The role of elevated alanine aminotransferase (ALT), FasL and atherogenic dyslipidemia in type II diabetes mellitus

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Received 5 May 2016; revised 28 September 2016; accepted 2 October 2016; Available online 14 November 2016

Abstract

Objectives: Many cross-sectional and prospective studies have shown that type 2 diabetes mellitus is a probable cause of non-alcoholic fatty liver disease (NAFLD) with fibrosis and cirrhosis. This research aimed to examine the plasma amino transaminase levels as biomarkers of NAFLD and their association with apoptosis markers (Fas and FasL) as well as the lipid profile in type II diabetic patients.

Methods: This cross-sectional comparative study included 120 type II diabetic and 100 non-diabetic patients, and their defined biomarkers were studied.

Results: The results showed that the mean ALT levels, FasL and triglyceride/high density lipoprotein (TG/HDL) ratio were significantly higher in patients with type II diabetes. According to the Atherogenic Index of Plasma (Log TG/HDL), approximately 45% of diabetic patients had a high risk and 11% had an intermediate risk.

Conclusion: Our results indicated the importance of regular medical control of type II diabetic patients in order to prevent the development of NAFLD.

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Peer review under responsibility of Taibah University.
risk of developing cardiovascular disease. Alanine aminotransferase (ALT) was significantly and positively correlated with FasL, TG, glucose levels and body mass index (BMI) in diabetic patients. Moreover, TG was positively correlated with blood glucose levels and BMI, whereas HDL was negatively correlated with FasL and ALT.

Conclusion: The results of this study showed that in diabetic patients, elevated ALT levels and FasL may play a role in the risk of developing liver disease and could be used as a distinct marker of NAFLD, indicating liver injury. Moreover, atherogenic dyslipidaemia is a prominent feature in type II diabetes mellitus. Low HDL-c is closely associated with hypertriglyceridaemia with an increased risk of cardiovascular disease and NAFLD in diabetics.

Keywords: Aminotransaminases; Apoptosis; Hyperglycaemia; Lipid profile; Type II diabetes mellitus

Introduction

Over the next 10–20 years, the expansion of diabetes is estimated to reach pandemic proportions. According to the World Health Organization, KSA is considered to have the seventh highest rate of diabetes in the world and the second highest in the Middle East.1

The damaging effect of diabetes mellitus on the retinal, renal, nervous and cardiovascular systems is known, but its influence on the liver has not been firmly established.2 Recently, it has been recognized that hepatic dysfunction in obesity is associated with oxidative stress and steatosis accompanying insulin resistance. The resulting consequence is non-alcoholic fatty liver disease, a familiar spectrum of disease extending from simple steatosis (fatty infiltration) to inflammatory steatohepatitis to possible long-term injury (fibrosis and cirrhosis) and subsequent liver failure.3

Type 2 diabetes is a risk factor for the development of non-alcoholic fatty liver disease (NAFLD) with fibrosis and cirrhosis. It is important to note that recognizing type 2 diabetic patients who are at risk of acquiring cirrhosis and hepatocellular carcinoma is very difficult. ALT is the liver enzyme that is most associated with liver fat accumulation,4 and therefore, ALT has been applied as an indicator of NAFLD. Some cross-sectional studies have noticed that ALT is connected to multiple characteristics of metabolic syndrome. Currently, ALT is frequently applied in epidemiological studies as a substitute indicator for NAFLD.5 Regularly accessible laboratory analysis has been established to be insufficient, and a variety of scoring systems constructed on clinical and laboratory considerations have been suggested, but have not been confirmed as satisfactorily consistent in assessing individual patients.6 It is well documented that the presence of insulin metabolic syndrome (diabetes mellitus, obesity, dyslipidaemia and hypertension) is associated with a possibly progressive, severe liver disease. Visceral adipose tissue, which releases adipokines is a predictor of altered liver function and insulin resistance. Free fatty acid (FFA) lipolysis from visceral adipocytes pass through the liver, and because of insulin resistance, the oxidative capacity is reduced, which leads to overburdened hepatocytes with fat and hepatic triglyceride accumulation.7 Necrosis or apoptosis are damaged hepatocyte responses. The physiological way to remove injured cells is apoptosis through the Fas–FasL mechanism.8

The present study aims to examine the plasma level of the aminotransaminases (ALT and AST) as markers of non-alcoholic fatty liver disease (NAFLD) and the levels of both Fas & FasL as markers of apoptosis as well as their association with type II diabetic Saudi female patients compared to healthy females.

Materials and Methods

One-hundred-twenty patients with type 2 diabetes mellitus matched for age and sex with one-hundred normal control subjects enrolled from Prince Maged Ben Abdel Aziz diabetic centre – Almadinah Almunawwarah, S.A. were studied in 2015. The exclusion criteria for both diabetic and control subjects were the following:

- Hypertension (defined as blood pressure greater than 150/90 mmHg),
- Hypercholesterolaemia (defined as LDL-cholesterol 75 percentile for age and sex),
- Tobacco use within the past 5 years,
- Current use of insulin, anti-oxidants or hormone replacement therapy
- Laboratory evidence of renal, hepatic, or haematological abnormalities.
- Alcohol use

Consent was obtained from all patients before the research was conducted.

The two groups were subjected to the following laboratory investigations:

1) Estimation of glycated haemoglobin A1C (HbA1C)%
2) Serum glucose concentration determination.
3) Serum liver enzyme ALT and AST concentration determination.
4) Levels of Fas and FasL determination.
5) Serum lipid profile [Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides (TG) and total cholesterol] concentration determination.
6) Serum kidney function tests and electrolytes.

Blood collection

Five-millilitre blood samples were collected in plain and EDTA tubes, and whole blood from the EDTA tubes was used for HbA1C% estimation. Then, serum separation was performed for each sample using a centrifuge at 3000 rpm for 5 min to estimate the liver enzymes ALT and AST as well as...
the lipid profile [LDL, HDL, TG and cholesterol] on the same day of sampling. Additionally, estimation of fasting blood glucose was conducted, as well as kidney function tests and Major minerals. All of the tests were performed using the clinical chemistry automated machine Dimension X Pand, Siemens Healthcare Diagnostics Ltd. (Frimley, Camberley, UK). Kits, sampling, reagent delivery, mixing, processing and printing of results were automatically performed by the Dimension System. The rest of the samples were kept at –20 °C for Fas and FasL analyses. Fas and FasL were determined using Fas enzyme-linked immunosorbent assay (ELISA) kit (Sigma–Aldrich, St. Louis, U.S.A.), with a minimum detectable dose of 5 and 2 pg/ml in serum, respectively. All procedures were performed at room temperature according to the manufacturer’s instructions. Each sample and standard protein were assayed in duplicate. The optical density at 450 nm for FasL and Fas was measured with a spectrophotometric microtiter plate reader (Labsystems iEMS Reader, Helsinki, Finland). A standard curve obtained with FasL or Fas samples provided with the kit was used to determine FasL and Fas in each sample.

Statistical analysis

All of the obtained data were subjected to statistical analysis using SPSS for Windows (version 20, SPSS, Chicago, IL, USA). Data are presented as the means ± standard deviation for continuous variables. Student’s t test was used for comparison of the baseline continuous characteristics between the two groups (control and type 2 diabetes). The correlations were found using the Spearman correlation. Differences between groups, control group, controlled diabetics and uncontrolled diabetics, were tested using one way analysis of variance (ANOVA) test; p < 0.05 was considered to be significant. The studied population was divided into six BMI ranges according to the WHO categorization (<18.5, 18.5–25, 25–30, 30–35, 35–40, and >40 kg/m²).

Results

A total of 120 female diabetic patients with a mean age of 53.72 ± 9.82 years old and mean duration of disease of 7.41 ± 6.01 years were included in the final analysis. They were compared to 100 healthy control subjects with a mean age of 47.25 ± 10.15, p = 0.36. The prevalence of metabolic syndrome was 23.5% among diabetic patients, which was determined by using the National Cholesterol Education Program, Adult Treatment Panel III (2002 panel guidelines), in which metabolic syndrome was defined by the presence of three or more of the following components: abdominal obesity, hypertriglyceridemia, low HDL-C, high blood pressure, and high fasting glucose. The results of this study showed that the ALT levels were significantly higher in type II diabetics (39.35 ± 12.02) compared to the non-diabetic healthy control group (34.38 ± 7.3), p < 0.001 (Table 1). Our results revealed a significant difference in the levels of FasL between patients and the control group (179.36 ± 20.34 vs. 153.90 ± 21.58) (p < 0.01). The results also showed that the TG concentration significantly increased in the type II diabetic group (1.82 ± 1.06) compared with the control group (0.71 ± 0.42), p < 0.001. The serum high-density lipoprotein (HDL) levels decreased significantly in type II diabetics compared to the control group (1.16 ± 0.64 vs. 1.55 ± 0.39), (p < 0.001) (Tables 1 and 2). The TG/HDL ratio significantly increased in diabetic patients (1.84 ± 1.54) compared to the control group (0.52 ± 0.47) (p < 0.001) (Table 1). The Atherogenic Index of Plasma (AIP = Log TG/HDL) predicts cardiovascular risk, for which AIP < 0.11 indicates low risk, AIP (0.11–0.21) indicates intermediate risk and AIP > 0.21 indicates increased risk. In this study, 45% of our diabetic patients had and increased risk and 11% had an intermediate risk. Na was significantly lower in diabetic patients compared to controls (139.6 ± 4.3 vs. 142.71 ± 3.42, p < 0.001) (Table 1). Correction for the hyperglycaemia effect on Na levels was applied. Thus, to obtain the “true” sodium level in cases of extreme hyperglycaemia, the addition of 2.4 mmol/L to the measured concentration for every 100 mg/dl increment in plasma glucose above normal levels was required. There were no significant difference in the levels of Fas, AST, CI, K, Ca, BUN, creatinine and uric

| Variables | Control | Patients | p values |
|-----------|---------|----------|----------|
|           | n = 100 | n = 120  |
| BMI kg/m² | Mean ± SD | Mean ± SD | < 0.01   |
| Duration of the disease/years | — | 7.41 ± 6.01 | — |
| Age/years | 47.25 ± 10.15 | 53.72 ± 9.82 | p = 0.360 |
| LDL mmol/L | 2.66 ± 0.63 | 2.58 ± 0.90 | p = 0.823 |
| HDL mmol/L | 1.55 ± 0.39 | 1.16 ± 0.64 | p < 0.001 |
| Cholesterol mmol/L | 4.58 ± 0.84 | 4.57 ± 1.15 | p = 0.541 |
| Triglycerides mmol/L | 0.71 ± 0.42 | 1.82 ± 1.06 | p < 0.001 |
| TG/HDL-atherogenic dyslipidaemia | 0.52 ± 0.47 | 1.84 ± 1.54 | p < 0.001 |
| Glucose mmol/L | 5.16 ± 0.41 | 9.77 ± 4.03 | p < 0.001 |
| ALT U/L | 34.38 ± 7.3 | 39.35 ± 12.02 | p < 0.001 |
| AST U/L | 20.78 ± 5.56 | 22.51 ± 9.67 | p = 0.154 |
| Glycated Hb % | — | 8.82 ± 1.95 | — |
| Fasting glucose | 5.23 ± 0.73 | 9.66 ± 3.8 | p < 0.001 |
| Na (mmol/L) | 142.71 ± 3.42 | 139.6 ± 4.30 | p < 0.001 |
| Cl (mmol/L) | 103.53 ± 2.22 | 101.77 ± 11.7 | p = 0.065 |
| K (mmol/L) | 4.2 ± 0.38 | 4.15 ± 0.42 | p = 0.299 |
| Ca (mmol/L) | 2.25 ± 0.09 | 2.27 ± 0.100 | p = 0.592 |
| BUN (mmol/L) | 3.79 ± 0.84 | 4.69 ± 3.6 | p = 0.160 |
| Creatinine (µmol/L) | 69.87 ± 10.54 | 72.53 ± 26.70 | p = 0.193 |
| Uric acid (µmol/L) | 231.28 ± 51.43 | 238.29 ± 104.58 | p = 0.59 |
| Fas (pg/ml) | 145.14 ± 23.79 | 149.80 ± 24.41 | p = 0.508 |
| (n = 35) | (n = 40) | |
| FasL (pg/ml) | 153.90 ± 21.58 | 179.36 ± 20.34 | P < 0.01 |
| (n = 35) | (n = 40) | |

p < 0.05 consider significance.
acid in type II diabetics compared to the non-diabetic healthy control group (Tables 1 and 2).

Regarding the correlation between variables, the results show that in type II diabetic patients, there was a significant positive correlation found between ALT and FasL, TG, glucose levels, BMI. A significant negative correlation was found between HDL and FasL, ALT, TG, glucose levels, and BMI. Additionally, a significant negative correlation was found in diabetic patients between Na and ALT, TG, glucose levels, and glycated Hb% (Figures 1 and 2).

Analysis of the biochemical parameters using ANOVA revealed a significant difference between the means of the three groups, control subjects, controlled diabetics and uncontrolled diabetics, for ALT (p < 0.001) and triglycerides (P < 0.05); between the control and diabetic groups for HDL (p < 0.001); and between the control subjects and uncontrolled diabetic group as well as between the two diabetic groups for glucose (p < 0.001). The FasL levels were different in both diabetics and control subjects (p < 0.001). Additionally, the Na levels were different in uncontrolled diabetics and control subjects (p < 0.001). The results show significant differences in the ALT, TG, HDL, FasL, Na and glucose mean levels in the three studied groups. In multivariate analysis, outpatients who were older, had low high density lipoprotein and showed high blood glucose levels displayed the most significant clinical explanatory variables associated with abnormal ALT.

There was a significant difference between patients with abnormal ALT and normal ALT in glucose concentration, HDL and Age, Wilk’s λ = 0.883, F (3, 107) = 4.714, p = 0.004 partial η² = 0.117. A separate ANOVA was conducted for each dependent variable, with each ANOVA evaluated at an alpha level of 0.025. There was a significant difference between patients with abnormal ALT and normal ALT as a function of age, F (1—109) = 7.857, mean-square error (MSE) = 84.914, p < 0.006, partial η² = 0.067 (6.7%), and observed Power = 0.793. Patients with elevated ALT (Mean = 55.54 years) scored higher than normal ALT patients (Mean = 50.51 years). There was no significant difference between abnormal ALT patients and normal ALT patients in glucose levels, F (1—109) = 4.250, MSE = 16.052, p < 0.042, Partial η² = 0.036 (3.6%), observed

![Figure 1](https://example.com/figure1.png)  
**Figure 1:** The correlation between Alanine aminotransferase (ALT) and FasL in diabetic patients was a significant positive correlation ($r = 0.385^{**}$, $p = 0.006$).

![Figure 2](https://example.com/figure2.png)  
**Figure 2:** The correlation between TG concentration and ALT activity (U/L) in diabetic patients was a significant positive correlation ($r = 0.252$, $p < 0.001$).
Power = 0.533. Similarly, the ALT levels in diabetic patient differed insignificantly as a function of the HDL levels, F (1–109) = 5.056, MSE = 0.085, p < 0.027, Partial η² = 0.044 (4.4%), and Observed Power = 0.606.

Regarding BMI in the diabetic group, the mean value of body mass index (BMI) was 32.9 ± 6.52 kg/m². More than 50% of patients were observed to be obese, with a BMI over 30% in the uncontrolled diabetics, and approximately 42% of controlled diabetics had a BMI over 30%.

Discussion

Elevated ALT and AST were observed in 4.5% and 5.3% of our diabetic patients, respectively. However, the mean values were within the normal range. At least 50% of patients with type 2 diabetes had NAFLD. This result is in agreement with that of the study by Erbey and his co-worker, which reported that the prevalence of elevated ALT levels among U.S. type 2 diabetes was 7.8%, and this prevalence was higher among obese (BMI > 25 kg/m²) compared to non-obese diabetics (10.6% vs. 6.6%). In support of our finding regarding ALT elevation in type II diabetic female patients, the study by Chen et al. found that 3245 adults suffering from NAFLD had elevated ALT, obesity, diabetes mellitus, hypercholesterolaemia. Previous papers have revealed that the prevalence of NAFLD and its development to fibrosis and cirrhosis rises with age. Our results are in accordance with those of another study that reported that elevated ALT levels were significantly related to a BMI >25 kg/m² among type 2 diabetics in a study conducted in India. A positive correlation was also reported between glycaemic control (FBS and PPBS) and the duration of diabetes mellitus with ALT levels.

Our results revealed that there was a significant increase in FasL in diabetic patients, which indicated an increase in the rate of apoptosis, similar to another study that revealed increasing β-cell apoptosis in type II diabetes mellitus. It is known that an increasing rate of apoptosis in β-cells is a trigger of type II diabetes mellitus. Additionally, in diabetes, reactive oxygen species stimulate the expression of FasL on hepatocytes, which bind to its receptor (Fas) on the neighbouring hepatocyte and accelerate apoptosis.

The association of a microsatellite in FASL to type II diabetes and of the FAS-670G > A genotype to insulin resistance was found in another study. The non-significant increase in the levels of Fas in our results could be explained by the fact that the Fas receptor is not expressed normally by Islet β-cells and the FasL is expressed normally. Moreover, the expression of the Fas receptor is an initial measurable indicator of apoptosis compared to FasL, and most of the patients in our research had diabetes for a long duration and a high BMI.

A positive correlation existed between FasL and ALT in our study, as was previously reported by another study in which the correlation between ALT and the stimulation of FasL intrahepatic mRNA was observed.

The prevalence of hypertriglyceridaemia in our study in type 2 diabetic patients was 36% and of low HDL was 41%. A similar finding was reported for most diabetic patients with NAFLD. A net retaining of lipids within hepatocytes, generally in the form of triglycerides, is a requirement for the occurrence of NAFLD. The abnormal blood lipid component is most often associated with obesity and insulin resistance. In our investigation, the Triglyceride: HDL ratio (atherogenic dyslipidaemia) significantly increased in diabetic patients compared with the control group. Forty-five percent of our diabetic patients had an increased risk, and 11% had an intermediate risk of cardiovascular disease according to the Atherogenic Index of Plasma (Log TG/HDL), which predicts cardiovascular risk. The atherogenic lipid profile is often found in patients with type 2 diabetes, which leads to significant increases in the risk of coronary heart disease (CHD) in diabetic patients compared with people without diabetes. The greatest difference between people with and without diabetes in lipid profile occurs in triglycerides and high-density lipoprotein cholesterol (HDL). HDL tends to be lower in patients with diabetes, whereas triglycerides markedly increase. However, the atherogenic form of LDL is more likely to be found in patients with type 2 diabetes than people without diabetes. Additionally, low HDL levels restrict reverse cholesterol transport, which is usually associated with diabetes and may also be associated with increased lipid oxidation.

Regarding the hyponatremia noticed in this study, diabetes is considered to be a disorder with an increased electrolyte imbalance because of the influences of impaired renal function, acid-base disorders, malabsorption syndromes and multidrug treatments (which often exists in diabetes). Osmotic diuresis frequently occurs in uncontrolled DM and may additionally cause hypovolemic-hyponatremia. Forced urinary electrolyte losses and aggravation of renal sodium loss occurs in diabetic ketoacidosis as a result of ketone bodies (β-hydroxybutyrate and acetoacetate). The changed metabolism of vasopressin, communication between vasopressin and insulin (both hormones work in the renal collecting duct), and reabsorption of more hypotonic fluid due to delayed stomach emptying have been suggested as likely important mechanisms of this association.

Conclusion

ALT and FasL were the variables that were most strongly associated with diabetes mellitus. NAFLD is the most common cause of a mild elevation of serum ALT and also the most prevalent liver disease in type 2 diabetes. The Triglyceride: HDL ratio (atherogenic dyslipidaemia) significantly increased in diabetic patients. This ratio was most related to diabetic patients with older age, long duration of the disease and increased glucose levels. These data support a possible contribution of hyperglycaemia (glycaemic status) in type 2 diabetics to the pathogenesis of hypertriglyceridaemia and atherogenic dyslipidaemia. Additionally, he ALT and FasL levels play a role in the risk of developing liver disease and can be used as markers for NAFLD.

Therapy to inhibit apoptosis may be important in treating type II diabetes, especially its complications.

Recommendations

Based on this research, it is recommended to determine the levels of ALT and FasL in type 2 diabetes patients because they are good indicators of NAFLD. Developing a...
Acknowledgments

The authors have critically reviewed and approved the final draft and helped to write the scientific publication. All of the authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript. DA participated in collecting the scientific material for the project and participated in collecting the scientific material. DAA coordinated the plan of the project and participated in collecting the scientific material. DL analysed and interpreted the practical part, provided research materials and helped to write the scientific publication. QJM 2012; 105: 425—432.

Authors’ contributions

DH conceived and designed the study, is responsible for the practical part, provided research materials and helped to write the scientific publication. DL analysed and interpreted the practical part, provided research materials and helped to write the scientific publication. DAA coordinated the plan of the project and participated in collecting the scientific material. DA participated in collecting the scientific material and helped to write the scientific publication. All of the authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgments

This work was supported by the project No. 4012/1435 from Deanship of Scientific-Research; Taibah-University Almadinah Almunawwarah, KSA. Additionally, we thank the staff of the Prince Maged Ben Abd Al Aziz diabetic centre — Almadinah Almunawwarah, KSA for their support of this study.

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26. How to cite this article: Mahran HN, Saber LM, Alghaithy AA, Elareefy AA. A role in elevated alanine aminotransferase (ALT), FasL and atherogenic dyslipidem- 13.