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Clinical correlates of persistently elevated liver enzymes in type 2 diabetic outpatients

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ABSTRACT

Aims: To evaluate the prevalence and the clinical implication of persistently elevated liver enzymes in diabetic subjects, with no evidence of viral hepatitis infection or alcohol abuse.
Methods: Clinical, lifestyle, anthropometric data and laboratory test values were collected in 916 type 2 diabetic subjects, examined for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltranspeptidase (γ-GT) levels at two different time points.
Results: Five hundred forty four patients (59.4%) showed normal (NLT group) and 182 (19.9%) persistently elevated (ELT group) liver tests in both determinations. ELT patients were prevalently men ($P = 0.016$), younger ($P < 0.0001$) and with a lower duration of diabetes ($P = 0.008$). Adjusting for age and sex, ELT subjects had significantly higher BMI ($P < 0.001$), waist circumference ($P = 0.010$), systolic ($P = 0.017$) and diastolic blood pressure ($P < 0.001$), and higher levels of fasting blood glucose ($P = 0.023$), and triglycerides ($P < 0.0001$). Current hypoglycemic and/or hypolipidemic drugs were comparable between the two groups. At multivariate analysis, male gender (OR = 3.017, $P = 0.012$), worse metabolic control (HbA1c, OR = 1.408, $P = 0.017$), and a younger age (OR = 1.054, $P = 0.007$) predicted the presence of persistently elevated liver enzymes.
Conclusions: Persistently elevated liver enzymes are a common finding in outpatient type 2 diabetic subjects, particularly in young men with suboptimal metabolic control and with the features of metabolic syndrome. The persistence of abnormal liver tests may be of potential utilization in clinical practice for the screening of patients at high risk of NAFLD.

1. Introduction

The pathogenic and epidemiological relationship between liver function and type 2 diabetes is fairly complex and not fully elucidated yet. This relationship has been only partly uncovered by studies on non-alcoholic fatty liver disease (NAFLD), a condition that may progress toward chronic hepatitis, liver cirrhosis and hepatocellular carcinoma [1–3], especially when it occurs in diabetic subjects [4,5].

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In industrialized countries, including Italy, persistently elevated transaminases levels are mainly related to virus infection (hepatitis C virus, HCV and hepatitis B virus, HBV) or alcohol abuse [6].

Although other causes may be implicated, NAFLD is the most frequent cause of persistent non-virus and non-alcohol related increase in liver enzymes levels [6].

Circulating levels of liver enzymes are a good indicator of hepatocellular damage. In patients with metabolic disorders, alanine aminotransferase (ALT) and γ-glutamyltranspeptidase (γ-GT) levels are considered a valid surrogate marker of NAFLD, whereas alanine aminotransferase (AST) is less specific [7]. High circulating levels of liver enzymes may also independently predict later development of diabetes [8–10], as well as cardiovascular (CVD) events and mortality, also in subjects with type 2 diabetes [11–13]. Furthermore, there is evidence that elevated liver enzymes might be related to liver or whole-body insulin sensitivity and/or insulin secretion [8] and metabolic syndrome [14].

In spite of the growing interest in this field, however, several important epidemiological and clinical issues concerning liver biochemistry in diabetic subjects are still to be elucidated.

Indeed, mild elevations in levels of ALT, AST and γ-GT are commonly discovered in asymptomatic diabetic patients, but evidence to guide the diagnostic work-up in these patients is still limited.

In the present study, we evaluated the potential of clinical utilization of persistently elevated liver enzymes, confirmed by at least two measurements, as a screening tool for type 2 diabetic subjects who are at high risk of NAFLD.

2. Subjects, materials and methods

2.1. Study population

Study subjects were recruited among those regularly attending the metabolic outpatient clinic at the Department of Clinical and Experimental Medicine at the Messina University.

Nine-hundred and twenty-two type 2 diabetic subjects with no evidence of liver disease, with two determinations of ALT, AST and γ-GT levels were included in the present analysis. Liver function tests were measured at least on two occasions, with a time lag of at least 3 months, according to the routine outpatient visits which are usually scheduled two–three/times per year. Although ALT and γ-GT are the enzymes involved in the metabolic derangement of the liver, measurement of AST levels was also included as part of the complete laboratory assessment of liver function in these patients [15].

Exclusion criteria, valid for all participants, were history of acute or chronic liver disease, blood transfusions, drug or alcohol abuse, defined as self-reported daily intake of alcohol >30 g for men and >20 g for women, or current treatment with hypoglycaemic drugs potentially influencing liver function tests (pioglitazone, GLP-1 receptor agonists, DPP4 inhibitors). None of participants were treated with SGLT-2 inhibitors at the time of the study.

The study was approved by the local ethics committee and informed consent was obtained from all participants.

Table 1 – Clinical characteristics of type 2 diabetic subjects participating in the study.

N	916
Age (years)	66.4 ± 10.5
Male sex *n* (%)	482 (52.6%)
Post-menopausal women *n* (%)	415 (95.6%)
Diabetes duration (years)	10.4 ± 8.7
BMI (kg/m^2)	29.9 ± 5.6
Waist circumference (cm)	101.4 ± 12.0
Systolic BP (mmHg)	134.1 ± 17.3
Diastolic BP (mmHg)	79.0 ± 9.8
Fasting blood glucose (mg/dl)	150.8 ± 50.0
HbA_{1c} (%)	7.3 ± 1.4
Total-cholesterol (mg/dl)	194.5 ± 42.4
HDL-cholesterol (mg/dl)	50.8 ± 13.6
LDL-cholesterol (mg/dl)	115.8 ± 39.5
Triglycerides (mg/dl)	141.4 ± 71.6
Creatinine (mg/dl)	1.0 ± 0.3
OHA *n* (%)	640 (69.9%)
Insulin *n* (%)	90 (9.8%)
OHA + insulin *n* (%)	99 (10.8%)
Fibrates *n* (%)	26 (2.8%)
Statins *n* (%)	341 (37.2%)
Smokers *n* (%)	109 (21.8%)
Moderate drinkers[a] *n* (%)	216 (40.1%)

Data are n, %, mean ± SD. BP, blood pressure; OHA, oral hypoglycemic agents.
[a] Self-reported daily alcohol intake <20 g for women, <30 g for men.

2.2. Measurements and assays

Type 2 diabetes diagnosis was performed according to ADA guidelines [16]. Lifestyle and clinical data were collected from all the participants through ad hoc designed questionnaire, specifically including information on potential liver diseases.

Furthermore, information on diabetes-related variables, such as diabetes duration, long-term diabetes complications, current therapy with hypoglycemic and hypolipidemic agents was recorded through an electronic chart.

Subjects were defined as non-smokers or current smokers, the latter category including also those who had quit within one year.

Weight, height, BMI, waist circumference (WC) and blood pressure (BP) were measured according to standard procedures.

Fasting plasma glucose, and serum levels of creatinine and lipid concentrations were measured with standard automated laboratory methods (Roche Diagnostics, Milan, Italy). LDL cholesterol value was calculated by the Friedewald formula [17]. Glycated hemoglobin (HbA1c) was measured using an automated high-performance liquid chromatography (HPLC) analyzer (Diamat; Bio-Rad Laboratories, Milan, Italy); normal range values in our laboratory are 4–6%.

Serum levels of ALT, AST and γ-GT were measured in all participants with standard automated laboratory methods (Cobas Roche Diagnostics, Milan, Italy); normal range values in our laboratory were: 0–50 U/L for ALT; 0–42 U/L for AST; 0–50 U/L for γ-GT, respectively; elevation of liver enzymes was defined by any ALT and/or AST and/or γ-GT value above the upper limit of our laboratory range.

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