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Hepatic Dysfunction in Type-2 Diabetes Mellitus

Authors
Dr Butungeshwar Pradhan[1], Dr Jyotiprakash Patel[2]
[1]Associate Professor, Department of Internal Medicine, VSSIMSAR, Burla
[2]Junior Resident, Department of Internal Medicine, VSSIMSAR, Burla
*Corresponding Author
Dr Jyotiprakash Patel
Junior Resident, Department of Internal Medicine, VSSIMSAR, Burla, Sambalpur, Odisha, 768017

Abstract
Background: *Type-2 Diabetes Mellitus (T-2 DM) patients, with hyperglycemia, have increased intracellular glycogen storage and Free Fatty Acid (FFA) accumulation in hepatocyte in response to insulin resistance leading to increase glycogen synthesis and FFA production which are toxic to hepatocytes, causing hepatocellular injury, fatty changes in liver and elevation of aminotransferases levels. Raised liver enzymes are marker of hepatocellular injury and can be used as an indirect evidence of insulin resistance in Type-2 DM.*
Objective: *To know the extent of liver structure and functions are modified in Type-2 DM patients, by estimating serum biochemical analysis of liver functions in relation to glycemic status and Ultrasound study of liver to detect fatty changes.*
Material and Method: *This was an observational cross sectional study on 100 T2DM patients and 100 age and sex matched controlled non-diabetic cases attending the Department of Medicine, VSSIMSAR. BURLA from October 2017 to November 2019. Biochemical tests were done for assessment of glycemic status were, FBS, PPBS, HbA1C and for liver functions, total, direct and indirect bilirubin, ALT, AST, ALP, Total protein and serum Albumin. Ultrasonography study of liver was done for detection of hepatic structure and pathology.*
Result: *Total bilirubin was elevated in 13% and Direct bilirubin elevated in 36%, AST, ALT, ALP was increased in 46%, 62%, and 46% cases respectively from normal cutoff values. Serum albumin value was decreased in 44%. On USG study 16 T-2DM patients (17.39%) had Fatty liver changes. Type-2 DM patients with fatty liver changes had raised liver enzymes, PPBG and HbA1C, suggesting high insulin resistance state in comparison to patients without fatty liver changes..*
Conclusion: *Mild raised liver enzymes and fatty liver changes may be used as an indirect biomarker of insulin resistance in type-2 DM.*
Keywords: *Type-2 Diabetes, Liver Functions, Insulin resistance, Fatty liver, ALT, AST, ALP, HbA1c.*

Introduction

Diabetes mellitus (DM) refers to a group of metabolic disorders characterized by hyperglycemia with disturbances in carbohydrate, lipid, and protein metabolism due to absolute or relative deficiency of insulin secretion. Type 2 DM is mainly associated with insulin resistance and inadequate compensatory insulin secretory

response.[1] Worldwide the prevalence of diabetes was estimated to be 2.8% in 2000 and approaching to 4.4% in 2030. The total number of diabetes is projected to increase from 171 million in 2000 to 366 million in 2030.[2]

Hepatocellular glycogen accumulation occurs due to increased glycogen synthesis, leading to hepatomegaly and liver enzymes abnormalities in poorly controlled T2D with typical abnormal biochemical findings of mild to moderately elevated aminotransferases levels and with normal liver synthetic function. All these biochemical disturbances and hepatomegaly are reversible with good glycemic control.[2]

Non-alcoholic fatty liver disease (NAFLD) is associated with insulin resistance and is the main cause of chronic liver disease associated with diabetes, obesity and metabolic syndrome. Insulin resistance associated with increased lipolysis, leading to increase production of Free Fatty Acid (FFA) and accumulation in hepatocytes, which is toxic to hepatocyte and causing hepatocellular injury. Liver enzymes are marker of hepatocellular injury and can be used asevidence of insulin resistance in Type-2 DM and non-alcoholic steatohepatitis (NASH). Without treatment, NAFLD will eventually lead to decompensated steatosis with necroinflammation and fibrosis, i.e stage of non alcoholic steatohepatitis (NASH). NASH is a leading cause of end-stage liver disease and also contributor of cardiovascular disease in T-2DM.[3] Chronic hyperinsulinemia and relative insulin resistance also associated with increased lipogenesis and fattyliver changes. Moreover, hepatocellular accumulation of free fatty acid is leads to increased oxidative stress levels and increase in proinflammatory cytokines production, i.e. Tissue Necrotic Factor.[4]

The Aim of this study: Primary aim was to find out the extend of liver function derangement in Type 2 DM patients in comparison to non-diabetic healthy subjects and the secondary aim was to compare the liver function derangement in Type-2 Diabetes mellitus with fatty liver changes and patients without fatty liver changes.

Material and Method

The present study was conducted in 100 consecutive cases of Type-2 Diabetes mellitus patients and 100 cases of non-diabetic apparently healthy subjects attending the outdoor /indoor department of medicine, after obtaining written consent of patients and approval of institutional ethics committee. (Redg. No, ECR/861-Inst/OR/2016**,** Communication on VIREC Decision No.2017/I-F-CT -01/025).Inclusion criteria was :(1) Type-2 DM patients aged>15 years with or without antidiabetic drugs.(2) Newly diagnosed T2DM patients. Exclusion criteria were, Gestational Diabetes mellitus, Type-1 DM, NAFLD without T-2DM,ChronicAlcoholics, Type-2 DM patients taking hepatotoxic drugs i.e. on Anti Tubercular drugs, amiodarone, history of other acute and chronic liver diseases, HBsAg positive or HCV antibody positive, HIV antibody positive , or any other hepatobiliary disease screened by USG study of liver .

Under aseptic precaution venous blood is collected ,and measurement of FBG(Fasting blood glucose), PPBG (Post prandial blood glucose), HbA1c. Liver transaminase i.e. ALT, AST, and ALP levels was done. Serum total, direct and indirect bilirubin levels, and total serum protein, Serum albumin levels were done. USG study of liver was done in all cases. The normal reference range of LFT (liver function tests) for this study was taken as Total bilirubin: 0.3-1mg⁄dl, direct bilirubin <0.3 mg/dl, AST: 0-35 IU/L/, ALT: 0-35 IU/L, ALP: 30-120 IU/L and serum albumin: 3.5-53 g//dl⁄ and, Total protein: 6-8.3 g/dl.[5] Mean, SD, correlation parameter are calculated, statistical significant was accepted at P value of <0.05.Data were analysed through SPSS-21.0 Software and result was interpreted in tabular and graphical methods.

Results

Table 1- Showing elevated FBG, PPBG and Liver enzymes and decreased serum albumin levels in Type-2 DM population in comparison to non-diabetic apparently healthy population. Total serum bilirubin levels were not statically significant($p>0.05$), but FBG,/PPBS,SBD,AST,ALT and ALP, Serum Albumin and Total serum Proteins were statically significant ($p<0.05$).

PARAMETER	APPARENTLY HEALTHY	TYPE-2 DM	P VALUE
AGE	53.27±12.40	56.43±10.35	0.05
FBG	98.24±17.41	204.77±83.44	P<0.0001
PostprandialBG(PPBG)	124.21±16.34	285.78±116.76	P<0.0001
Total Serum bilirubin	0.56±0.41	0.622 ± 0.344	0.248
Direct Serum Bilirubin(SBD)	0.21±0.19	0.298 ±0.21	0.002
AST	28.48±17.89	39.1 ± 21.27	0.0002
ALT	23.54±17.15	47.45 ± 22.49	P<0.0001
ALP	71.9±22.28	139.64 ± 78.48	P<0.0001
Serum Albumin	3.69±0.56	3.45±0.79	0.014
Total Protein	6.01±0.69	6.59 ± 0.96	P<0.0001

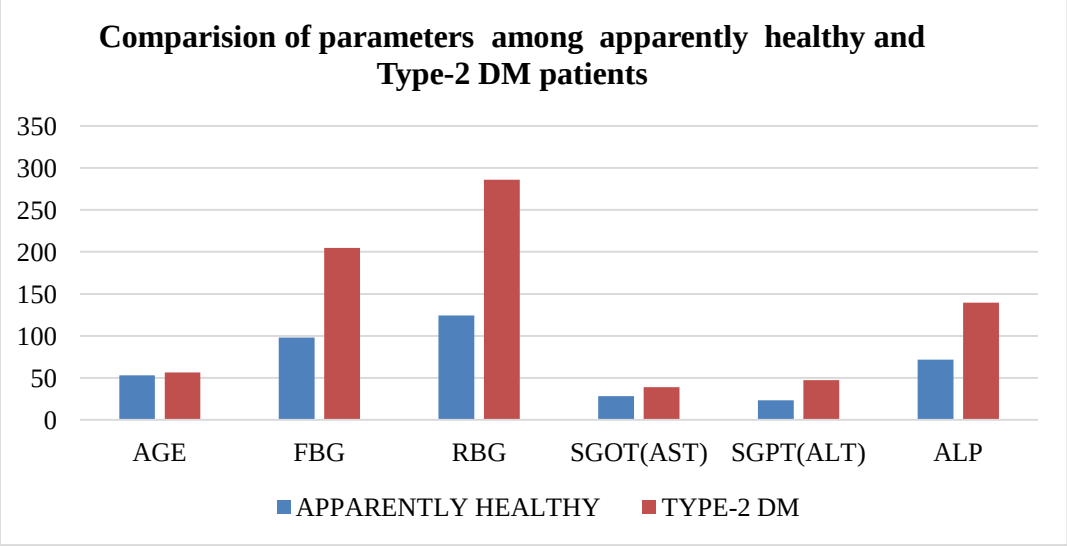

Figure-1-Showing elevated FBG, RBG (PPBG)/and Liver enzymes AST, ALT, ALP levels in Type-2 DM population in comparison to non-diabetic healthy population.

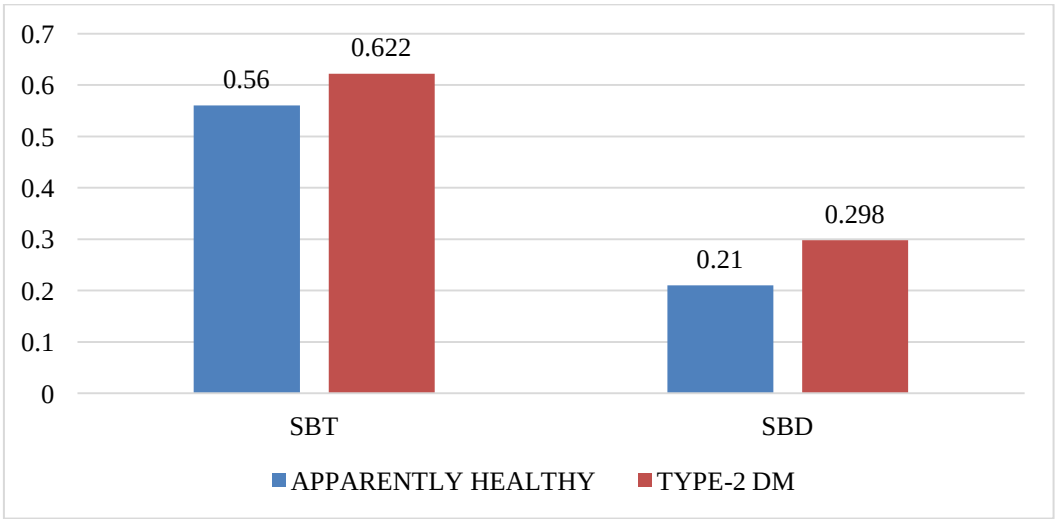

Figure-2- Showing relative increase in serum total bilirubin (SBT) and serum direct bilirubin (SBD) in Type-2 DM patients in comparison to non-diabetic apparently healthy population.

Table 2- Showing correlation analysis between HbA1c and liver parameters. There was positive correlation between HbA1c and ALP (r=0.231, p<0.05).There was also positive correlation between HbA1c and AST (r=0.139), but statistically not significant

CORRELATION ANALYSIS BETWEEN HbA1c AND LIVER FUNCTION TESTS IN TYPE-2 DM PATIENTS.		
LIVER PARAMETER	**CORRELATION COEFFICENT(r) VALUE**	**P VALUE**
SBT	-0.05	0.621
SBD	-.016	0.11
AST	0.139	0.167
ALT	0.231	0.02
ALP	-0.162	0.10
SERUM ALBUMIN	-0.001	0.99

Table-3-Showing relatively more increase in liver enzymes in Type-2 DM with fatty liver than Type-2 DM without fatty liver. P value of serum bilirubin total and direct serum bilirubin were statically significant (p<0.05).

LIVER PARAMETERS	**TYPE-2 DM WITHOUT FATTY LIVER CHANGES**	**TYPE-2 DM WITH FATTY LIVER CHANGES**	**P VALUE**
AGE	54.84 ± 10.39	53.25 ± 9.93	0.693
FBG	191.92 ± 89.69	181.87 ± 64.52	0.765
PPBG	251.84 ± 98.95	271.5 ± 88.37	0.60
RBG	283.52 ± 126.60	275.5 ± 120.09	0.862
HbA1c	7.85 ± 2.55	8.17 ± 1.82	0.738
SBT	0.56 ± 0.20	1.30 ± 0.25	P<0.0001
SBD	0.25 ± 0.14	0.57 ± 0.19	P<0.0001
SGOT (AST)	39.86 ± 22.77	45 ± 17.75	0.552
SGPT (ALT)	42 ± 21.09	50.62 ± 16.07	0.282
ALP	124.68 ± 70.49	144.37 ± 87.22	0.494
Sr.ALB	3.47 ± 0.68	3.43 ± 0.91	1
Tot. Protein	6.43 ± 0.84	6.75 ± 0.99	0.347

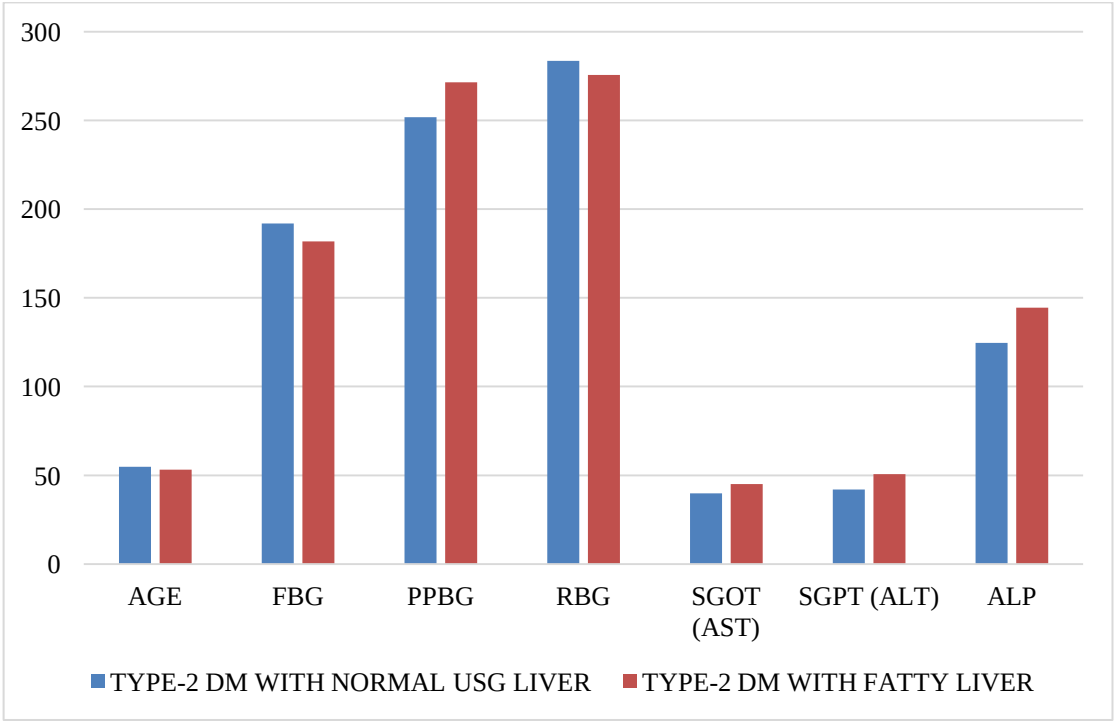

Figure -3-showing relative increase in FBG, PPBG, RBG, AST, ALT, and ALP in Type-2 DM patients with fatty liver in comparison to Type-2 DM with normal USG of liver.

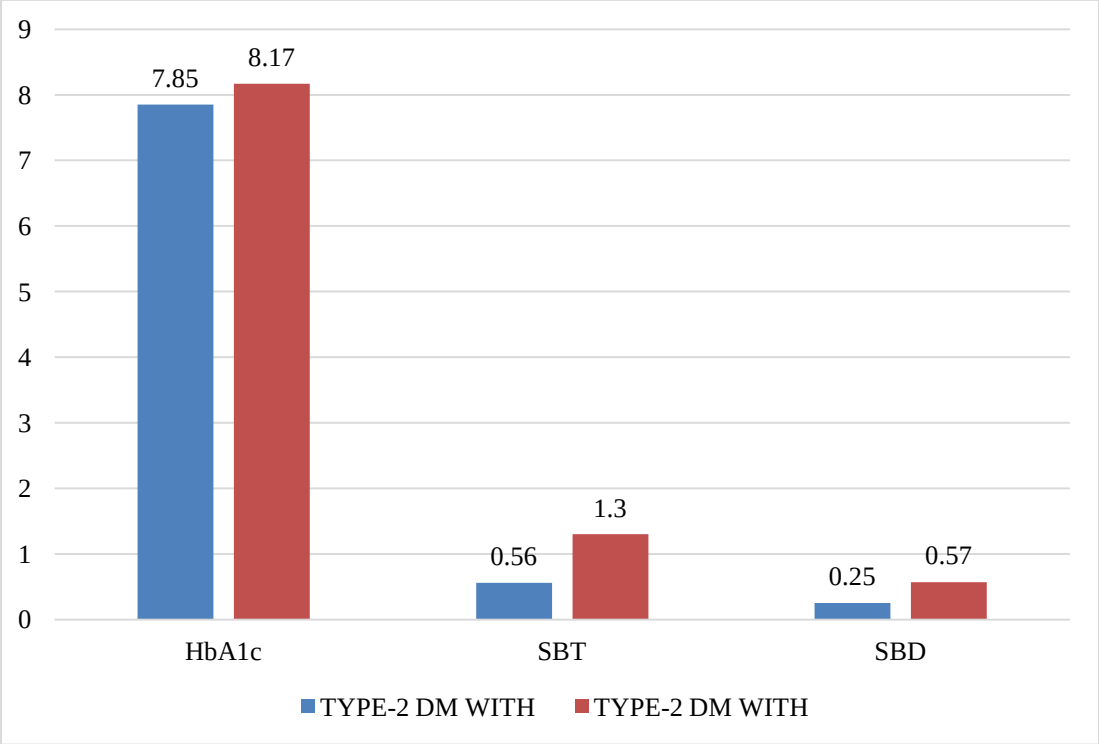

Figure-4- Showing relative increased in serum HbA1c, serum total bilirubin, serum direct bilirubin in Type-2 DM patients with fatty liver changes (Red), in comparison to Type-2 DM without fatty liver changes (Blue).

Discussion

Out of 200 cases of study subjects, there were 41% male and 59% female in apparently healthy group and there were 54% male 46% female in Type-2DM group. The mean (±SD) age of apparently healthy non-diabetic group was 53.27±12.40 years, and mean (±SD) age of Type-2 DM populations was56.43±10.36 years. In T-2DM patients group the mean value of FBG was 204.77±83.44mg/dl, and PPBG was 285±116.76mg/dl, Serum total bilirubin was 0.62±0.34 mg/dl, Serum direct bilirubin was 0.3±0.21mg/dl, AST levels were 39.1±21.26IU/L,ALT levels were 39.1±21.26IU/L, ALP was139.64±78.48 IU/L , mean serum albumin was3.45±0.79g/dl ,total protein was 6.62±0.69g/dl . Mean value of HbA1c % in Type-2 DM was 8.03 ± 2.17 %. The liver enzymes in Type-2 DM patients were mildly elevated above normal reference range.

The mean value of all parameters of liver function tests were deranged in type 2 DM cases. There was elevated FBG, PPBG, HbA1c% and Liver enzymes. The total serum bilirubin was increased in 13% cases and serum direct bilirubin was increased in 36% cases ,AST levels was increased in 46% cases, ALT levels were increased in 62% cases and ALP levels were increased in 46% cases .Serum albumin levels were decreased in 44% cases and serum total protein decreased in 18% cases .On comparison of FBG,PPBG, Serum direct bilirubin, Serum total bilirubin, AST , ALT, ALP , Serum albumin and Total Protein of non-diabetic and Type-2 DM ,all parameter were raised significantly in T2DM patients ($p<0.05$), except serum total bilirubin were not raised.

Ni et al. in a study of 81 T-2DM patients in Myanmar, reported that around 20% of the patients had elevated level of ALT and AST levels.[6] Gonem *et al.* in study of 959T-2DM patients reported raised ALP, ALT and bilirubin levels, similar to present study .[7]In a cross sectional study by Meybodi et al, reported raised levels of ALT and AST in 10.4% and 3.3% of type 2 DM patients respectively.[8] Bora et al[9] from India and Balogun et al.[10] from Nigeria reported a high prevalence of deranged LFTs in

71.2% and 70% respectively among T2DM patients. On Pearson's correlation coefficient (r) test, it was observed that rise in concentration of serum ALT levels correlate significantly with rise in HbA1c% levels (r=0.231,p=0.02, p<0.05) and statistically significant in Type-2 DM patients. Fatema. K et al observed positive correlation which was statically significant (p<0.05) between HbA1c with ALT levels similar to this study. [11]Abnormal liver function tests in diabetes patients can be attributed to several factors. Firstly, Hyperinsulinemia might directly associate with hepatic insulin resistance and associated fatty liver changes. Enhanced FFA accumulation in liver is known to be directly toxic to hepatocytes, leading to increase in transaminases and diminished synthetic capacity of liver.[12]Secondly, The insulin-resistant state is also characterized by an increase in pro-inflammatory cytokines such as tumor necrosis factor (TNF), which may also contribute to hepatocellular injury.[13] In our study of Type 2 –DM patients with fatty liver had marked increased in total Serum bilirubin, serum direct bilirubin, AST, ALT, ALP levels in comparison to Type 2 DM with no fatty liver changes. Raised total serum bilirubin, serum direct bilirubin were statistically significant (p<0.05)and rest liver parameter AST, ALT, ALP, Serum. albumin, and total Protein were not raised significantly (p>0.05). In this study of Type-2 DM patients with fatty liver has raised Liver function test and raised PPBG and HbA1c in comparison to Type-2 DM without fatty liver suggesting higher insulin resistance state in Type-2 DM with fatty liver changes. The higher mean value of PPBG and HbA1c in Type- 2 DM with fatty liver associated with poor glycemic control due to marked insulin resistance in the liver.

Conclusion

Liver function test parameters such as serum direct bilirubin, AST, ALT, and ALP levels were higher and serum albumin is lower in patient with Type-2 DM in comparison to healthy subjects. These raised levels of liver function tests might be similar to non-alcoholic steatohepatitis (NASH) pathology, dueto insulin resistance in the liver. Moreover, our study suggested that Type-2 DM with fatty liver have deranged liver function tests and had raised FBS, PPBG and HbA1c% in comparison to Type-2 DM without fatty liver suggesting insulin resistance may be the main factor. Therefore, routine screening of liver function test should be done to know the indirect evidence of insulin resistance and treatment strategy should beaim to target insulin resistance for better glycemic control in Type-2 DM with fatty liver changes as well as to prevent further hepatic damage.

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