EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 6
349-352
Year: 2016

ASSOCIATION BETWEEN HbA1c AND ALT IN TYPE 2 DIABETES MELLITUS

Pavithra Venkatesan[1], Revathy Kuppusamy[2], Dhananjayan Rangan[3] and Swaminathan Selvanayagan[4*]

[1]Laboratory Technologist, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai 600 095.
[2]Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai 600 095.
[3]Consultant, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai 600 095.
[4*]Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai 600 095.

***Author for Correspondence: Dr. Swaminathan Selvanayagan**
Senior Consultant and Head, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai 600 095.

Article Received on 31/03/2016 **Article Revised on 20/04/2016** **Article Accepted on 11/05/2016**

ABSTRACT
HbA1c is the gold standard for monitoring the control of DM and the prevalence of NAFLD has been linked to uncontrolled T2DM. Many studies done in the past have found out a link between T2DM and alterations in liver functions, particularly enzymes among which ALT is more pronounced. The purpose of this study is to link HbA1c to ALT in a selected number of T2DM in comparison with controls. Very good associations were found between HbA1c and ALT both within control and patient groups as well as between controls and patients for these analytes. Hence this study strongly recommends evaluation of liver enzymes for T2DM patients.

KEYWORDS: ALT, HbA1c, Diabetes Mellitus, Liver Enzymes.

INTRODUCTION

It has been established by many studies that all uncontrolled Type 2 Diabetes Mellitus (T2DM) patients are subjected to alterations in liver functions as predicted by elevation in liver enzymes, particularly ALT. As HbA1c is a predictor of diabetic control, ALT elevation predicts the liver function alterations. This study is primarily to establish the association between HbA1c and ALT for controls, patients and between controls & patients for the above two analytes.

REVIEW OF LITERATURE

The liver plays a major role in the pathogenesis of T2DM. Moderately elevated liver enzymes are found in T2DM. Glucose, HbA1c, AST, ALT and GGT were estimated on base line and after 90 days. The participants in the test group showed statistically significant results.[1] The prevalence of Non Alcoholic Fatty Liver Disease (NAFLD) was significantly higher in subjects with increased serum glycated haemoglobin (HbA1c) level than in those with normal range of serum HbA1c level, and the prevalence increased along with progressively higher serum HbA1c levels. Stepwise logistic regression analysis showed that serum HbA1c level was significantly associated with the risk for NAFLD, suggesting that serum HbA1c level is associated with NAFLD and increased serum HbA1c level is an independent risk factor for NAFLD in elderly Chinese. [2] Key features of the Metabolic Syndrome (MetS) are Insulin Resistance (IR) and diabetes. The liver as central metabolic organ is not only affected by MetS as NAFLD, but may contribute to IR and metabolic alterations. Alanine Transaminase (ALT) and Aspartate Transaminase (AST) values were significantly higher in males than in females. Adiponectin and vitamin D both correlated inversely with Body Mass Index (BMI). ALT, AST, and γ - Glutamyl Transaminase (GGT) correlated with BMI, C-Reactive Protein (CRP) and HbA1c and inversely correlated with adiponectin levels. Logistic regression models using HbA1c and adiponectin or HbA1c and BMI were able to predict diabetes with high accuracy. Transaminase levels within normal ranges were closely associated with the BMI and diabetes risk. Transaminase levels and adiponectin were inversely associated. Re-assessment of current normal range limits should be considered, to provide a more exact indicator for chronic metabolic liver injury, in particular to reflect the situation in diabetic or obese individuals.[3]

T2DM is characterized by hyperglycemia and is associated with dyslipidemia and disturbed liver function. All the glycemic control parameters, lipid profile parameters except HDL-C and liver enzymes were found increased in diabetes group and significantly differ from non-diabetes group. ALT showed significant positive correlation with fasting glucose, post prandial glucose, HbA1c, Total Cholesterol (TC), Triacylglycerol (Tg), LDL-C and GGT at $p > 0.05$. AST showed very weak relation with all parameters while GGT was positively associated with fasting glucose, post prandial

glucose, HbA1c, TC, Tg, LDL-C and ALT at $p<0.05$. T2DM incline to elevate liver enzymes, especially ALT and GGT were of significance. Routine screening of ALT and GGT in T2DM patients may assists early detection of liver abnormalities and to arrest the progress of disease.[4]

Associations between HbA1c and liver enzymes and hepatic steatosis in adjusted models, HbA1c, 4.0% was strongly associated with elevated ALT and AST. Low HbA1c values were associated with liver enzymes and steatosis in the U.S. population. Liver disease may partially explain the association of HbA1c with mortality and other long-term outcomes.[5] ALT was elevated in patients, who tended to be older, heavier and more likely to be male, with higher Tg and lower HDL-C. There were no statistically significant differences in HBA1c or TC. In a well-defined population of newly diagnosed people with T2DM, there is a high incidence of abnormal ALT levels, which is associated with features of the mets, but not glycemic control.[6] There was association between liver enzymes and development of T2DM in a general Korean population. After adjusting for comprehensive diabetes risk factor, the risk of T2DM was significantly higher in the highest ALT quartile than in the lowest quartile. Similar results were observed for GGT quartiles, but in the fully adjusted analysis, the OR for the highest versus lowest quartiles was significant only for females. The results suggest that serum ALT concentrations were independently associated with T2DM in both sexes, and that GGT was also independently associated but only in females.[7] In T1DM an elevated ALT was associated with worse glycaemic control, age > 55 years and elevated Tg. Investigation of these patients revealed a cause in 43.6% of patients, predominantly NAFLD. Elevated ALT is not uncommon in T1DM and is associated with NAFLD-related risk factors. Patients with T1DM and elevated ALT should be investigated as significant abnormalities may be found which are amenable to interventions.[8]

The risk of Chronic Liver Disease is higher in diabetics and serum ALT is a sensitive predictor of mortality from liver disease. Elevated ALT was found in 9.5% of patients with T1DM and 12.1% of those with T2DM. The risk of elevated ALT in patients with T2DM increased with increasing BMI and was lower in those taking insulin. The prevalence of elevated ALT is 3–4 times higher in patients with either T1DM or T2DM than in the general population. [9] Associations of ALT and GGT with fasting glucose and HbA1c and of ALT with fasting insulin are stronger in women with diabetes compared to women without diabetes. GGT is associated with fasting insulin and HOMA to the same extent in all women, irrespective of diabetes status. Elevation of liver enzymes and hepatic IR as reflected by fasting insulin occur in the early stages of IR and highlight the central role of the liver in IR in the general population.[10] The occurrence of liver disease and raised liver enzymes is common in T2DM and may be multifactorial in origin. The high prevalence of elevated liver enzymes in T2DM is in keeping with the well-demonstrated risk of progressive liver disease. A large amount of diabetes patients may require a thorough clinical, laboratory and histological investigation.[11]

A study shows that serum AST, ALT, ALP, GGT significantly increase in T2DM patients when compared to T1DM subjects. No association was observed in values of serum total bilirubin, total protein and albumin of type T2 DM subject when compared to type T1 DM. Thus the emerging evidence suggests the abnormal LFTs may be marker for diagnosis and prognosis of diabetes mellitus.[12] MetS and T2DM are associated with IR and hepatic steatosis, which are common causes of ALT elevation. Individuals with elevated ALT had higher BMI, fasting glucose and higher HbA1c levels and ALT values correlated with HbA1c. In patients with T1DM, elevated ALT values are associated with BMI, fasting glucose and HbA1c.[13]

In stepwise regression, incorporating ALT and CRP together with MetS criteria, elevated ALT and CRP predicted incident diabetes, but not the low HDL-C and hypertension.

Thus, elevated ALT levels within the "normal" range predict incident diabetes.[14] The liver enzymes (ALT, AST, and ALP) have shown higher activity with T2DM patients than individuals who do not have DM. The most common abnormality seen among these liver enzymes is elevated AST activity.[15] Idiosyncratic liver toxicity observed with troglitazone is unlikely to be a thiazolidinedione or a PPAR- agonist class effect. Poorly controlled patients with T2DM may have moderate elevations of serum ALT that will decrease with improved glycemic control during treatment with rosiglitazone or other antihyperglycemic agents. [16]

Age of the patient did not seem to have definite influence on effect of diabetes on liver function tests. But, the duration of diabetes did seem to have some influence on effect of diabetes on the functions of liver. These results show that poor the glycemic control, the frequency of abnormal liver function increases.[17] Liver function tests might predict the risk of T2DM. Liver function tests modestly improve prediction for medium-term risk of incident diabetes above basic and extended clinical prediction models, only if no HbA1c is incorporated.[18]

MATERIALS AND METHODS

A total of 100 patients and an equal number of controls in the age group of 30-80 years were selected for this study. For controls, patients attending Master Health Check-up (MHC) were enrolled and for patients, those attending the Diabetic Clinic were selected. The main objective of this study was to find out the association between HbA1c and ALT both for Controls and Patients with T2DM.

Diuri CS 1300 B analyser and Dialab reagents were used to measure ALT and Biorad D10 analyser and the kit supplied by that company was used to measure HbA1c. The accuracy of these analytes were validated by the use of Bio-Rad accuracy controls at two levels.

Inclusion criteria

Patients who attended the Endocrine Clinic and whose HbA1c >6.5% were included. 100 patients who attended the routine Master Health Check-up and whose HbA1c levels were < 6.0 served as controls.

Exclusion criteria

Patients who attended the Diabetic Clinic and whose HbA1c values <6.5% were excluded.

For statistical analysis of data, a software downloaded from the website http://www.graphpadquickcalcs.com was used to calculate, students 't' distribution (t) and probability (p) between the group of analytes studied for both controls and between controls and patients.

RESULTS

Table I

Controls with HbA1c < 6.0

S.No	Groups	HbA1c		ALT	
		Mean	SD	Mean	SD
1	All Controls (n=100)	5.84	0.36	25.88	9.62
2	Males (n=50)	5.89	0.32	29.48	9.69
3	Females (n=50)	5.79	0.39	22.28	8.15

Table II

Patients with HbA1c > 6.5

S.No	Groups	HbA1c		ALT	
		Mean	SD	Mean	SD
1	All Patients (n=100)	9.14	1.49	28.7	10.92
2	Males (n=50)	9.06	1.52	31.38	12.93
3	Females (n=50)	9.22	1.46	26.02	7.68

Table III

Controls Vs Patients

S.No.	Groups	Analytes Compared	t	P
1	All Controls Vs All Patients (n=100)	HbA1c	21.528	0.0001
		ALT	1.9377	0.0541
2	C. Male Vs P. Male (n=50)	HbA1c	14.43	0.0001
		ALT	0.8315	0.4077
3	C. Female Vs P. Female (n=50)	HbA1c	16.049	0.0001
		ALT	2.3616	0.0202

Table IV

Controls (between Analytes)

S.No.	Groups	t	P
1	C. HbA1c Vs C. ALT (n=100)	20.817	0.0001
2	C. HbA1c Vs C. ALT (Male; n=50)	17.2049	0.0001
3	C. HbA1c Vs C. ALT (Female; n=50)	14.2906	0.0001

Table V

Patients (between Analytes)

S.No.	Groups	t	P
1	P. HbA1c Vs P. ALT (n=100)	17.7476	0.0001
2	P. HbA1c Vs P. ALT (Male; n=50)	12.1227	0.0001
3	P. HbA1c Vs P. ALT (Female; n=50)	15.1958	0.0001

Table I and II shows the mean and SD values for control and patient groups. Table III gives the statistical parameters, viz., t and p between controls and patients when HbA1c and ALT for all controls, males and females were compared. It is clear from these Tables that the correlation between controls and patients in highly significant for HbA1c ($p< 0.0001$) and moderate significance for ALT ($p<0.05$), predicting that significant difference always exists for HbA1c between controls and patients. Tables IV and V give similar data for controls and patients between analytes. All the comparison shows highly significant correlations ($p<0.0001$). These observations confirm that HbA1c and ALT show good correlation suggesting the inclusion of ALT assay for all T2DM patients.

DISCUSSION

Many previous studies have highlighted the importance of ALT in T2DM patients linking the association of the enzyme to HbA1c (3). The present study was done to confirm earlier observations and age matched controls were included to compare such associations. Other enzymes such as AST and GGT have been linked to T2DM (4,5), but majority of the studies did not link ALT to HbA1c and in this study we have established very good correlation of HbA1c to ALT not only among controls, but for patients with T2DM. Good correlations were also found. Previous studies have linked other analytes like GGT, BMI and inflammatory markers (7, 8), but we have solely selected to link HbA1c to ALT since majority of uncontrolled T2DM patients showed some mild elevation in ALT only.

CONCLUSION

This study was done with a reasonable number of patients and controls and the outcome of this study has given very good association between HbA1c and ALT both for controls and patients and between controls and patients. More such studies have to be done in future to link HbA1c to other liver enzymes such as AST, GGT

and also to inflammatory markers like TNF-α and CRP and to select a set of liver enzymes to use them occasionally to predict the control of T2DM patients based on liver enzyme levels.

ACKNOWLEDGEMENT

The authors would like to thank Dr.Mitra Ghosh, Chief of Lab Services at Apollo Speciality Hospital, Ayanambakkam, Chennai, Tamil Nadu for giving permission to undertake this study.

Conflict of Interest: None

REFERENCES

1. Beenarani K and Sreekumaran E. Management of elevated liver enzymes in geriatric diabetes by yogic practice. International Multidisciplinary Research Journal, 2012; 2(8): 27-31.
2. Han Ma, Chengfu Xu, Lei Xu, Chaohui Yu, Min Miao and Youming Li. Independent association of HbA1c and nonalcoholic fatty liver disease in an elderly Chinese population. MC Gastroenterology, 2013; 13: 3.
3. Julia Kalsch, Lars P. Bechmann, Dominik Heider, Jan Best, Paul Manka, Hagen Kalsch, Jan-Peter Sowa, Susanne Moebus, Uta Slomiany, Karl-Heinz Jockel, Raimund Erbel, Guido Gerken & Ali Canbay. Normal liver enzymes are correlated with severity of metabolic syndrome in a large population based cohort., 2015; 13058.
4. Noura Al-Jameil, Farah A Khan, Sadia Arjum, Mohammad F Khan, Hajera Tabassum. Associated liver enzymes with hyperlipidemic profile in type 2 diabetes patients. Int J Clin Exp Pathol, 2014; 7(7): 4345–4349.
5. Andrea I. Christman, Mariana Lazo, Jeanne M. Clark, Elizabeth Selvin. Low Glycated Hemoglobin and Liver Disease in the U.S. Population. Diabetes Care, 2011; 34: 2548–2550.
6. Shreyas Saligram, Elizabeth J. Williams and Michael G. Masding. Raised liver enzymes in newly diagnosed Type 2 diabetes are associated with weight and lipids, but not glycaemic control. Indian J Endocrinol Metab, 2012; 16(6): 1012–1014.
7. Hye-Ran Ahn, Min-Ho Shin, Hae-Sung Nam, Kyeong-Soo Park, Young-Hoon Lee, Seul-Ki Jeong, Jin-Su Choi and Sun-Seog Kweon. The association between liver enzymes and risk of type 2 diabetes: the Namwon study. Diabetology & Metabolic Syndrome, 2014; 6:14.
8. Leeds JS, Forman EM, Morley S, Scott AR, Tesfaye S, Sanders DS. Abnormal liver function tests in patients with Type 1 diabetes mellitus: prevalence, clinical correlations and underlying pathologies. Diabet Med, 2009; 26(12): 1235-41.
9. J. West, J. Brousil, A. Gazis, L. Jackson, P. Mansell, A. Bennett, G.P. Aithal. Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes mellitus. QJM, 2006; 99(12): 871-6.
10. Abigail Fraser, Shah Ebrahim, George Davey Smith and Debbie A Lawlor. A Comparison of Associations of Alanine Aminotransferase and Gamma-Glutamyltransferase with Fasting Glucose, Fasting Insulin, and Glycated Hemoglobin in Women With and Without Diabetes. Hepatology, 2007; 46(1): 158-165.
11. Forlani G, Di Bonito P, Mannucci E, Capaldo B, Genovese S, Orrasch M, Scaldaferri L, Di Bartolo P, Melandri P, Dei Cas A, Zavaroni I, Marchesini G. Prevalence of elevated liver enzymes in Type 2 diabetes mellitus and its association with the metabolic syndrome. J Endocrinol Invest, 2008;31(2):146-52.
12. Mamta Choudhary, Surendra Kumar Jinger, Yogita, Ghanshyam Gahlot and Rachit Saxena. Comparative study of liver function test in type-1 and type-2 diabetes mellitus. Indian J. Sci. Res, 2014; 5(2): 143-147.
13. Hatanaka SA1, Silva NO, Colombo BS, Correa CG, Alcaire BP, Coral MH, Schiavon LL, Narciso-Schiavon JL. Factors associated with elevated serum alanine aminotransferase in patients with type 1 diabetes mellitus. Minerva Gastroenterol Dietol, 2015; 61(3): 137-43.
14. Naveed Sattar, Olga Scherbakova, Ian Ford, Denis St. J. O'Reilly, Adrian Stanley, Ewan Forrest, Peter W. MacFarlane, Chris J. Packard, Stuart M. Cobbe, James Shepherd. Elevated Alanine Aminotransferase Predicts New-Onset Type 2 Diabetes Independently of Classical Risk Factors, Metabolic Syndrome, and C-Reactive Protein in the West of Scotland Coronary Prevention Study. Diabetes, 2004; 53(11).
15. Shipra Mathur, Debij Kumar Mehta , Sangeeta Kapoor , Sushil Yadav. Liver Function in Type-2 Diabetes Mellitus Patients. International Journal of Scientific Study, 2016; 3(10): 43-47.
16. Harold E. Lebovitz, Margaret Kreider, Martin I. Freed. Evaluation of Liver Function in Type 2 Diabetic Patients During Clinical Trials Evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care, 2002; 25(5): 815-821.
17. Prabhudeva, Ghouse Pasha and K. Mounika. Hepatic Dysfunction in Diabetes Mellitus: Biochemical and Ultrasonological Study N. Journal of Academia and Industrial Research (JAIR), 2014; 3(4): 164 – 167.
18. Abbasi A, Bakker SJ, Corpeleijn E, van der A DL, Gansevoort RT, Gans RO, Peelen LM, van der Schouw YT, Stolk RP, Navis G, Spijkerman AM, Beulens JW. Liver function tests and risk prediction of incident type 2 diabetes: evaluation in two independent cohorts., 2012; 7(12): e51496.