently associated with the occurrence of abnormal hepatic enzyme activities (*v* normal activities). Statistical analyses were performed using JMP software (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Hyperlipidemic Cohort

The principal clinical and biological data for the population displaying either normal or abnormal values of ALT are summarized in Table 1. All patients had been referred for hyperlipidemia; at the time of referral, however, a small proportion not treated by lipid-lowering drugs exhibited normal lipid values as a result of either random fluctuation of lipid parameters or dietary modification. Our population consisted of 59.2% male and 40.8% female subjects. Their mean age was 48.7 years; 73.8% were non-mokers. Among this population, 31.6% were receiving lipid-lowering treatment at the time of the sampling. Among these patients, 41% were taking statins, 45.9% were taking fibrates, and the remainder were taking resins. Nicotinic acid is not available in France. When comparing elevations in hepatic enzyme activities in relation to treatment, 27.2% of patients on lipid-lowering therapy presented ALT activities above the upper limit of normal values.

Patients With Abnormal Levels of ALT

Patients with abnormal levels of ALT were distinct from patients with normal liver function tests for all parameters studied, with the exception of age and the mean number of cigarettes smoked per day (Table 1). The percentage of patients with ALT activities above the upper limit of normal values was 27.6% in the whole study population and was higher in women as compared to men (28.8% *v* 26.7%, $P = .04$), in overweight men as compared to non-overweight men (30.2% *v* 18.1%, $P = .0001$), in obese men as compared to overweight men (45.2% *v* 30.2%, $P = .0001$), in overweight women as compared to non-overweight women (33.7% *v* 22%, $P = .0001$), in obese women as compared to overweight women (45.8% *v* 33.7% $P = .0001$), and in patients with diabetes mellitus as compared to nondiabetic subjects (37.5% *v* 26.9%, $P = .0001$). Among women, 861 (24.8%) subjects displayed ALT levels up to twice the normal value, 89 (2.56%) 2 to 3 times the normal value, and 49 (1.41%) more than 3-fold the normal value. In men, 1090 (21.7%) subjects exhibited ALT levels up to twice the normal value, 190 (3.78%) 2 to 3 times the normal value, and 66 (1.31%) more than 3-fold the normal value. Men and women with abnormal levels of ALT were compared to those who exhibited normal levels (Tables 2 and 3). Men with abnormally elevated levels of alanine aminotransferase were characterized primarily by a higher BMI, SBP, DBP, alcohol intake, and serum levels of the following parameters: cholesterol, triglycerides, HDL-cholesterol, uric acid, and blood glucose. Women were characterized by being older and by higher values of BMI, SBP, DBP, alcohol intake, and serum levels of triglyceride, uric acid, and blood glucose.

Table 1. Clinical and Biologic Characteristics (mean ± SD) in the Whole Study Population of 8,501 Patients Displaying Hyperlipidemia and in the Subgroup of Patients With ALT Above the Upper Limit of Normal

Characteristic	Normal ALT (n = 6,157)	Elevated ALT (n = 2,345)	*P* Value
Age (yr)	48.6 ± 12.6	49 ± 11.2	NS
BMI	25.1 ± 4.1	27.1 ± 4.8	<.0001
SBP (mm Hg)	131.9 ± 17.2	135.5 ± 17.8	<.0001
DBP (mm Hg)	81.4 ± 10.0	83.5 ± 10.4	<.0001
Alcohol intake (g/d)	9.9 ± 19.0	14.5 ± 30.1	<.0001
Cholesterol (mg/dL)	259 ± 58	265 ± 62	<.0001
Triglyceride (mg/dL)	159 ± 398	230 ± 669	<.0001
HDL-cholesterol (mg/dL)	51 ± 17	50 ± 18	.02
Uric acid (μmol/L)	304 ± 71	333 ± 97	<.0001
Glucose (mmol/L)	5.28 ± 1.30	5.57 ± 1.50	<.0001
ALT (U/L)	21.5 ± 6.3	50 ± 35	<.0001
AST (U/L)	20.9 ± 11.2	37 ± 30	<.0001
GGT (U/L)	28.8 ± 29	75 ± 121	<.0001
Patients with			
Abnormal GGT	5,164	993	
Abnormal AST and GGT	5,749	408	

Abbreviation: NS, not significant.

Correlation Coefficients

We analyzed the potential relationships among the 3 hepatic enzymes (AST, ALT and GGT) and the clinical characteristics and biologic parameters of our patients. There were no clinically significant differences regarding the correlation coefficients when we chose either AST or ALT or GGT with the

Table 2. Clinical Data in the Male Population (n = 5,030)

Parameter	Normal ALT (n = 3,684)	Abnormal ALT (n = 1,346)	*P* Value
Age (yr)	48.0 ± 12	46.2 ± 9.9	NS
BMI	25.5 ± 3.4	27.4 ± 4.1	.0001
SBP (mm Hg)	134.1 ± 16.6	136.8 ± 17.6	.0001
DBP (mm Hg)	83.1 ± 9.9	85.1 ± 10.3	.0001
Alcohol intake (g/d)	14 ± 22	21 ± 36	.0001
Cigarettes/d	4.8 ± 9.6	5.2 ± 10.7	NS
Cholesterol (mg/dL)	255 ± 57	263 ± 63	.0001
Triglyceride (mg/dL)	187 ± 457	274 ± 835	.0001
HDL-cholesterol (mg/dL)	46 ± 14	44 ± 14	.0002
Uric acid (μmol/L)	339.4 ± 81.2	371.9 ± 87.5	.0001
Glucose (mmol/L)	5.43 ± 1.32	5.69 ± 1.57	.0001
ALT (U/L)	23 ± 6	57 ± 39	.0001
AST (U/L)	22 ± 12	40 ± 31	.0001
GGT (U/L)	34 ± 34	90 ± 137	.0001

NOTE. Patients are divided into 2 groups according to ALT levels. Comparisons were made by 2-tailed *t* test.

exception of a higher correlation between GGT and alcohol intake ($r = 0.19$ versus $r = 0.12$), together with a lower correlation of GGT with BMI ($r = 0.11$ versus $r = 0.21$). The correlation coefficients determined for AST were almost identical to values found for ALT.

Age, BMI, SBP, DBP, triglyceride, blood glucose, uric acid, and alcohol intake were correlated with ALT in the whole population. These parameters remained correlated to ALT when data in men and women were analyzed separately, with the notable exception of HDL-cholesterol (Table 4).

Multivariate/Logistic Analyses

In multivariate analysis, we analyzed the risk factors independently associated with ALT; such analyses were performed in men and women. When both groups were combined and gender entered into the model, our results were comparable (data not shown). In both groups, BMI, uric acid, and blood glucose were independent predictors of ALT levels. Age was an independent predictor only in males, while both triglyceride and HDL-cholesterol levels were correlated with ALT only in women (Table 5). When we restricted the analysis to patients who were not under treatment with lipid-lowering drugs or to those not taking any drugs, our results were almost identical, ie, BMI, blood glucose, gender, uric acid, and blood glucose were independent and significant predictors of ALT activities (data not shown). In logistic analysis, we analyzed the risk factors independently associated with the occurrence of ALT levels above the upper limit of the normal range. The factors inde-

Table 3. Clinical Data in the Female Population of 3,471 Patients Displaying Hyperlipidemia

Parameter	Normal ALT (n = 2,472)	Abnormal ALT (n = 999)	*P* Value
Age (yr)	49.5 ± 13.5	52.8 ± 11.6	.0001
BMI	24.4 ± 4.8	26.8 ± 5.7	.0001
SBP (mm Hg)	128.9 ± 17.6	133.8 ± 17.8	.0001
DBP (mm Hg)	79 ± 9.7	81.2 ± 10.1	.0001
Cigarettes/d	3.3 ± 7.9	2.9 ± 8.2	NS
Alcohol intake (g/d)	4.0 ± 9.9	5.3 ± 13.5	.0035
Cholesterol (mg/dL)	264 ± 59	268 ± 60	NS
Triglyceride (mg/dL)	117 ± 283	171 ± 327	.0001
HDL-cholesterol (mg/dL)	59 ± 18	59 ± 19	NS
Uric acid (μmol/L)	253 ± 74	279 ± 84	.0001
Glucose (mmol/L)	5.05 ± 1.24	5.41 ± 1.44	.0001
ALAT (U/L)	18 ± 5	41 ± 25	.0001
ASAT (U/L)	18 ± 7	33 ± 27	.0001
GGT (U/IL)	21 ± 16.	54 ± 92	.0001

NOTE. Patients are divided into 2 groups according to ALT levels. Comparisons were made by 2-tailed *t* test.

Table 4. Correlation Coefficients Between ALT and Other Clinical and Biologic Parameters in the Whole Study Population and in Female and Male Dyslipidemic Patients Separately.

	Correlation Coefficients With ALT		
Parameter	All (n = 8,501)	Men (n = 5,030)	Women (n = 3,471)
Age (yr)	−0.04§	−0.08§	0.08§
BMI	0.21§	0.20§	0.21§
SBP	0.10§	0.06§	0.12§
DBP	0.11§	0.07§	0.10§
Cigarettes/d	0.02§	0.01§	0.03
Alcohol intake*	0.12§	0.09§	0.04†
Cholesterol	0.04‡	0.03	0.03
Triglyceride	0.08§	0.06§	0.09§
HDL-cholesterol	−0.09§	−0.04‡	0.00
Uric acid	0.22§	0.15§	0.18§
Glucose	0.13§	0.08§	0.18§
GGT	0.40§	0.37§	0.47§
AST	0.60§	0.57§	0.68§

GGT, ALT and AST are activities of glutamyl transpeptidase, alanine aminotransferase and aspartate aminotransferase, respectively. HDL-C, HDL-cholesterol; BMI, Body Mass Index, SBP and DBP are systolic and diastolic blood pressure, respectively.

*Alcohol intake was available for 7,478 patients

†$P < .05$.

‡$P < .001$.

§$P < .0001$.

Table 5. Multivariate Analysis of Parameters Associated With ALT in Male and Female Hyperlipidemic Patients

Variable	Whole Population Coefficient	*P* Value	Male Subjects Coefficient	*P* Value	Female Subjects Coefficient	*P* Value
Age	−0.08	.0001	−0.12	.0001	0.00	NS
BMI	0.15	.0001	0.18	.0001	0.14	.0001
DBP	0.03	.022	0.02	NS	0.03	NS
Alcohol*	0.06	.0001	0.05	NS	0.02	NS
HDL-c	0.04	.0025	0.03	NS	0.05	.004
Triglycerides	0.03	.0032	0.02	NS	0.06	.0007
Uric acid	0.13	.0001	0.12	.0001	0.11	.0001
Blood glucose	0.06	.0001	0.04	.01	0.13	.0001
Treatment	0.01	NS	0.00	NS	0.00	NS
Gender	0.07	.0001	—	—	—	—
Whole model	0.29	.0001		.0001	0.29	.0001

*Alcohol intake was available for 7,478 patients.

pendently associated were the followings: BMI ($P = .0001$), uric acid ($P = .0001$), gender ($P = .0001$), DBP ($P = .0001$), age ($P = .0018$), and triglycerides ($P = .0029$). Treatment with lipid-lowering drugs, alcohol intake, and HDL-cholesterol levels were not independently associated with abnormal enzyme levels.

DISCUSSION

The original findings of this study show that (1) up to one third of hyperlipidemic patients display hepatic enzyme levels that are superior to the upper limit of normal; (2) 3 independent risk factors are primarily associated with abnormal hepatic enzyme levels in both men and women—BMI, blood glucose, and serum uric acid levels; and (3) in the multivariate analysis, serum levels of triglyceride and HDL-cholesterol are positively and negatively associated, respectively, with hepatic enzyme activities in women, but not in men.

We have characterized patients with ALT or AST values above the upper limit of normal and analyzed the cardiovascular and metabolic risk factors associated with such abnormalities. Since we did not detect any consistent difference when analyses were conducted on each of the hepatic enzymes, we chose to present results for ALT, as this enzyme is more commonly elevated in NASH compared to AST, which tends to be elevated frequently in alcoholic steatohepatitis.[26]

Our study reveals the high frequency of abnormal elevation of liver enzymes: up to 27.6% of our population displayed levels of ALT that exceeded the upper limit of normal. Although we cannot exclude a referral bias, our population is representative, as all patients were referred for hyperlipidemia rather than for elevation of hepatic enzymes. Furthermore, our results are in line with previous data showing a high frequency of NASH or elevated hepatic enzyme activities in both hyperlipidemic and/or obese patients.[1-4,27]

The frequency of elevated hepatic enzyme levels was 26.7 % and 28.8 % in male and female subjects, respectively. Patients with diabetes mellitus and who were either overweight or obese were also characterized by a high frequency of elevated ALT levels. Several studies have already observed that high levels of hepatic enzymes are more likely to occur in female, obese, and diabetic patients.[3,4,13,14,25,28,29] Indeed, Araujo et al[28] showed that among 217 asymptomatic obese women, steatosis was found in 32.2% of nondiabetic patients. In an autopsy study of 351 apparently nonalcoholic patients, steatohepatitis was present in 18.5% of markedly obese patients.[30] We did not observe any differences between elevations of ALT activity with or without treatment by lipid-lowering drugs. However, due to the design of the study, we cannot exclude the possibility that patients in this group were selected on the basis of the absence of abnormal hepatic enzymes, since their physicians may have been reluctant to prescribe such drugs in the presence of enzyme elevation. In addition, some patients may display elevations in hepatic enzymes due to drug treatment. Obviously, this cannot be of consequence, since large clinical trials with statins, including the recent unpublished Heart Protection Study (HPS) trial, demonstrated that few patients display elevated transaminase levels due to statin treatment.

We did not perform tests for hepatitis in this large population, nor did we dispose of ultrasonographic evaluation of liver tissue. Therefore, we were not able to analyze risk factors in those who may have had NASH versus other unrecognized hepatic diseases (mainly associated with viral infection). In France, the prevalence of hepatitis C virus (HCV) liver disease is approximately 1.2%, while that of hepatitis B virus (HBV) liver disease is less than 0.5%.[31] Since we also excluded patients with known hepatic diseases, it is likely that the vast majority of our population display NASH. Risk factors identified for NASH include obesity, diabetes, and gender. Our study clearly identifies BMI as a major risk factor for abnormal hepatic enzyme activities in dyslipidemic patients. In the context of our study, detailed information regarding the period of time for which a participant has been overweight is not available. Therefore, we cannot answer the question of whether there may be a strong relationship between duration of overweight status and ALT elevations. However, because age and duration of overweight status would have obviously been highly correlated, a strong relationship is unlikely since the correlation coefficient ($r = 0.04$) between age and ALT levels found in the whole population is very low. There is no threshold value for BMI above which ALT increases, but rather a continuous relationship. Therefore, NASH is not a condition specific to severely obese patients. Similarly, significant correlation coefficients were detected in the univariate analysis between other characteristics of the metabolic syndrome, ie, blood glucose, SBP and DBP, triglyceride, uric acid, and ALT levels. HDL-cholesterol was the only variable whose correlation in the whole study population reflected differences between male and female subjects: female patients exhibited higher HDL-cholesterol levels, as expected, and equally a higher frequency of ALT abnormalities. In the multivariate analysis, the main difference between men and women concerned the independent relationship of triglyceride and HDL-cholesterol with ALT in women. In our study of 93 patients who underwent liver biopsy, triglycerides were clearly a risk factor for extensive fibrosis.[32] We also found a significant correlation between triglyceride and ALT levels. The lack of an independent relationship between triglyceride levels and ALT in men might be explained by the fact that a majority of our patients had a mild degree of steatosis. It is well established that triglyceride and HDL-cholesterol concentrations are stronger predictors of cardiovascular morbidity in women,[33] but it remains to be established whether this may be explained by the stronger association with hepatic abnormalities and subsequent consequences of steatosis (such as PAI-1 elevation). The independent risk factors found in the multivariate analysis for both men and women were BMI, blood glucose, and, surprisingly, uric acid. The latter variable was the most strongly associated with abnormal hepatic enzymes in both univariate and multivariate analyses. Uric acid was clearly identified as a key component of the obesity-insulin resistance syndrome, which may explain the relationship between uric acid and coronary atherosclerosis.[34] The strong relationship that we detected between uric acid and elevated hepatic enzyme levels should be taken into account when analyzing the relationship between uric acid and atherosclerosis or coronary heart disease in future studies. Interestingly, alcohol intake was not an independent risk factor in this population of moderate drinkers, a finding

that strengthens the significance of the fact that this hepatic abnormality is referred to as "nonalcoholic" steatohepatitis.

Drugs such as amiodarone and perhexiline maleate, which are inhibitors of mitochondrial betaoxidation, may be associated with NASH.[5] Clearly, our multivariate analysis ruled out a significant role of either cardiovascular or lipid-lowering drugs in the observed association between ALT and risk factors. We were also able to exclude a protective role of fibrates, which are known to be associated with increases in mitochondrial betaoxidation. However, because patients with abnormal enzyme levels were less likely to have been treated with lipid-lowering drugs, we were not able to rule out a protective or aggravating role of such agents. However, the high frequency of hepatic enzyme elevation in our population of hyperlipidemic patients emphasizes the urgent need for specific evaluation of the tolerance of lipid-lowering drugs in these patients, who are typically excluded from clinical drug trials.

The significance of the somewhat unexpected relationship between serum uric acid and hepatic enzyme levels remains to be elucidated. Our study has ruled out the possibility that alcohol intake acts as a confounding factor, since the relationship between ALT and serum uric acid was independent of alcohol intake in the multivariate analysis. In addition, the same correlation was found in the subgroup of nondrinkers (data not shown). It is interesting that this relationship remained highly significant ($P = .0001$) even after taking into account both gender and BMI, which may also have been confounders. Tissue damage in ischemia/reperfusion of the liver may be mediated by oxidative stress, the origin of which resides in reactive oxidant species. Serum uric acid is often used as an antioxidant marker of oxidative stress and can increase by 300% after hepatic ischemia in rats.[35] To a lesser extent, serum uric acid levels increased significantly after exhaustive exercise, and presumably through xanthine oxidase–derived hepatic oxidative damage.[36] More recently, experimental evidence suggested that hyperuricemia may be in part a compensatory mechanism attempting to counteract oxidative damage.[37] As cytosolic triglyceride may provoke oxidative damage through mitochondrial free radical production,[38] we hypothesized that uric acid level may be a marker of hepatic tissue damage in our population of hyperlipidemic subjects. In addition, a fructose load may induce a higher increase of uric acid in patients with chronic hepatitis.[39] Uric acid in blood serum was elevated in patients with chronic liver lesions, especially of noninfectious origin, and was dependent on the severity of the lesions.[40] Since our study was not prospective, we cannot determine the degree to which the increase in uric acid level was acquired or could have occurred prior to liver disease.

In conclusion, elevation of hepatic enzyme activities occurs frequently in nonselected hyperlipidemic patients and the associated cardiovascular and metabolic risk factors are mainly components of the plurimetabolic syndrome, including serum uric acid. The degree of tissue damage associated with abnormal ALT in dyslipidemic patients remains to be established. Equally, a better understanding of the pathophysiology of such tissue damage requires further studies. The high frequency of NASH[41] and the possibility that hepatic enzyme elevation is reversible[42] and indicates a poor prognosis[32] emphasizes the need for further studies to assess the mechanism underlying this disorder and the practical consequences for clinicians.

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