E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2019; 1(2): 54-57
Received: 02-01-2019
Accepted: 20-10-2019

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A study of liver dysfunction in type 2 diabetes mellitus and its correlation with microalbuminuria

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DOI: https://doi.org/10.22271/27069567.2019.v1.i2a.376

Abstract
Diabetes mellitus is a chronic condition that occurs when the body cannot produce enough or effectively use of insulin. Compared with individuals without diabetes, patients with type 2 diabetes mellitus have a considerably higher risk of cardiovascular morbidity and mortality, and are disproportionately affected by cardiovascular disease. Most of this excess risk is it associated with an augmented prevalence of well-known risk factors such as hypertension, dyslipidaemia and obesity in these patients. However the improved cardiovascular disease in type 2 diabetes mellitus patients can not be attributed solely to the higher prevalence of traditional risk factors. Therefore other non-traditional risk factors may be important in people with type 2 diabetes mellitus. Cardiovascular disease is increased in type 2 diabetes mellitus subjects due to a complex combination of various traditional and non-traditional risk factors that have an important role to play in the beginning and the evolution of atherosclerosis over its long natural history from endothelial function to clinical events. Statistical analysis was performed using student t test at level of significance 0.0001 and Pearson's correlation coefficient at level of significance of 0.05. The study subjects were chosen after performing liver function tests. Ultrasonography was performed to diagnose hepatic changes such as fatty infiltration, Non-alcoholic fatty liver disease (NAFLD) and Non-alcoholic steatohepatitis (NASH); secondary to Diabetes mellitus. Those found to have NAFLD and elevated levels of enzymes were further evaluated for presence of microalbuminuria. Among the liver enzymes, SGOT, SGPT and ALP showed highly significant positive correlation with duration of the disease, HbA1c levels, altered liver echotexture, age and BMI of the patients at $p< 0.05$. 31 (31%) among these study subjects were found to have microalbuminuria. Thus presence of renal dysfunction among diabetic subjects with liver dysfunction was found to be highly significant at $p< 0.0001$.
In conclusion, our study found that pathophysiology of T2DM indeed contributes to an elevation in liver enzymes, especially SGOT, SGPT and ALP and results in an alteration of hepatic echotexture as evidenced on Ultrasonography. Microalbuminuria is a commonly used for screening for nephropathy. In addition, evaluation of liver enzymes by biochemical tests and performing ultrasonography in T2DM patients at regular intervals may assist in preventing undue progression and worsening of disease by enabling earlier initiation of appropriate management.

Keywords: Type 2 Diabetes mellitus, SGOT, SGPT, ALP, GGT, microalbuminuria

Introduction
Diabetes Mellitus remains a tremendous challenge to public health worldwide. Diabetes and Hypertension are common diseases that coexist at a greater frequency than chance alone would predict. Hypertension in the diabetic individual markedly increases the risk and accelerates the course of cardiac disease, peripheral vascular disease, stroke, retinopathy, and nephropathy. Type 2 Diabetic patients may be hypertensive for years prior to the onset of overt diabetes. At the time of diagnosis of type 2 Diabetes Mellitus, hypertension is found in approximately 70-80% of patients. Still blood pressure rises further in those patients who subsequently develop diabetic nephropathy. Obesity, insulin resistance, hypertriglyceridemia, elevated levels of low-density lipoproteins, decreased levels of high-density lipoproteins, and abnormal glucose tolerance and hypertension, together with genetic susceptibility and abdominal obesity are predisposing risk factors for vascular inflammation which by the release of excess of reactive oxygen species initiate degradative processes in multiple organ systems, notably the hepatic and renal system. There exists an early phase of diabetic renal disease called incipient diabetic nephropathy characterised by increased albumin excretion in the range of 30-300mg/day. This stage of microalbuminuria has been proved to be reversible with adequate and regular glycemic control. Without treatment this stage of disease can progress to overt nephropathy and gradually such patients develop end-stage renal disease.

Microalbuminuria in patients with DM has been positively associated with advancing age, female sex, poor glycemic control, longer duration of DM, diabetic retinopathy, and coexisting hypertension. Diabetes mellitus is reaching epidemic proportion in India. The level of morbidity and mortality due to diabetes and its potential complications are enormous and pose significant health care burden on family and society. India has more than 62 million individuals currently diagnosed with the disease. It is predicted that by 2030, India may have 100 million individuals afflicted with diabetes mellitus. Studies done in different parts of the world on the prevalence of NAFLD in type 2 diabetes mellitus have shown varying figures. Also the prevalence of NAFLD in association with the duration of diabetes mellitus has been studied and the results show conflicting views. However studies correlating hepatic dysfunction and nephropathy in diabetes mellitus are very few. Hence this study was conducted to correlate liver dysfunction and renal dysfunction in diabetes mellitus by comparing various parameters such as liver enzymes, abdominal ultrasonography and urine spot micro albumin which can serve as a better aid in diagnosis and management.[2]

Objectives of the study

1. To study liver dysfunction in type 2 Diabetes Mellitus.
2. To correlate liver dysfunction with microalbuminuria.

Materials and methods

Source of data

Patients admitted in Shadan Institute of Medical Sciences, aged more than 30 years diagnosed with type 2 diabetes mellitus.

Study design

This was a correlative study on 200 patients carried out over a period of 18 months starting from SIMS Hyderabad, January 2017 to June 2018.

Informed consent was taken from the individuals prior to including them in the study. Patient details, detailed history, clinical features along with investigation report were documented in a preformed sheet.

Investigations included Complete Blood Count, Serum Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Total Serum Protein, Serum Albumin, Serum Globulin, Prothrombin Time and International Normalized Ratio, Fasting Lipid Profile, Ultrasound Abdomen, HBs Ag, HCV, Serum Urea, Serum Creatinine, Urine Spot Microalbumin, HbA1c and GGTP.

The results of liver function tests were correlated with Microalbuminuria.

Inclusion Criteria

All patients above 30 years diagnosed with type 2 diabetes mellitus (recently and previously diagnosed).

Exclusion Criteria

1. Patients with history of alcohol intake more than 9 units per week.
2. Patients with history of Hepatitis B and Hepatitis C.
3. Patients with history of intake of methotrexate, amiodarone, glucocorticoids, synthetic estrogens, nucleoside analogues for more than a month.
4. Patients with history of renal dysfunction prior to onset of diabetes mellitus.

Data Analysis

Collected data was analyzed by frequency, percentage, mean, standard deviation, Karl-pearson correlation coefficient, student t-test and Chi-square test using SPSS 21.0 for Windows.

Results

This study was done on a total number of hundred patients with Type 2 Diabetes Mellitus admitted to Shadan Institute of Medical Sciences. The complete profile of patients studied is presented below:

Overall, the 100 participants of the study had a mean age of 58.15 years, mean body mass index (BMI) of 23.62 kg/m^2, mean HbA1c of 10.3% and mean duration of diabetes of 9.48 years.

Table 1: Demographic characteristics of patients

Demographic categories	Characteristics	N	(%)
Age group (years)	40 and below	16	8.0
	41 – 50	44	22.0
	51 – 60	56	28.0
	61 – 70	60	30.0
	Above 70	24	12.0
Gender	Male	100	50.0
	Female	100	50.0
BMI (kg/m^2)	≤18	14	7.0
	≥25	92	46.0
	18-25	94	47.0
Total		200	100

Liver dysfunction

Liver dysfunction among study subjects was estimated based on elevated laboratory values of liver enzymes such as SGOT, SGPT, Alanine aminotransferase (ALP), GGTP, Bilirubin, Prothrombin Time and INR.

46 % of the study subjects were found to have elevated levels of SGPT, 38% with SGOT, 35% with ALP, 15% with GGT and 19% with elevated Total Bilirubin levels.

Table 2: Elevated Liver enzymes

Elevated Liver enzymes		Number (n)		Percentage (%)	
SGPT(>300IU/L)	Mild (< 5 times the upper limit)	92	20	46.0	21.7
	Moderate (5-10 times the upper limit)		20		21.7
	Severe (>10 times the upper limit)		52		56.5
SGOT(>200IU/L)		76		38.0	
ALP(>120IU/L)		70		35.0	
GGT(>45IU/L)		30		15.0	
Bilirubin(>1.04 mg/dL)		38		19.0	

Table 3: Distribution of impaired Liver Function test parameters

	Number (n)	Percentage (%)
PT(>14 seconds)	28	14.0
INR(>1.20)	32	16.0

Duration of diabetes in study subjects

Among the patients in our study, a majority of our study subjects i.e. 142 patients(71.0%) had Type 2 Diabetes Mellitus for duration of ≤ 5 years (including the recently diagnosed patients) with the remaining 29% having been on treatment for ≥5 years.

Table 4: Correlation of Liver function test parameters with Duration of Diabetes mellitus

		Duration of Disease		Total	p value
		≤5 years	≥5 years		
Elevated Liver Function Test parameters	SGOT	6	70	76	0.005(HS)
	SGPT	10	82	92	0.005(HS)
	ALP	12	58	70	0.000(HS)
	GGTP	10	20	30	0.000(HS)
	Bilirubin	16	22	38	0.0189(sig)
	PT	10	18	28	0.000(HS)
	INR	8	24	32	0.000(HS)

HS-Highly significant, NS- non significant

Table 5: Distribution of patients based on HbA1c values

HBA1C (%)	Number (n)	Percentage (%)
≤8	36	18.0
8-10	82	41.0
≥10	82	41.0
Total	200	100.0

Correlation of Liver dysfunction with elevated Glycated Hemoglobin

Table 7 shows the correlation between degree of abnormality in HbA1C values and liver dysfunction. This shows statistical significance with p value of 0.003 and 0.000 for mildly and grossly elevated HbA1C levels respectively.

Table 6: Correlation of Liver dysfunction with elevated Glycated Hemoglobin

		Liver Dysfunction		Total	p value
		≤5 years	≥5 years		
Glycated Hemoglobin (%)	≤8	20	16	36	0.187 (NS)
	8-10	26	56	82	0.003(HS)
	≥10	30	52	82	0.000(HS)

HS-Highly significant, NS- non significant

Out of the 200 patients, 110 (51%) were on both OHA and Insulin, 1 patient (1%) on Insulin alone and the remaining 48 (48%) on only anti diabetic drugs for management of Diabetes.

Table 7: Correlation of Liver dysfunction with BMI of patients

		Liver Dysfunction	p value
BMI (kg/m^2)	≤18	14	0.056 (NS)
	18-25	94	0.0001(HS)
	≥25	92	0.0001(HS)

HS-highly significant, NS- not significant

As shown in Table 10, there was a statistical significance between increased BMI and presence of liver dysfunction among patients with Diabetes mellitus.

Table 8: Correlation of Liver dysfunction with Ultrasonography findings

Liver Dysfunction	Ultrasonography findings			
	Normal	Abnormal	Total	P value
	112	88	200	0.0001(HS)

It was found that among patients with elevated liver enzymes, 44% had hepatic changes on Ultrasonography. This was found to be highly significant with p=0.0001

Table 9: Comparison of age and BMI with microalbuminuria

			Pearson coefficient	p value
Age group (in years)	40 and below	16	0.379	**0.000 (HS)**
	41 – 50	44		
	51 – 60	56		
	61 – 70	60		
	Above 70	24		
BMI (kg/m^2)	≤18	14	0.347	**0.000 (HS)**
	≥25	92		
	18-25	94		

HS-highly significant

Age and BMI were found to have positive correlation with elevated urine microalbumin with p value <0.0001.

Discussion

The present study assessed the prevalence of liver dysfunction and renal microvascular complications in a group of patients with type 2 diabetes admitted at a tertiary care hospital in Mangalore. In our study we found that most of the subjects belonged to the age range of 61-70 years with a mean age of 58.15 years.

Among the patients in our study, liver dysfunction, as characterized by elevated levels of one or more of the liver

enzymes; ALT, AST, GGT and ALP was found to have positive correlation with the age of the patients, duration of Diabetes mellitus and glycemic control (HbA1C). There was also a statistical significance between increased BMI and presence of liver dysfunction. These findings are in agreement with a similar study by Idris [5] *et al*. where liver dysfunction in diabetic patients was strongly correlated with age, BMI, duration of disease and glycemic control of the study subjects.

GGT is a known as a marker of hepatobiliary disorder. In Diabetes, there is a release of free radicals which consume glutathione and induces the expression of GGT in the liver. In our study we found a significant proportion of individuals (15%) with elevated GGT. Various studies have explained the association of GGT with Type 2 diabetes and its role in hyperglycemic state which supports the findings of our study [5, 6, 7].

NAFLD is commonly seen in Diabetic individuals. The possible reason behind this pathogenesis as explained by prior research is said to be insulin resistance which promotes lipolysis and therefore increased fatty infiltration of the hepatic tissue [7]. The resultant inflammation and oxidative stress leads to elevated liver enzymes. The findings of our study are consistent with this hypothesis as we found a strong correlation between liver dysfunction as estimated by biochemical tests and presence of radiological evidence of the same.

Renal dysfunction among patients with type 2 diabetes mellitus

The presence of microalbuminuria is a marker of endothelial dysfunction, and indicates a gradual progression to nephropathy and end stage renal disease. In our study we found that 31% of the subjects with elevated liver enzymes and fatty changes on ultrasonography had microalbuminuria.

Our study similarly concludes that Non-alcoholic fatty liver disease is indeed associated with an increased prevalence of microalbuminuria- an early indicator of nephropathy, and a risk of developing kidney disease in type 2 diabetic patients [6, 7].

The difference in results with this study might be related to the difference in characteristics of the Korean participants in terms of race, a greater proportion of female subjects in the study, lower body mass index (BMI) and more patients belonging to younger age group with poorer glycemic control compared with those of our study [7].

Conclusion

The present study was undertaken to study liver dysfunction in Diabetes and to correlate these findings with microalbuminuria among these patients. The objective was to assess whether there is a relationship between these parameters in diabetic patients in order to predict the onset and development of renal dysfunction, before landing into the stage of nephropathy and end stage renal disease.

Hepatic dysfunction in diabetic patients showed a correlation with BMI, age, duration of disease and glycemic control. Moreover, 31% patients with hepatic dysfunction had microalbuminuria.

These findings of our study further stress on the need for early and adequate patient care to provide good glycemic control in patients with type 2 diabetes. Regular screening should be done, even for detection of NAFLD during routine workup as it will further serve as an indicator to look for coexistence of other chronic diabetic complications (such as Retinopathy) in an otherwise asymptomatic patient.

It is concluded that increase in circulating liver enzymes is an early manifestation of diabetic renal disease (micro vascular complication) and hence estimation of both microalbuminuria and hepatic enzymes along with radiological evidence of NAFLD is useful in assessing the progress of disease and identifying the risk category for complications, such as diabetic nephropathy which are main causes for mortality and morbidity among diabetes mellitus patients.

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