http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 11 (18): 2274-2277, 2008
ISSN 1028-8880

Prevalence of Abnormal Serum Alanine Aminotransferase Levels in Type 2 Diabetic Patients in Iran

M.A. Meybodi, M. Afkhami-Ardekani and M. Rashidi
Yazd Diabetes Research Center,
Shaheed Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

Abstract: This study was performed to estimate prevalence of transaminase levels in type 2 diabetic patients and identify contributing risk factors. In this cross-sectional study 348 patients with type 2 diabetes, who attended the diabetic clinic of Yazd Diabetes Research Center, were studied from October 2004 to December 2005. Patients with history of viral hepatitis, alcohol abuse and use of drug such as Amiodarone, Bleomycin, methotrexate, tamoxifen and sodium valporate was excluded. To examine the relationships between ALT, AST in individuals with type II diabetes and relation to various metabolic parameters like triglyceride, cholesterol, age, duration of diabetes, gender and BMI. Of 348 patients that entered the study, mean age was 58.8±11.5. Elevated ALT and AST were found in 10.4 and 3.3% of type 2 diabetic patients, respectively. Although the prevalence of elevated ALT increased with increasing age, FBS and triglyceride levels in subjects, but it was not statistically significant. There was a significant association between elevated ALT and gender as well as diabetes duration. The prevalence of elevated of ALT in type 2 diabetic patients is 1.6 times higher than general population in Iran unrelated to age, BMI, glycemic control, triglyceride levels. Identification risk factors and mechanisms of these elevations are very important and require further evaluation.

Key words: Type 2 diabetes, alanine transaminase, aspartate transaminase

INTRODUCTION

Diabetes and obesity are the most prevalent causes of nonalcoholic steatohepatitis (NASH). NASH is the main cases of chronic liver disease and AST and ALT as primary screening test for NASH (Daniel *et al*., 1999).

Among patients with diabetes, the risk of chronic liver disease is doubled; independent of alcoholic liver disease or viral hepatitis (El-Serag *et al*., 2004). Diabetes also increases the risk of primary liver cancers (Davila *et al*., 2005; Shaib *et al*., 2005) and death from liver cirrhosis (de Marco *et al*., 1999; Trombetta *et al*., 2005).

Type 2 diabetes, a frequent complication of obesity, has been described in 34 to 75% of patients with NASH (Hermos *et al*., 2008).

Aminotransferase, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), measure the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury (Erbey *et al*., 2000).

The aminotransferases AST and ALT are normally between 5-40 U L^{-1} (Kaplan, 2002; Prati *et al*., 2002). Chronic mild elevation of transaminases is frequently found in type 2 diabetic patients. Despite this, the sources of this elevation did not well known and epidemiological study of this type is not very popular (Piton *et al*., 1998). Erbey *et al*. (2000) analyzed 18,825 non-institutionalized patients in the United States. Of those with type 2 diabetes, the prevalence of elevated ALT was 7.8%, compared to 3.8% in those without diabetes (Erbey *et al*., 2000). Salmela *et al*. (1984) study (1984) in Finland multivariate analysis showed BMI more than 25 kg m^{-2} and poor diabetic control (fasting blood glucose >11.88 mmol L^{-1}) were the most significant clinical variables associated with elevated ALT (Salmela *et al*., 1984). This study was conducted to assess the prevalence of elevated AST and ALT in type 2 diabetic patients and determine the relations between this elevation to age, gender and other metabolic parameters.

MATERIALS AND METHODS

In this cross-sectional study 348 patients with type 2 diabetes, who attended the diabetic clinic of Diabetes Research Center (Yazd, Iran), were studied from October 2004 to December 2005.

Corresponding Author: Mohammad Afkhami-Ardekani, Diabetes Research Center,
Shahid Sadougdi University of Medical Science and Health Services, Jomhoori blvd,
Afshar Hospital, Yazd, Iran Tel: +983515223999 Fax: +983515258354

The criteria for diagnosis of type 2 diabetes were the American Diabetes Association criteria (2004), fasting blood sugar of 126 mg dL^{-1} at two occasions or random blood sugar of 200 mg dL^{-1} with diabetic symptoms or taking hypoglycemic drugs or insulin and did not have any episodes of ketosis in the past.

The institution's Research Ethics Committee approval was obtained prior to study enrollment. Informed consent was obtained in all subjects. Clinical data of all patients which included sex, height, weight, age at onset of diabetes, duration of diabetes, family history of diabetes and liver diseases, as well as a history of medication, were obtained by reviewing the medical records and direct patient interview.

The patients were excluded if their history indicated the presence of any of the following conditions: (1) history of known liver disease or other medical problems thought to cause an elevation in liver enzymes, (2) history of viral hepatitis and /or significant alcohol consumption, defined as greater than one alcoholic beverage per day and (3) history of any medication use thought to cause elevation in liver enzymes such as Corticosteroids, Amiodarone, Bleomycin, Methotrexate ,Tamoxifen and Sodium valporate. Moreover those with a diagnosis of Maturity Onset Diabetes of the Young, secondary diabetes, gestational diabetes or uncertain type of diabetes were excluded.

Blood sampling and biochemical analysis: Venous blood samples were collected after an overnight fasting, Plasma glucose, glycated hemoglobin (HbA_{1C}) and triglyceride as determined by enzymatic methods (PARS AZMON-Iran). AST and ALT were estimated using enzymatic methods (PARS AZMON kit -Iran). We defined Alt and AST more than 40 U L^{-1} as abnormal. A complementary viral test performed in patients who have elevated AST and ALT. Ultrasonography was performed in patients who have two times elevation in ALT and also viral profile to rule out viral infection.

Statistical analysis: Statistical analysis were performed using SPSS for windows, version 11.5. Data are presented as Mean±SD. Two unrelated samples were compared by student t-test. A significant level of $p<0.05$ was used for univariate test. ANOVA, Pierson and Tokay test were used for evaluating the relationship between mean of AST and ALT and metabolic parameters.

RESULTS

Of 348 type 2 diabetic patients, mean age of patients were 58.8±11.5 years. (ranging from 17-82). Mean duration of diabetes mellitus was 8.59±6.65 years that maximum duration of diabetes was 31 years. Mean body weight was 70.48 kg (Ranging from 38-110) and mean BMI was 27.25 (ranging from 42 to 32). Mean of AST and ALT were 24.57±15 and 24.67±23 U L^{-1}, respectively.

Table 1 shows the characteristics of type 2 diabetic patients studied. Elevated ALT and AST were found in 10.4 and 3.3% of type 2 diabetic patients, respectively. Ninety percent of patients had ALT less than 40 U L^{-1} and 9.2% had ALT between 40-80 U L^{-1} and only 0.09 had ALT over more than twice the upper limit of normal range.

Although the prevalence of elevated ALT increased with increasing age in subjects, but it was not statistically significant (Table 2). The risk of elevated ALT and AST increased with increasing triglyceride, but it was not significant at 5% level (TG level less than 150 and 150 mg dL^{-1} and above). There is no difference in the means of AST and ALT in subgroups of patient with different FBS levels. Also in type 2 diabetic patients, the risk of elevated ALT significantly decreased with increasing duration of diabetes ($p = 0.006$) (Fig. 1).

BMI is divided in three subgroups: less than 25, 25-30 and over 30 kg m^{-2}, mean of AST and ALT levels were not different in the subgroup of BMI ($p = 0.796$).

Table 1: Characteristics of type 2 diabetic patients studied

Age (years)	58.84±11.5
Duration of diabetes (years)	8.59±6.65
BMI (kg m^{-2})	27.17±4.32
FBS (mg dL^{-1})	200.73±68.61
ALT (U L^{-1})	24.57±15.92
ASt (U L^{-1})	24.67±23.53
TG (mg dL^{-1})	270.81±151.08

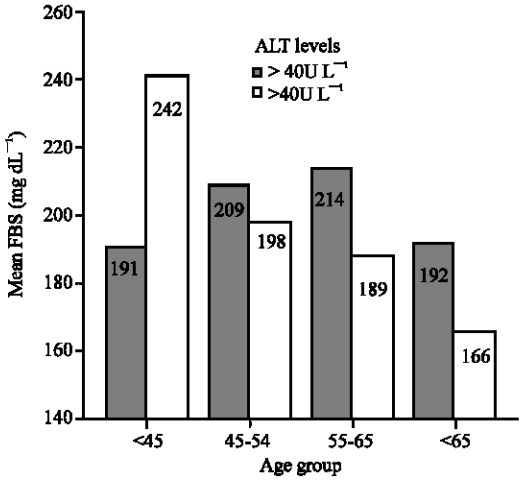

Fig. 1: Mean FBS levels in type 2 diabetic subjects with normal and elevated ALT levels in different age groups

Table 2: Frequency of ALT and AST levels and ORs in type 2 diabetic patients for various risk factors

		ALT			AST		
Risk factors		Normal (%)	Abnormal (%)	OR	Normal (%)	Abnormal (%)	OR
Age (years)	<45	26 (9.1)	6 (18.2)	1	31 (10)	1 (11.1-0)	1
	45-55	64 (22.4)	9 (27.3)	0.6 (0.19-1.88)	72 (23.2)	1 (11.1)	0.4 (0.02-7.1)
	55-65	100 (35)	14 (42.4)	0.6 (0.21-1.73)	109 (35.2)	5 (55.6)	1.42 (0.16-12)
	>65	96 (33.6)	4 (12.1)	0.18 (0.04-0.68)	31 (10)	1 (11.1)	0.63 (0.05-7.21`)
Gender	Female*	168 (62.2)	9 (32.1)	1	5 (100)	172(58.7)	1
	Male	102 (37.8)	19 (67.9)	3.47 (1.51-7.971)	---	121 (41.3)	1.02 (2-1.05)
BMI (kg m^{-2})	< 25*	88 (33.6)	9 (27.3)	1	94 (33.1)	3 (27.3)	1
	25-30	121 (46.2)	15 (45.5)	1.21 (0.5-2.8)	131 (46.1)	5 (45.5)	1.19 (0.27-5.12)
	>30	53 (20.2)	9 (27.3)	1.66 (0.6-4.44)	59 (20.8)	3 (27.3)	1.59 (0.31-8.15)
FBS (mg dL^{-1})	<140*	51 (18.3)	8 (30.8)	1	58 (918.9)	3 (37.5)	1
	140-200	100 (36)	8 (30.8)	0.54 (0.19-1.53)	105 (35.5)	3 (37.5)	0.37 (0.06-2.3)
	>200	127 (45.7)	10 (38.5)	0.47 (0.17-1.28)	135 (45.6)	2 (25)	0.4 (0.07-2.04)
Triglyceride (mg dL^{-1})	<150*	46 (19)	5 (16.7)	1	50 (18.9)	1 (14.3)	1
	≥150	196 (81)	25 (83.3)	1.17 (0.42-3.23)	215 (81.1)	6 (985.7)	1.39 (0.16-11.81)
Diabetes duration (year)	≤5*	114 (37.6)	23 (65.7)	1	131 (40.1)	6 (54.5)	1
	5-10	73 (24.1)	4 (11.4)	0.27 (0.09-0.81)	75 (22.9-0	2 (18.2-0)	0.58 (0.11-2.95)
	>10	116 (38.3)	8 (22.9)	0.34 (0.14-0.79)	121 (37)	3 (27.3)	0.54 (0.13-2.21)

*Reference category

There was negative correlation between ALT and age ($r = -0.14$, $p = 0.007$). Moreover, there was a negative significant correlation between AST and FBS ($r = -0.11$, $p = 0.042$) and HDL ($r = -0.18$, $p = 0.001$), but no significant correlation between AST and other variables was seen.

In nine patient who had elevated AST, ALT significantly, Hbs Ag and HCV was performed that were negative in all of them. Also ultrasonography was performed that in all of them fatty changes was seen.

DISCUSSION

The prevalence of elevated ALT and AST in type 2 diabetic patients was higher than general population (Mohamadnejad *et al*., 2003), but lower than studies done in diabetic patients (West *et al*., 2006). This suggests that aminotrasferase levels should be checked at least once in type 2 diabetic patients and elevated trasaminase levels may need further evaluation for the causes of raised trasaminase levels. One of our limitation was a single measure of trasaminase was performed. As fluctuation in transaminase is recognized in patients with chronic liver disease and a single measurement can underestimate disease burden (Clark and Diehl, 2003).

In non-hepatitis subjects, an elevation of ALT or GGT, even within the normal range, reflects deposition of excess fat in the liver (Wannamethee *et al*., 2005). High prevalence of transaminase levels in type 2 diabetic patients might be due to high prevalence of uncontrolled diabetic patients in present study (mean FBS: 200.73±68.61 mg dL^{-1}). As some studies showed hyperglycemia and hyperinsulinemia can promote fatty infiltration of the liver (de Marco *et al*., 1999).

In this study, only age and duration of diabetes, related to elevation of ALT in diabetic patients and there is no relationship between BMI and FBS levels and elevation of ALT. Elevated ALT was slightly more common in men and increased with increasing triglyceride, but it was not significant. ALT appeared to show some association with dislipidemia and microalbuminuria (West *et al*., 2006), but they could not show any relation with other risk factors included age, BMI, hypertension, oral hypoglycemic agent, insulin and HbA1c levels. In comparison to Salmela *et al*. (1984) showed that BMI > 25 kg m^{-2} and poor diabetic control (fasting blood glucose > 11.88 mmol L^{-1}) were the most significant clinical variables associated with elevated ALT, however in present study no relationship was observed between BMI an elevation of ALT (Salmela *et al*., 1984).

In other study elevation of ALT among older-aged patients, diabetes independently predicted elevated ALT, whereas BMI did not (Hermos *et al*., 2008). This study is in agreement with present study as ALT levels are significantly different between age lower than 52 year group and upper 64.

CONCLUSION

The prevalence of elevated of ALT in type 2 diabetic patients is 1.6 times higher than general population in Iran unrelated to age, BMI, glycemic control, triglyceride levels. Identification risk factors and mechanisms of these elevations are very important and require further evaluation.

ACKNOWLEDGMENTS

This study was supported by Yazd Diabetes Research Center and Shaheed Sadoughi University of Medical Sciences and Health Services (University Grant No. 626).

REFERENCES

American Diabetes Association, 2004. Standards of medical care in diabetes 2004. Diabetes Care, 27: S15-S35.

Clark, J.M. and A.M. Diehl, 2003. Defining nonalcoholic fatty liver disease: Implications for epidemiologic studies. Gastroenterology, 124: 248-250.

Daniel, S., T. Ben-Menachem, G. Vasudevan, C.K. Ma and M. Blumenkehl, 1999. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. Am. J. Gastroenterol., 94: 3010-3014.

Davila, J.A., R.O. Morgan, Y. Shaib, K.A. McGlynn and H.B. El-Serag, 2005. Diabetes increases the risk of hepatocellular carcinoma in the United States: A population based case control study. Br. Med. J., 54: 533-539.

de Marco, R., F. Locatelli, G. Zoppini, G. Verlato, E. Bonora and M. Muggeo, 1999. Cause-specific mortality in type 2 diabetes. The verona diabetes study. Diabetes Care, 22: 756-761.

El-Serag, H.B., T. Tran and J.E. Everhart, 2004. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology, 126: 460-468.

Erbey, J.R., C. Silberman and E. Lydick, 2000. Prevalence of abnormal serum alanine aminotransferase levels in obese patients and patients with type 2 diabetes. Am. J. Med., 109: 588-590.

Hermos, J.A., S.A. Cohen, R. HALL, D.R. Gagnon, M.T. Brophy and L.D. Fiore, 2008. Association of elevated alanine aminotransferase with BMI and diabetes in older veteran outpatients. Diabetes Res. Clin. Pract., 80: 153-158.

Kaplan, M.M., 2002. Alanine aminotransferase levels: What's normal?. Ann. Med. Int., 137: 49-51.

Mohamadnejad, M., A. Pourshams, R. Malekzadeh, A. Mohamadkhani and A. Rajabiani *et al*., 2003. Healthy ranges of serum alanine aminotransferase levels in Iranian blood donors. World J. Gastroenterol., 9: 2322-2324.

Piton, A., T. Poynard, F. Imbert-Bismut, L. Khalil, J. Delattre, E. Pelissier, N. Sansonetti and P. Opolon, 1998. Factors associated with serum alanine transaminase activity in healthy subjects: Consequences for the definition of normal values, for selection of blood donors and for patients with chronic hepatitis C. Hepatology, 27: 1213-1219.

Prati, D., E. Taioli, A. Zanella, E.D. Torre, S. Butelli and E. Del Vecchio *et al*., 2002. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann. Med. Int., 137: 1-1.

Salmela, P.I., E.A. Sotaniemi, M. Niemi and O. Maentausta, 1984. Liver function tests in diabetic patients. Diabetes Care, 7: 248-254.

Shaib, Y.H., H.B. El-serag, J.A. Davila, R. Morgan and K.A. McGlynn, 2005. Risk factors of intrahepatic cholangiocarcinoma in the United States: A case-control study. Gastroenterology, 128: 620-626.

Trombetta, M., G. Spiazzi, G. Zoppini and M. Muggeo, 2005. Review article: Type 2 diabetes and chronic liver disease in the verona diabetes study. Aliment. Pharmacol. Ther., 22: 24-27.

Wannamethee, S.G., A.G. Shaper, L. Lennon and P.H. Whincup, 2005. Hepatic enzymes, the metabolic syndrome and the risk of type 2 diabetes in older men. Diabetes Care, 28: 2913-2913.

West, J., J. Brousil, A. Gazis, L. Jackson, P. Mansell, A. Bennett and G.P. Aithal, 2006. Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes mellitus. Q. J. Med., 99: 871-876.