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Lack of correlation between serum alanine amino transferrase and abdominal ultrasound in the diagnosis non alcoholic fatty liver disease in type 2 diabetes

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Abstract
Non alcoholic fatty liver disease (NAFLD) and type II diabetes (DM II) are increasingly recognized. Screening of DM II patients for NAFLD includes serum alanine amino transferase (ALT) and abdominal ultrasound (US). A retrospective cohort study was used to examine the sensitivity of serum ALT in the diagnosis of NAFLD in type 2 DM patients when compared to abdominal ultrasound and to determine the predictive factors of serum ALT in type 2 DM patients. Patient's age, sex, and history of hypertension (HTN), hyperlipidemia, height and weight were obtained from type 2 DM patients attending Out-patient Clinics. The body mass index (BMI) was also measured. Then retrospectively, we collected results of liver function tests, fasting lipids and abdominal US. Out of the 72 patients (30 males, 42 females; mean age: 58.49), 38.9% had hyperlipidemia, 59.7 % had HNT. The mean BMI was 29.97. Females were more obese and morbidly obese compared to males ($p < 0.001$). 69 patients had normal serum ALT. Mean serum ALT for males was 39.29 U/L (95% CI 33.5-45.07) and the value for females was 30.9U/L (95% CI 33.55-36.2). The difference between the values in male and females was statistically significant ($p < 0.033$). The serum ALT in type 2 DM obese and morbidly obese patients was significantly ($p < 0.034$) higher than that of normal and overweight patients. 55.6% had NAFLD by US. ALT was not different in patients with US diagnosed NFLD from those without. HTN significantly increased the risk for NAFLD ($p < 0.018$). In conclusion, serum ALT correlates poorly with abdominal US in the diagnosis of NAFLD in type 2 diabetic patients. Sex and BMI significantly influence serum ALT in type 2 DM patients.

Keywords: Non-alcoholic liver disease, alanine amino transferase, ultrasound, Type 2 diabetes, liver function test

Introduction

Non alcoholic fatty liver disease (NAFLD) and metabolic syndromes are increasingly recognized worldwide. NAFLD is the most common cause of elevated liver enzymes in the United State and other countries.[1,2] Obesity is the main risk factor for NAFLD[3] but diabetes, hypertension (HTN) and hyperlipidemia also increase the risk for NAFLD. [4,5] Insulin resistance is often present in patients with NAFLD.[6] Similar to other countries, the prevalence of obesity is increasingly recognized among adult population in Saudi Arabia.[7,8] On the other hand the prevalence of diabetes among adults in Saudi Arabia is high (23.7%).[9] The combination of the two will predict a higher prevalence of NAFLD among adult population in the future. Many patients with NAFLD are asymptomatic,[10,11] but it should be suspected in patients with underlying risk factors. Simple fatty liver is the most common form of NAFLD, while advanced non alcoholic steatohepatitis (NASH) is less common.[10] In the out-patient setting, diabetic patients are screened for possible liver disease based on liver enzymes including serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT), which are the most sensitive markers for hepatocellular injury coupled with abdominal ultrasound examination. In previous reports, diabetic patients were found to have higher serum ALT level compared to normal population[12,13,14] and non diabetic NAFLD patients.[5] This indicates that normal serum ALT cannot be ruled out NAFLD in diabetics.[15] Elevated serum ALT in diabetics with NAFLD was found to be associated with more advanced fibrosis in liver histology,[16] and higher liver and cardiovascular related mortality especially in the presence of other co-morbid conditions like HTN and hyperlipidemia.[17,18] Currently, weight reduction and dietary modification are recommended in the treatment of NAFLD,[19] indicating that early detection and preventive dietary measures may reduce the risk of progression to advanced forms of NAFLD in patients at risk. In this paper we studied the accuracy of using the serum ALT as a marker for diagnosis of NAFLD in diabetics. We also looked for the effect of gender, body mass index (BMI), HTN, and hyerlipidemia on serum ALT in type 2 DM patients.

Methods and Study design

This cohort retrospective study was conducted from June 2008-Feb 2009 on patients with type 2 diabetes at the Diabetes Clinic, King Abdu Aziz University Hospital, Jeddah. Inclusion criteria was type 2 diabetes for 5-20 years with negative history of liver disease. An outpatient clinic nurse was assigned to collect the patient's information.

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Patients were interviewed and agreed to give their data. Patient's characteristics including age, sex, height, weight, were obtained. Data regarding the presence of HTN and hyperlipidemia were also collected. We defined HTN as diastolic blood pressure more than 89 mmHg and systolic blood pressure more than 139 mmHg based on the National Heart, Lung and Blood Institute definition of hypertension.[20] For each patient, the blood pressure was measured at the time of obtaining patient agreement and information. The BMI (weight/height in meters ^{2}) was calculated and categorized into either 1: underweight; 2: normal; 3: overweight. 4, 5 and 6 were identified as belonging to either class I obesity, class II obesity and morbid obesity, respectively, as defined by the National Heart, Lung and Blood Institute and by the Calorie Control Council.[20, 21] Then the following laboratory and radiological results including were obtained from the hospital information system retrospectively for each patient: means of fasting and random blood sugar, hemoglobin A1C (HbA1C), fasting serum lipids done at least twice within the last one year of follow up, serial of 3 liver function tests including ALT serum obtained using the Dimension clinical chemistry system (Flex reagent cartridge). The normal range for ALT in the hospital lab 30-65u/L (the mean ALT was obtained from the 3 readings), renal function tests and electrolytes and serology for hepatitis B virus HBV [hepatitis B surface antigen HBSAg by ELISA (enzyme linked immunosorbent assay)], hepatitis C virus antibodies (HCVAb) by ELISA. We also obtain result of abdominal US examination done within the last 6 -12 months. The patients were included if the complete blood count, renal function tests and electrolytes were normal and if the serology for HBV and HCV were negative. Patients were excluded if the patient information or the laboratory data are incomplete patient with coexisting liver disease other than NAFLD.

Statistical Analysis: The statistical package for social science system (SPSS) for window, version 15.1 was used to calculate the mean, standard deviation and frequencies. The independent *t* test was used to compare the independent variables (ALT with sex, obesity, hypertension and hyperlipidemia). Chi-square test was used to compare the BMI between males and females. P value of 0.05 or less was considered as statistically significant.

Results

After exclusion of patients with incomplete data, 72 patients were included in the analysis. 30 (41.7%) were male and 42 (58.3%) were females. The mean age was 58.49 years, where the minimum age was 32 years and the maximum was 80 years. Only 3 patients were below the age of 40 years. 28 patients (38.9%) had hyperlipidemia. 43 patients (59.7%) had HTN. 53 patients (73.6%) have a higher BMI above the normal range, while 25 patients (34.7%) were just overweight (Category 3). Table 1 shows the BMI for males and females. The mean BMI was 29.97 with a minimum 22.07 and a maximum of 43.9. Females were more likely to be obese or have morbid obesity compared to males ($p < 0.001$). All patients except three had serum ALT level less than the upper limit of normal for the reference laboratory value. The mean serum ALT for males was 39.29 U/L (95% CI 33.5-45.07), while that of females was 30.9U/L (95%CI 33.55-36.2). The difference between serum ALT for males and females was statistically significant ($p < 0.033$). Serum ALT level in diabetic patient with obesity and morbid obesity was significantly higher than in patient with normal BMI or in the overweight category ($p < 0.034$). Abdominal US showed fatty liver changes in 40 patients (55.6%), 27 of them (67.5%) were obese or morbidly obese.

There was no significant difference in the serum ALT between patients with fatty liver on US as compared to those with normal abdominal US ($p < 0.68$). Similarly, the effect of HTN and hyperlipidemia of serum ALT were not statistically significant ($p < 0.849$; $p < 0.332$), respectively. HTN was associated with statistically significant increase risk of US diagnosed NAFLD ($p < 0.018$), while hyperlipidemia was associated with statistically non significant increase rate of US diagnosed NAFLD ($p < 0.572$). Hemoglobin AIC (HbA_{1C}) result was available for 56 patients, and was elevated (6.5-12) in 51 patients (70.8% mean of 8.3%). Patients with uncontrolled blood glucose as reflected by elevated HbA_{1C} were more likely to have US diagnosed NAFLD compared to those with normal HbA_{1C} ($p < 0.034$).

Discussion

Our data showed that serum ALT is not a sensitive marker for the assessment of NAFLD in diabetic patients as only 3 out of 40 patients with NAFLD were detected by abdominal US examination had serum ALT above the upper limit of the reference range. In total, 29 of 40 patients with US diagnosed NAFLD had serum ALT of 40U/L or less. This finding is similar to previously reported data by Mofrad and colleagues in 2003.[15] More recently Prashanth and colleagues have reported similar data.[11] Mofrad and associates also reported that some patients with normal ALT had an entire histological spectrum of NAFLD. We observed that the sex and BMI were the main predictors of serum ALT level in our cohort of patients. Parti and colleagues, in their study of normal serum ALT, reported similar association between serum ALT with sex and BMI.[22] Abdominal US examination is usually sufficient for radiological diagnosis of NAFLD [23,24] but more advanced radiological technology like magnetic resonance spectroscopy[25] and CT scan[26] were evaluated but cannot be recommended for routine evaluation of NAFLD in type 2 DM. The majority of our patients had serum ALT within the normal reference range even those with ultrasound detected fatty liver, reflecting that ALT level is not sensitive in the diagnosis of NAFLD in diabetics. Chang and colleagues observed that higher serum ALT even within the reference interval was an independent predictor of NAFLD.[27] Combination or risk factors for metabolic syndrome would increase the risk for NAFLD.[28] In our cohort of patients, we observed that HTN and obesity had significantly increased the risk of NAFLD in type 2 DM patients. Parti and colleagues defined the lower levels of serum ALT for both males and females, [22] using that level as a reference value

Table 1: Cross-tabulation of Sex and BMI categories for type 2 diabetic patients:

		BMI category					Total
		Normal	Over weight	Obesity	Very high	Morbid obesity	Normal
Sex	Male	13	8	5	3	1	30
	Female	6	17	9	7	3	42
Total		19	25	14	10	4	72

will increase the sensitivity of ALT as a marker for NAFLD but on the other hand it will increase false negative results because of higher prevalence of obesity. Since many type 2 DM patients are usually on medication for DM or hyperlipidemia, a transient or mild elevation of ALT may be observed. In view of increasing prevalence of diabetes and obesity, more sensitive markers for the detection of NAFLD and hepatic steatosis are needed. Many markers are under evaluation but none is yet approved for the diagnosis of NAFLD in patients at risk.[10,29] Liver biopsy cannot be recommended in all patients with suspected NAFLD, especially in the presence of normal ALT in large number of patients.

In conclusion, our study showed a lack of correlation between serum ALT level and abdominal US in the diagnosis of NAFLD in type 2 diabetic patients.

Currently used reference biochemical levels for serum ALT may not be helpful for the diagnosis of NAFLD in type 2 diabetic patients in outpatient setting. Sex and BMI are the independent factors that predict serum ALT level in type 2 diabetics.

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