Association between Liver enzymes and HbA1c to lipid profile in Non-hospitalised T2DM patients

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ABSTRACT

Many previous studies have linked both DM, especially T2DM as well as altered liver function to CVD.Uncontrolled DM is said to affect cardiac function. This study was undertaken on non-hospitalised T2DM patients (both males and females) to find out if liver enzymes and HbA1c are associated to cardiac function by linking their associations to individual lipid profile tests.In all patients comprising of a total of 50, significant associations of both negative and positive were observed between each liver enzyme and HbA1c analyte studied to individual lipid profile tests at a p value ranging from <0.05 to < 0.001 justifying that both liver and DM are associated to cardiac function. While γ-GT and HbA1c showed associations to TC, TGs and VLDL-c in the case of males, females showed associations to all analytes compared to all lipid profile parameters at p ranging from <0.08 to <0.01.The outcome the results in this study strongly recommends that to assess cardiac functions in T2DM patients, along with lipid profile, the clinicians should occasionally recommend HbA1c as well as liver enzymes as additional package tests. More studies are needed in this field to arrive at a consensus package tests related to both DM and liver function to do occasionally in all T2DM patients attending Cardiology clinics.

Introduction

Diabetes Mellitus is a Global Health problem and this is attributed to lifestyle modifications, genetic, and various other factors such as obesity induced Insulin resistance. The objective of this present study is to assess the association between liver specific enzymes and the diabetic control monitoring HbA1c to lipid profile to assess the effect of these in inducing cardiac related problems.

Isolated alterations of biochemical markers of liver damage in a seemingly healthy patient can present a challenge. When Alanine amino transferase (ALT) test alone is made available even an experienced clinician usually set off a battery of further, costly tests and consultations that may ultimately prove unnecessary.[1] The serum levels of Aspartate amino transferase (AST) and ALT in coronary heart disease (CHD) patients are higher than those in controls. High serum AST and ALT are biochemical markers which can be used to predict the severity of CHD and also serve as independent risk factors of CHD.[2] AST to ALT, AST/ALT ratio (AAR), reflecting liver disease severity, has been associated with increased risk of cardiovascular disease (CVD). Elevated AAR is significantly associated with increased risk of developing CVD in men but not in women. However, the ratio does not confer any additional benefits over established CVD risk prediction tools in the general population, but may have clinical utility in certain subgroups.[3]

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of obesity and metabolic syndrome (MetS). ALT levels are used to detect NAFLD and have also been associated with increased risk for MetS, Diabetes Mellitus (DM) and CVD. Both normal and increased levels of ALT are associated with long-term development of multiple metabolic disorders. These observations indicate the potential for ALT values as biomarkers for the risk for metabolic disease.[4] Positive relationship for MetS was also observed in elevated AST group, but within the reference range, the AST level was not associated with MetS. Serum ALT level, even within the reference range, was significantly associated with MetS. However, only elevated AST levels above 40 U/L was positively associated with MetS.[5] AST may not be associated with angiographically determined coronary atherosclerosis. Albumin may be more sensitive to demonstrate the burden of atherosclerosis. Hence the association between the liver function tests and coronary atherosclerosis may be more complex than generally appreciated.[6]

Liver enzymes are associated with CVD risk. Minimal lumen diameter (MLD) and percent stenosis diameter (SD) were determined from quantitative coronary angiography. Age, alkaline phosphatase (ALP), AST, and MLD differed significantly between SD ≥50 and SD<50. Age, AST, ALT, and troponin correlated significantly with SD, whereas MLD correlated inversely with SD. M10 (age, BMI, AP, AST, ALT, gamma-glutamyltransferase(γ-GT),creatinine, troponin. Routine liver parameters are associated with SD in AMI. A small set of noninvasively determined parameters can identify SD in AMI, and might avoid unnecessary coronary angiography in patients with low risk.[7] Men who had sustained elevation of serum AST during 2 subsequent liver enzyme tests showed a significantly higher risk of CVD mortality.[8]

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The serum ALT activity has been regarded as a reliable and sensitive marker of liver disease. ALT may also be a good indicator of overall health, particularly in the context of obesity, the MetS, and presence of CVD, as many patients affected by these conditions also are at risk of having NAFLD. ALT is an integral part of the evaluation of patients with liver disease. Its importance as a screening test for liver disease is highlighted by the fact that most patients with common liver diseases such as viral hepatitis B and C (HBV, HCV) and NAFLD have elevated ALT, even though they remain without symptoms to prompt a medical evaluation. Although the interpretation and practical use of ALT analysis may differ across specific liver disease categories, ALT is a sensitive test to detect individuals with liver disease. The importance of ALT activity as an indicator of liver disease has recently been demonstrated in population-based studies which documented a strong association between ALT and subsequent mortality from liver disease. Furthermore, emerging data suggest that ALT has a role as a predictor of mortality independent of liver disease. This association is generally construed to signify NAFLD as a component of the metabolic consequences of insulin resistance (IR), which facilitates the development of atherosclerotic CVD. ALT activity may be important not only as a marker of liver diseases but also as an indicator of general health.[9] NAFLD is characterized by excessive fat accumulation in the liver (hepatic steatosis).Nonalcoholicsteatohepatitis (NASH) is characterized by steatosis, liver cell injury, and inflammation. The mechanism of NAFLD is unknown but involves the development of IR, steatosis, inflammatory cytokines, and oxidative stress (OS).[10]

AST levels were found to be associated with an increased risk of only diabetes. Both normal and increased levels of ALT are associated with long-term development of multiple metabolic disorders, indicating potential for ALT values as biomarkers for the risk of metabolic disease.[11] γ-GT, ALT, AST and ALP, commonly used markers of liver dysfunction, have been implicated with risk of CVD. Tests for nonlinearity were suggestive of linear relationships of γ-GT and ALP levels with CVD risk. Baseline levels of GGT and ALP are each positively associated with CVD risk and in a log-linear fashion. There may be variations in the associations of ALT with case specific cardiovascular endpoints, findings which require further investigation.[12] Mild elevations of liver enzymes in the upper normal range are associated with features of MetS and NAFLD even in Impaired Glucose Tolerance (IGT) and recently detected T2DM patients. Novel cut-offs for liver enzymes are warranted in order to prevent unnecessary diagnostic work-ups and early detection of NAFLD to reduce the risk of cirrhosis, hepatocellular carcinoma (HCC) and classical CVD in T2DM and IGT patients. [13]

Statistically significant interactions of smoking were observed with both alcohol consumption AST and ALT, each with BMI. The interactions of all were in the same directions as for γ-GT, i.e. synergistic with alcohol and opposite with BMI.The patterns of interaction between smoking and alcohol consumption or BMI with respect to AST and ALT resembled those observed for γ-GT. This renders enzyme induction a less probable mechanism for these associations, whereas it might implicate exacerbated hepatocellular vulnerability and injury.[14] Levels of both AST and ALT were low in Chronic kidney disease (CKD) with and without End Stage Renal failure (ESRD) and the levels become lower as the severity of CKD increases. There is need for separate reference ranges of serum aminotransferases in different stages of CKD.[15] An AST/ALT (AAR) ratio >1.67 was associated with an odds ratio (OR) of 2.0 for Critical Limb Ischemia (CLI) even after adjustment for other well-established vascular risk factors. An increased AAR is significantly associated with patients at high risk for CLI and other cardiovascular endpoints. The AAR is a broadly available and cheap marker, which might be useful to highlight patients at high risk for vascular endpoints.[16]

The AAR ratio, AST to Platelet ratio index (APRI), and Nephrotic Fibrosis Syndrome give widely disparate predictions of liver fibrosis. Participants with a high risk for fibrosis based on NFS had wider pulse pressure and increased odds of hypertension. Whether modifying these risk factors impacts cardiovascular endpoints in NAFLD patients remains unknown.[17] NAFLD is now considered as a hepatic component of MetS. This condition puts patients with NAFLD at an increased risk of atherosclerosis and CVD. [18]

ALT and AST are markers of hepatocellular injury but are highly concentrated in muscle cells. Consequently, muscular dystrophies such as Duchenne muscular dystrophy (DMS), lead to hypertransaminasemia. Elevation in ALT and AST is most striking during the early stages of disease, before onset of or when only subtle signs of muscle disease are present. Thus, the incidental finding of elevated AAR may be the presenting sign of muscle disease in many children and provides an opportunity for early diagnosis. Many physicians, however, pursue extensive workup for liver disease in children who present with the incidental finding of elevated AAR. This results in delayed diagnosis and initiation of treatment and increased expense and may lead to unnecessary invasive procedures. [19]

Impaired lipid metabolism resulting from uncontrolled hyperglycaemia has been implicated in cardiovascular complications in diabetes patients. There was a highly significant correlation between HbA_{1c} and Fasting Plasma Glucose (FPG). Both HbA_{1c} and FPG exhibited direct correlations with Total Cholesterol (TC),Triglycerides (TGs) and LDL-c and inverse correlation with HDL-c; the magnitude of significance for all these lipid parameters being greater with HbA_{1c} than FPG. There was a linear relationship between HbA_{1c} and dyslipidaemia. The levels of serum cholesterol and TGs were significantly higher and of HDL-c significantly lower in patients with worse glycaemic control as compared to patients with good glycaemic control. [20]

It was found that the trend of complexity of Coronary Artery Disease (CAD) increased with increasing age, high HbA1c, high LDL-c, high serum TGs, and low HDL-c levels.[21] Dyslipidemia is one of the major risk factor for CVD in T2DM, characterized by elevated TC, TGs, LDL-c and decreased HDL-c. HbA1c is widely used as an index of mean glycaemia, a measure of risk for the development of diabetes complications and a measure of the quality of diabetes care. The age of T2DM patients were not significantly correlated with FBG and HbA1c. The level of HbA1c shows highly significant correlation with FPG. The Age of T2DM were highly significant and inversely correlated with TC, TGS, LDL-c, where it was not significantly correlated with HDL-c.[22]

Lipid profile level and HbA1c concentration were significantly higher in diabetic patients than control group. There was statistically no significant difference between male and female diabetic patients.

There was positive correlation between age and level of TGs but negative correlation between age and HbA1c in diabetic patients[23]. DM, the ticking bomb has multifaceted impact on the lifestyle of a patient. Apart from physical limitations and stress, diabetes adds to economic burden for the patients. Diagnosis of diabetes mostly do not happen at the right time and many live with it till it was explored through the lab tests done when the patient goes for the treatment of some other ailment. Except for HDL-c & TGs, all other clinical parameters like FPG, PPPG, HbA1c, LDL-c, VLDL-c & TC showed significant positive changes in 4th visit compared to baseline. There was no correlation between HbA1C and lipid values both at the baseline (except some small association in TGs values) and that too at the fourth visit. The limitation of high dropout rates in a study should not be ignored while interpreting the results of this study.[24]

There were no significant differences in the mean values of the different parameters between males and females except the significantly lower mean HbA1c and higher mean HDL-c in females. This may reflect better adherence to diabetic management by females as well as the known higher HDL-c in females due to gender effect particularly estrogen effect during reproductive age. According to Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP), 25% males out of 64 and 41.6% females out of 59 were dyslipidemia. Dyslipidemia was improved in many diabetics with better glycemic control as reflected by HbA1c. Hence, achieving the target of HbA1c will contribute in improving the lipid state, and hence may lessen the diabetic complications in T2DM Patients.[25]

Atherosclerosis leading to Ischemic Heart Disease (IHD) remains the major cause of death and premature disability in developed countries and its prevalence is rising constantly in developing countries. Dyslipidemia due to IR, the major cause of coronary atherosclerosis and IHD is frequently associated with T2DM and is an emerging pandemic with the number of patients increasing rapidly in both developed and developing countries around the world. There was highly significant correlation between HbA1c & TC, LDL-c, TGs, TC/HDL-c ratio and HbA1C & non HDL cholesterol. Also, highly significant inverse correlation between HbA1C & HDL-c was found. Prevalence of dyslipidemia was alarmingly high in T2DM patients. Thus, HbA1c can be considered as a marker of dyslipidemia in T2DM.[26]

Materials and Methods
Selection of patients
Inclusion Criteria: Non-Hospitalised T2DM patients attending diabetic clinic whose HbA1c values > 6.5 were enrolled for this study.
Exclusion Criteria: Non-hospitalised T2DM patients whose HbA1c values <6.5 were excluded for this study.

50 T2DM non hospitalised patients comparing of both males & females (each 25 Nos) in the age group of 27 to 82 years were enrolled for this study. Results available for these patients in the lab were used for this study.

5mL fasting blood samples were collected in a plain tube for enzymes & lipid profile and EDTA tube was used to collect whole blood for HbA1c measurement. All standard precautions were followed such as the use of sterile needle and syringe and vacutainer for sample collections. State of art sophisticated analyser, RX Imola and biorad D-10 analysers were used to measure the analytes in this study.

Accuracy controls obtained from Bio-Rad at two levels were used daily to validate the results obtained in this study.

For statistical analysis, excel software was used to calculate Mean, Standard deviation, Correlation Coefficient and vassarstats software to calculate p values between the analytes compared.

Results

Table II. presents the statistical data (r and p) for all patients, males and females.

S.No.	Patient Group	Analytes Compared	r	p
1	All Diabetic (n=50)	AST Vs TC	-0.262	<0.05
		Vs HDL-c	-0.461	<0.001
		Vs LDL-c	-0.270	<0.05
		ALT Vs TC	-0.298	<0.01
		Vs LDL-c	-0.267	<0.05
		AAR Vs HDL-c	0.261	<0.05
		γ- GT Vs TC	-0.318	<0.01
		Vs HDL-c	-0.488	<0.001
		Vs LDL-c	-0.324	<0.01
		HbA1c Vs TC	0.247	<0.05
		Vs TGs	0.319	<0.01
		Vs VLDL-c	0.319	<0.01
2	Diabetic Male (n=25)	γ- GT Vs TC	-0.374	<0.05
		HbA1c Vs TGs	0.503	<0.01
		Vs VLDL-c	0.503	<0.01
3	Diabetic Females (n=25)	AST Vs TC	-0.440	<0.05
		Vs HDL-c	-0.552	<0.01
		Vs LDL-c	-0.507	<0.01
		Vs TGs	0.501	<0.01
		Vs VLDL-c	0.500	<0.01
		ALT Vs TC	-0.500	<0.01
		Vs LDL-c	-0.505	<0.01
		AAR Vs HDL-c	0.403	<0.05
		Vs TGs	-0.426	<0.05
		Vs VLDL-c	-0.425	<0.05
		γ- GT Vs TC	-0.279	0.08
		Vs HDL-c	-0.565	<0.01
		Vs LDL-c	-0.352	<0.05
		Vs TGs	0.568	<0.01
		Vs VLDL-c	0.567	<0.01

In the case of all patients, AST shows significant negative correlation to TC and LDL-c at p <0.05 and to a highly significant correlation to HDL-c at p <0.001 indicating

Table 1. Mean & SD of Patients studied (all Patients, males & females).

Patient Group		All Patients (n=50)		Males (n=25)		Females (n=25)	
S.No	Test Name	Mean	SD	Mean	SD	Mean	SD
1.	AST	32.7	39.4	23.5	14.2	44.1	53.8
2.	ALT	31.2	29.2	26.3	13.9	37.2	39.4
3.	AST/ALT Ratio	1.1	0.3	1.2	0.3	1.0	0.4
4.	γ- GT	44.2	46.0	45.8	42.1	46.6	52.1
5.	HbA1c	9.1	2.6	8.7	2.6	9.3	3.0
6.	TC	183.4	52.1	184.0	63.2	175.5	49.0
7.	HDL-c	41.7	9.2	41.2	9.7	38.2	9.2
8.	TGs	163.5	92.7	181.8	118.3	150.3	66.5
9.	LDL-c	109.4	45.4	107.7	53.3	108.0	40.8
10.	VLDL-c	32.7	18.5	36.4	23.7	30.1	13.3

that this enzyme is indeed related to lipid profile parameters. ALT shows negative correlations to both TC and LDL-c at P <0.01 and 0.05 respectively. However, AAR gives a positive correlation at P <0.05. When γ-GT is compared, it gives similar significant negative correlations as observed in the case of AST, suggesting that both AST and γ-GT show association to lipid profile in a similar way. HbA1c, on the other hand shows significant positive correlations to TC at p <0.05 and to both TGs and VLDL-c at p<0.01.

When the statistical parameters were compared for males and females separately, while γ-GT shows a significant negative correlation at p< 0.05, it shows significant positive correlations at p<0.01 to both TGs and VLDL-c.

In the case of females, AST shows significant negative correlations to TC, HDL-c and LDL-c, but positive correlations to both TGs and VLDL-c justifying that AST is associated with all the lipid profile. ALT when compared to lipid profile, a significant negative correlations are observed only for TC and LDL-c but the combined AAR gives a positive and negative associations to HDL-c and TGs and VLDL-c respectively. It is interesting to observe that γ-GT shows significant negative correlations to TC, HDL-c and LDL-c, but positive correlations to both TGs and VLDL-c.
From the statistical presentation shown above, all liver enzymes are associated with all lipid profile parameters highlighting the outcome of this study and liver function is related to all cardio vascular diseases.

While HbA1c showed good correlations to many lipid profile parameters in the case of all patients as well in males, it did not show any association to any of the lipid profile parameters and this does not mean that HbA1c, a diabetic monitoring test is not linked to lipid profile and CVD.

Discussion

Many studies have been done in the past on this similar topics and they have predicted AST,ALT,γ-GT and AAR as the three principal liver enzymes which showed associations to each of the lipid profile test and we have proved such findings in our study too (2,3). Among the liver enzymes, ALT has been shown as a prominent marker to assess the cardiac function and in our study too we found out that observation for all patients as well as males and females separately (7,8). Previous study has mentioned that AST test is used only to assess only diabetic risk, but in our study we found out that along with AST, ALT as well as AAR are showing significant correlations to each lipid profile test (11). γ-GT is an important liver specific enzymes and it showed good associations to each lipid profile test in all patients as well as in males and females and this observations are in agreement with previous studies (13,15). Both impaired liver function and hyperglycemia have been implicated in the development of CVD and hence we included all important liver specific enzymes as well as HbA1c to find out their associations to lipid profile and we have shown good associations which are in agreement with previous studies (19, 20). Among the lipid profile tests, LDL-c. HDL-c as well as VLDL-c showed good associations to AST. AST, γ-GT and AAR suggesting that these four parameters are very important indicators to depict alterations in cardiac functions, which are in good agreement with previous observations (25, 26). HbA1c, an important diabetic control monitoring test was also included in this study to link DM also to CVD alterations to see if uncontrolled DM affects cardiac functions. Our inclusion of HbA1 test justified that this test has shown good associations to all lipid profile test in the

case of all patients as well as in males, but we could not find such association in the case of females. We did not include other diabetic profile tests such as FPG and PPPG as these tests may show variability at times due to previous diets. Hence our study has predicted that along with liver specific enzymes such as AST,ALT and γ-GT, HbA1c too was found to be important as additional tests to assess CVD and its alterations.

Conclusions

This study has established that liver enzymes AST, ALT, y-GT, AAR as well as HbA1C are the important tests all of which showed both negative and positive significant correlations to each lipid profile parameters in all patients as well as in males and females. This study suggests that patients who have been diagnosed to have liver dysfunction as well as uncontrolled DM should be screened occasionally for cardiac related diseases. Tests such as AST, ALT, γ-GT and HbA1c should be designed as cardiac function marker tests and such tests should be recommended to clinicians to investigate them occasionally to screen all patients attending cardio clinic. More studies are required in this direction with large number of both non-hospitalised and hospitalized cardiac patients who are having liver diseases as well as DM along with CVD to screen the tests done in this study.

Conflict of Interest

None

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