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Aminotransferase and gamma-glutamyltranspeptidase levels in obesity are associated with insulin resistance and the metabolic syndrome

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ABSTRACT. Fatty liver at ultrasounds, with/without raised plasma levels of hepatic enzymes, is common in obesity. In most cases, it is the hallmark of non-alcoholic fatty liver disease (NAFLD), a potentially progressive disease associated with insulin resistance and the metabolic syndrome (MS). We tested the hypothesis that insulin resistance *per se* might be associated with hepatocellular necrosis. Alanine and aspartate aminotransferases (ALT and AST; no.=799) and gamma-glutamyltranspeptidase (GGT; no.=459) were analyzed in a group of treatment-seeking obese patients recruited in 12 Italian medical centers. Insulin resistance was calculated by the homeostasis model assessment method (HOMA-IR; no.=522). Median ALT and AST increased with increasing obesity class (p=0.001 and p=0.005) and exceeded normal limits in 21.0% of cases. Also HOMA-IR increased with the obesity class (p<0.0001), and was higher in subjects with elevated ALT (median, 4.93 vs 2.89; p<0.0001). A significant correlation was observed between HOMA-IR and ALT (R^2=0.208; p<0.0001), as well as between HOMA-IR and AST or GGT (R^2=0.112 and R^2=0.080; p<0.0001). The correlation was maintained when cases with elevated enzyme levels were omitted from analysis. Diabetes and hypertriglyceridemia were the features of the MS most commonly associated with raised liver enzymes. In logistic regression, after correction for age, gender, BMI and features of the MS, HOMA-IR maintained a highly predictive value for raised ALT, AST and GGT. We conclude that in obesity insulin resistance is a risk factor for raised liver enzyme levels, possibly related to NAFLD.

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INTRODUCTION

The spreading of obesity epidemics has prompted an intensive research on obesity-associated conditions (1). Obesity, namely visceral fat accumulation, is part of the metabolic syndrome (MS), whose limits and diagnostic criteria have provisionally been set by different working teams (2, 3). Accordingly, glucose and lipid levels are frequently altered, but other metabolic abnormalities may be present as well.

A bright liver at ultrasounds and increased levels of hepatic enzymes are also common in obesity. In most cases, they are the hallmarks of non-alcoholic fatty liver disease (NAFLD)(4), a potentially progressive

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condition associated with MS (5-7), also having insulin resistance as a common pathogenic determinant (8). Ultrasound studies show evidence of hepatic steatosis in 76% of obese subjects not drinking alcohol in toxic amounts (9), and liver histology is compatible with NAFLD of various disease severity in over 80% of morbidly obese subjects (10, 11). High levels of alanine and aspartate aminotransferases (ALT and AST), as well as raised gamma-glutamyltranspeptidase (GGT) activity, are frequently observed, in association with body mass index (BMI) and raised insulin levels (12, 13), but the prevalence in treatment-seeking obese subjects without overt liver disease is unknown.

Although an association between the severity of liver disease and raised aminotransferases is not unequivocally demonstrated (14, 15), raised enzymes are the most common reason for patients' concern and extensive diagnostic workup. Vozarova et al. (16) first showed that raised liver enzymes were associated with body fat and insulin resistance, measured by the clamp technique. In addition, higher ALT (16, 17) or GGT (18) were prospectively associated with the development of Type 2 diabetes.

We examined the association of liver enzymes with clinical features of MS as well as with quantitative insulin resistance [homeostasis model assessment (HOMA)- insulin resistance (IR) (19)] in a large series of treatment-seeking obese subjects enrolled in a large observational Italian study. Our aims were to examine: a) the prevalence of raised liver enzyme levels in relation to obesity class; b) whether insulin resistance was independently associated with raised enzyme levels, after adjustment for features of MS.

MATERIALS AND METHODS

QUOVADIS Study

The QUOVADIS study (QUality of life in Obesity: eVAluation and DIsease Surveillance) is an observational study providing a complete picture of obese patients seeking treatment at obesity Italian centers. It was set up in 1998-2000, and its final database includes data of 1944 obese subjects, consecutively seen in 25 centers (20). Specifically aimed at studying quality of life and psychological distress, the Case Report Form (CRF) also contained a detailed checklist on civil and educational status, on personal history of disease (including liver diseases), on specific conditions associated with obesity, and on current or previous drug and alcohol use. In addition, laboratory and clinical variables were recorded at the time of enrolment, to have a complete picture of somatic diseases. All data were collected through an extranet system, which guarantees up-front quality controls (on client side) and consistency checks (on server side).

All obese subjects seeking treatment were eligible for the study, provided their BMI was in the obesity range (>30 kg/m^2), they were not on active treatment at the time of enrolment, were in the age range between 25 and 65, agreed to fill the whole package of self-administered questionnaires, and signed an informed consent to participate.

Liver enzyme and insulin levels were not mandatory at the time of enrolment, but were available in 812 of the 974 patients (83.4%) recruited by the 12 centers (77% females). In 13 cases, the CRF reported a carrier state of hepatitis B (2 cases) or C virus (11 cases), and these cases were removed from the final analysis. The CRF of the remaining subjects was negative for history of liver disease. The clinical and laboratory parameters of the study population are reported in Table 1.

The protocol was approved by the Ethical Committees of the individual centers, after approval of the Ethical Committee of the coordinating center (Azienda Ospedaliera di Bologna, Policlinico S. Orsola-Malpighi).

Methods

Body weight was measured in light clothing and without shoes to the nearest half-kg. Height was measured to the nearest half centimetre. Waist circumference was measured at the nearest half centimetre at the shortest point below the lower rib margin and the iliac crest, whereas hip circumference was similarly obtained at the widest point between hip and buttock.

Obesity was scored as class I (BMI, 30.0-34.9 kg/m^2), class II (BMI, 35.0-39.9 kg/m^2) and class III (BMI ≥40 kg/m^2). Blood pressure measurements were obtained according to the guidelines of the International Society of Hypertension (21). Three blood pressure readings were obtained at 1-min intervals, and the second and third systolic and diastolic pressure readings were averaged and used in the analyses.

Plasma glucose, both in the fasting state and in response to a standard glucose load, total cholesterol, HDL-cholesterol and triglycerides were measured in individual centers at the time of enrolment by common standard laboratory techniques [CHOL, HDL-C plus (2nd generation) and TG assays (Roche Diagnostics Co, Indianapolis, IN)]. Aminotransferases (no.=799) and GGT (no.=459) were also measured by standard assays (ALT, AST and GGT, Roche Diagnostics Co, Indianapolis, IN). According to these methods, the upper normal limit of ALT, AST and GGT was set at 40, 37 and 50 IU/l, respectively. Insulin levels (no.=552) were measured by means of ADVIA Insulin Ready Pack 100 (Bayer Diagnostics srl, Milan, Italy). HOMA-IR values were calculated as (19):

fasting glucose (mmol/l) x fasting insulin (μU/ml) /22.5.

The prevalence of MS was calculated according to the proposal of the Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) (3), as the presence of 3 or more of the following criteria: 1) abdominal obesity: waist circumference >102 cm in males and >88 cm in females; 2) hypertriglyceridemia: >150 mg/dl; 3) HDL cholesterol: <40 mg/dl in males and <50 mg/dl in females; 4) high blood pressure: >130/85 mm Hg; 5) fasting hyperglycemia [impaired fasting glucose (IFG)] >110 mg/dl. In addition, all subjects with a previous diagnosis and regularly treated for hypertension, diabetes or hypertriglyceridemia with fibrates were considered to fit the respective criteria, independently of measured values. In subjects no longer on active treatment, only measured values were considered.

Statistical analysis

Data are reported as median and range or as prevalence [95% confidence interval(CI)]. Differences between groups were analyzed by means of unpaired t test, Mann-Whitney or Kruskall-Wal-

Table 1 - *Clinical and laboratory data of patients being studied, grouped according to the presence of alanine aminotransferases (ALT) levels within or exceeding the normal limits. Data are reported as median and range or prevalence and 95% confidence intervals (CI).*

	Normal ALT (No.=631)	Elevated ALT (No.=168)	p values
Gender (M/F)	113/518	74/94	<0.0001
Age (yr)	46 (24-65)	44 (25-63)	=0.093
Alcohol consumption (%)	21.9 (18.8-25.2)	23.8 (17.7-30.5)	=0.603
BMI (kg/m^2)	36.2 (30.0-64.5)	39.0 (30.1-58.8)	=0.0021
Obesity class 1/2/3 (%)	41/28/31	33/27/40	=0.064
Waist circumference (cm)	120 (95-185)	122 (100-165)	<0.0001
Fasting glucose (mg/dl)	95 (64-306)	101 (70-284)	=0.0001
Fasting insulin (μU/ml)*	12.0 (4.0-49.0)	18.0 (5.0-56.0)	<0.0001
HOMA-IR*	3.4 (0.9-12.2)	5.6 (1.2-16.8)	<0.0001
HOMA-IR > 3.0 (%)	9.0 (5.9-12.9)	32.3 (27.1-37.7)	<0.0001
Systolic pressure (mm Hg)	135 (88-198)	135 (102-212)	=0.364
Diastolic pressure (mm Hg)	83 (54-134)	85 (62-122)	=0.550
HDL-cholesterol (mg/dl)	48 (19-99)	46 (23-91)	<0.0001
Triglycerides (mg/dl)	118 (42-432)	128 (43-900)	<0.0001
Waist circumference >102 cm (M) or >88 cm (F) (%)**	94 (91-96)	95 (93-96)	=0.196
Fasting blood glucose ≥110 mg/dl or treated for diabetes (%)**	18.9 (15.9-22.0)	33.3 (26.4-40.5)	<0.0001
Anti-hypertensive treatment or arterial pressure ≥130/85 mmHg (%)**	68.8 (65.0-72.2)	71.4 (63.9-77.5)	=0.572
Triglycerides ≥150 mg/dl or fibrate-treated (%)**	29.3 (25.8-32.9)	42.9 (35.3-50.1)	=0.0011
HDL-cholesterol <40 mg/dl (M), <50 mg/dl (F) (%)**	49.0 (45.1-52.9)	58.9 (51.1-65.8)	=0.024
Metabolic syndrome (%)**	52.9 (48.9-56.7)	69.6 (62.0-75.8)	=0.0001

* Fasting insulin and homeostasis model assessment-insulin resistance (HOMA-IR) values were available in 433 patients with normal ALT and in 119 cases with raised ALT. ** Data were scored according to ATP III criteria (3). BMI: body mass index; M: males; F: females.

lis test, whenever appropriate. Chi-square analysis was used for contingency tables. Correlation analysis was carried out by means of parametric and non-parametric methods (Spearman correlation). Log transformation of non-normally distributed values was also tested. Logistic regression analysis was used, and several models were tested. All final models were corrected for age, gender and BMI. A sensitivity analysis was also carried out, considering a different cut-off of liver enzymes as dependent variable. The statistical significance was set at $p<0.05$.

RESULTS

ALT levels exceeded normal limits in 21.0% of our cases (95% CI, 18.3-23.9). A lower prevalence of abnormalities was observed in AST (8.6%; 95% CI, 6.8-10.7) and GGT (13.7%; 10.8-17.1). The median value of ALT increased slightly, but significantly, with obesity class (24, 25 and 29 IU/l, respectively; p for trend: 0.001) (Fig. 1), but the prevalence of raised ALT was not significantly different (17.4, 21.0 and 25.4%, respectively; p=0.064). Also AST increased with obesity class (median: 21, 22 and 22 IU/l; p=0.005), whereas no systematic increase of GGT was present (median: 23, 24 and 25 IU/l; p=0.305). The ALT to AST ratio was >1 in 71% of cases, more frequently in males (86 vs 66% in females; p<0.0001), but it was >1 in 98% of cases with elevated ALT.

Regular alcohol consumption (mainly vine at meals) was reported by 22% of patients, the prevalence being higher in males (38 vs 17% in females; p<0.0001, Fisher's exact test). The reported alcohol intake was never estimated above the threshold of 40 g/day, suggested as minimum cut-off for the diagnosis of alcoholic fatty liver, and liver enzyme levels were not different between active-drinkers (ALT, 31±SD 17 U/l; AST, 25±11; GGT, 35±24) and non-drinkers (ALT, 31±SD 19 U/l; AST, 24±11; GGT, 31±26). Also, the prevalence of enzyme levels above the normal range was not different.

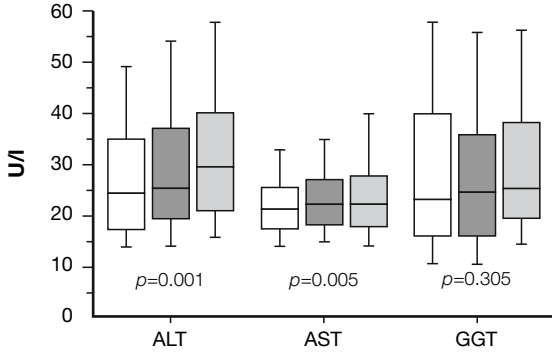

Fig. 1 - *Box plot representation of enzyme levels in obese subjects, grouped according to disease severity (Group 1, BMI 30-35 kg/m^2, white box; Group 2, BMI 35-40, dashed box; Group 3, BMI >40, grey box). The boxes represent the interquartile ranges (25 to 75th percentiles) and the horizontal lines are the medians. The "whiskers" (error bars) at the extremities indicate the 10 and the 90th percentiles. BMI: body mass index; ALT: alanine aminotransferase; AST: asportate aminotransferase; GGT: gamma-glutamyltranspeptidase.*

Glucose and insulin levels, as well as the prevalence of diabetes, increased systematically with obesity class (not reported in details), and were higher in subjects with elevated aminotransferases.

HOMA-IR values were not normally distributed, and their log transformation or non-parametric tests were used for analysis. Median HOMA-IR increased with obesity class (2.70, 3.40, and 4.27, respectively; p for trend, <0.0001), and was higher in subjects with elevated ALT (4.93 vs 2.89; p<0.0001, Mann-Whitney test). A significant correlation was observed between HOMA-IR and ALT (R^2=0.208; p<0.0001) (Fig. 2), as well as between HOMA-IR and AST or GGT (R^2=0.112 and R^2=0.080; p<0.0001). The log transformation of HOMA-IR did not change the results (R^2=0.196, R^2=0.096, R^2=0.073, respectively; p<0.0001). The correlation with ALT and GGT was maintained when cases with elevated levels (>40 IU/l for ALT, >37 for AST, and >50 for GGT) were omitted from analysis (R^2=0.094 and R^2=0.073; p<0.0001), whereas the correlation with AST was no longer significant (R^2=0.011).

The prevalence of raised aminotransferase levels was different when cases were grouped according to the parameters of MS. In particular, diabetes and hypertriglyceridemia were the features more commonly associated with high aminotransferases. According to ATP III criteria, the prevalence of MS was increased by 30% in the presence of elevated ALT.

In logistic regression analysis (Table 2), after correction for age, sex and BMI, the features of MS, excluding hypertension and large waist circumference - which was nearly the rule in our population - were associated with an increased risk of elevated ALT. No association

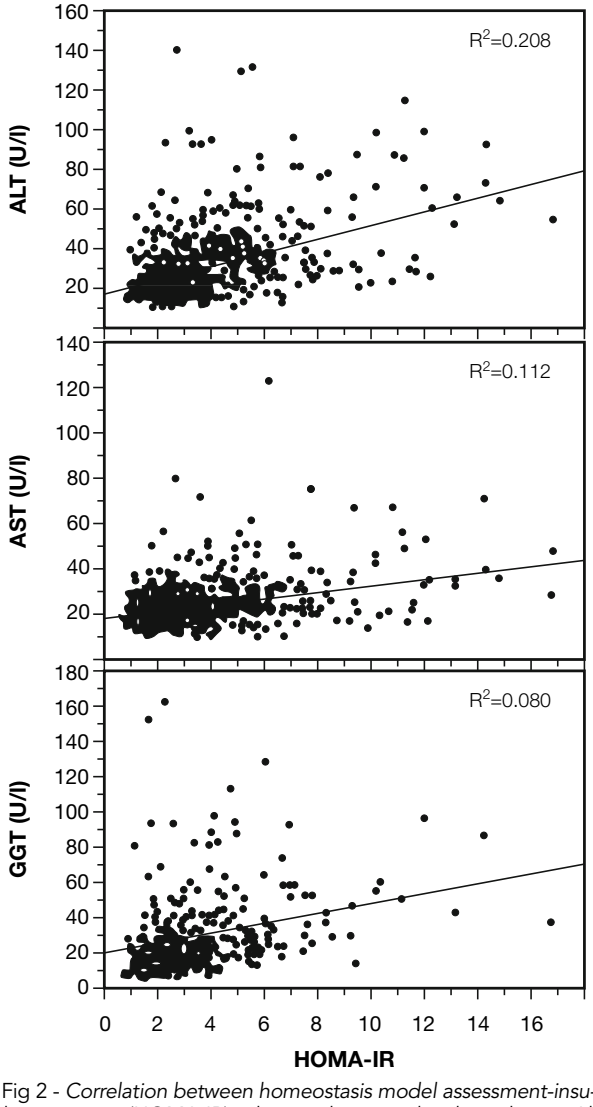

Fig 2 - *Correlation between homeostasis model assessment-insulin resistance (HOMA-IR) values and enzyme levels in obesity. All correlations are statistically significant with p<0.0001. ALT: alanine aminotransferase; AST: asportate aminotransferase; GGT: gamma-glutamyltranspeptidase.*

was found with elevated AST, whereas elevated GGT was associated with hyperglycemia or diabetes and hypertriglyceridemia. Also HOMA-IR values were significantly associated with raised liver enzymes, particularly with elevated ALT and GGT. A sensitivity analysis, considering the cut-off for elevated liver enzymes ≥1.5 or ≥2 times upper normal limits, did not change the results. As an example, the associations with elevated HOMA-IR, corrected for age, gender and BMI, were: odds ratio, 5.41 (95% CI, 2.00-14.62) and odds ratio, 7.17 (95% CI, 1.58-32.63), respectively.

Table 2 - *Association of elevated liver enzyme levels with features of the metabolic syndrome (MS) and homeostasis model assessment-insulin resistance (HOMA-IR), after correction for age, gender and BMI (odds ratio and 95% CI). The associations with features of the metabolic syndrome were not corrected for HOMA-IR.*

	ALT (>40 U/l)	AST (>37 U/l)	GGT (>50 U/l)
Large waist circumference	1.43 (0.57-3.61)	0.62 (0.20-1.88)	2.40 (0.53-10.94)
High triglycerides	1.48 (1.02-2.15)*	1.19 (0.70-2.02)	2.67 (1.52-4.69)**
Low HDL-cholesterol	1.76 (1.21-2.55)**	1.15 (0.69-1.93)	1.27 (0.72-2.23)
Raised blood pressure	0.99 (0.65-1.52)	1.15 (0.61-2.14)	1.43 (0.73-2.81)
Elevated glucose	2.11 (1.38-3.22)***	1.17 (0.64-2.12)	3.15 (1.66-5.96)***
Metabolic syndrome	2.05 (1.39-3.04)***	1.13 (0.67-1.93)	2.12 (1.15-3.95)***
HOMA-IR	1.34 (1.22-1.48)***	1.29 (1.16-1.43)***	1.28 (1.11-1.47)**

*$p<0.05$; **$p<0.005$; ***$p<0.0005$. CI: confidence interval.

When the association of HOMA-IR with raised liver enzymes (above upper normal limits) was tested after correction for all the features of the MS, the odds ratio for raised ALT (OR, 1.31; 95% CI, 1.19-1.46; p<0.0001), AST (OR, 1.39; 95% CI, 1.22-1.58; p<0.0001) and GGT (OR, 1.20; 95% CI, 1.04-1.39; p=0.014) remained statistically significant.

DISCUSSION

The study indicates that elevated liver enzymes are a common finding in obese patients without symptoms, signs and previous history of liver disease. Insulin resistance is significantly associated with high liver enzymes, and might contribute to hepatocellular necrosis, *via* liver fat accumulation.

Although retrospective in its design, the study included over 80% of cases recruited by 12 participating centers, and no systematic differences were observed among centers in enzyme levels. Only insulin was systematically higher in a single center, where morbidly obese subjects were prevalently recruited for bariatric surgery.

The most common cause of raised liver enzymes in our series was probably NAFLD. Drug-induced hepatitis was systematically ruled out at entry; congenital causes of liver disease were not excluded, but are much rarer compared with NAFLD. Also viral markers were not systematically searched for in our patients, and a few cases with raised enzymes might be due to unknown chronic viral hepatitis. The prevalence of hepatitis C virus carrier state is nearly 3% in Italy (22), considering the geographical distribution of our cases, and the prevalence of hepatitis B virus is even lower. Accordingly, approximately 30 positive cases were expected in our series, at least three times as many as those specifically excluded from analysis. Also assuming that, the number of cases positive for viral markers might treble, the association with insulin is not expected to change. Also HCV-infected patients may present steatosis at histology, due to interference of HCV core protein with the hepatic assembly and secretion of triglyceride-rich very low density lipoproteins (23), and steatosis is associated with features of the MS (24). This suggests that liver disease might be metabolically derived also in the presence of viral markers. When analyses were repeated on the whole database comprising the few cases positive for viral markers, the coefficients of correlation did not change significantly (R^2=0.203, R^2=0.097 and R^2=0.099 for ALT, AST and GGT, respectively).

No liver disease was clinically detectable in our patients. Our series is considerably different from the series described in the multicenter Italian NAFLD Study, reporting clinical, biochemical and histological data in NAFLD patients admitted to liver units for suspected liver disease and raised liver enzymes (25). However, also in that study, the presence of obesity was associated with more severe histology, and unexpected cirrhosis was only present in obese subjects.

The ALT to AST ratio was >1 in the large majority of cases, including 15 of the 16 patients with viral markers, suggesting that these cases also had either mild disease or liver involvement of metabolic origin (26). The high ALT/AST ratio also excludes a primary role of alcohol abuse. Alcohol consumption was only based on patients' reports, and might be underestimated. However, no differences in enzyme levels were observed between subjects who reported moderate alcohol consumption and abstainers, and alcohol did not enter the regression.

A role of obesity in high aminotransferases has been repeatedly demonstrated. Prati et al. (27) showed that ALT levels are significantly associated with BMI in healthy individuals, and their data led to consider revis-

ing the upper limits of normal ALT to improve the sensitivity for identifying liver disease. In the general population, Stranges et al. (28) demonstrated an independent role of central adiposity in predicting increased levels of aminotransferases and GGT, possible expression of an unrecognized hepatic disease. The majority of apparently healthy obese subjects with persistent ALT elevation had fatty liver at ultrasonography (29), the prevalence being higher in males and in relation to larger BMI. In the general population, an association of overweight/obesity with elevated ALT has been previously reported (13), and 65% of elevated enzyme levels probably depends on high BMI.

Insulin resistance seems to be the link among obesity, fatty liver and raised liver enzyme levels. Using the HOMA-IR technique, Hsiao et al. (29) identified insulin resistance as a major determinant of NAFLD in their treatment-seeking obese persons. In the general population, abnormal ALT levels were strongly associated with insulin concentrations (13), whereas BMI was not independently related. Similar data were obtained in pediatric patients (30), where NAFLD with persistent elevation of ALT was associated with the quantitative insulin sensitivity check index (31). Insulin resistance is also the common soil of MS (32), although recent data question the validity of ATP III proposal (33). Elevated liver enzymes were significantly associated with laboratory and clinical features of MS, supporting the hypothesis that NAFLD itself may be a feature of MS (14). However, our data expand the relationship between insulin resistance and liver enzymes beyond liver disease. Liver enzyme levels, namely ALT and GGT, were significantly associated with insulin resistance also within the normal range, supporting a possible role of decreased insulin sensitivity in liver cell necrosis or cholestasis in apparently healthy people. Very recently, Jeong et al. found a significant association between ALT exceeding 15 IU/l and MS in a large community sample of adult Koreans, independently of age, BMI, alcohol drinking, and sedentary lifestyle (34). They suggested that ALT could be a sensitive marker of hepatic dysfunction associated with MS, even in a range far below normal limits.

The exact pathogenesis of raised liver enzymes is far from clear. In NAFLD, insulin resistance reduces insulin-dependent suppression of lipolysis (35), and the release of very low-density lipoproteins from the liver may be reduced as well (36). Both conditions are likely to increase triglyceride contents in the hepatocytes, hence steatosis. Whether raised plasma enzymes are simply due to leaking of enzymes from fatty hepatocytes, or to the liver cell necrosis or apoptosis observed in NAFLD (37), is unknown.

In longitudinal studies raised liver enzymes (ALT and/or GGT) were highly predictive of the development of diabetes (16). Although cross-sectional in its design, our study confirms that raised liver enzymes are significantly more prevalent in obese subjects with impaired fasting glucose or diabetes, and that altered glucose levels increase the risk of elevated enzymes after correction for confounders. Vozarova et al. (16) found an inverse correlation between enzyme levels and hepatic insulin sensitivity, which was predictive of diabetes development. In our population, altered glucose levels or diabetes have a high specificity for the presence of MS (38).

Lifestyle changes are the primary approach to NAFLD (39), and improvements in ALT levels are observed in overweight patients with chronic liver disease after modest weight loss and physical activity, independently of etiology (40). A comprehensive approach to MS based on lifestyle changes is also likely to reduce the risks of progressive liver disease associated with NAFLD.

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