Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2017; 9(5): 358-362
doi: 10.25258/ijpcr.v9i5.8596

ISSN- 0975 1556

Research Article

A Cross Sectional Study to Assess Liver Fibrosis in Patients with Diabetes and Metabolic Syndrome

Syed Safiullah Ghori[2,3*], Hafsa Khalid[1,3], Mohammed Alim[1], Mohammed Abdul Quddus[3]

[1]Department of Endocrinology,Osmania General Hospital,Afzalgung,Hyderabad Telangana, India.
[2]Pharmacology Research Lab, Anwar-ul-Uloom College of Pharmacy, New Mallepally, Hyderabad 500016, Telangana, India.
[3]Department of Hospital and Clinical Pharmacy, Anwar-ul-Uloom College of Pharmacy, New Mallepally, Hyderabad 500016, Telangana, India.

Available Online: 25th May, 2017

ABSTRACT

The present study was conducted in Osmania General Hospital,Hyderabad.The study included evaluation of liver fibrosis in patients with diabetes and metabolic syndrome. Liver fibrosis is now being considered as reversible process which is characterized by excessive accumulation of extra cellular matrix. The use of non-invasive methods to assess liver fibrosis in patients with HCV, Non-Alcoholic Fatty Liver Disease (NAFLD) and alcohol abuse has been well validated. However use of these non-invasive methods in patients with diabetes mellitus and metabolic syndrome assessed might develop fibrosis during asymptomatic stages. Hence we tried to use these non-invasive methods in patients with diabetics and metabolic syndrome who are at high risk of developing NAFLD or liver fibrosis in routine clinical practice. This was a single center, prospective study. 50 patients with diabetes and metabolic syndrome attending the endocrinology department of Osmania General Hospital were assessed for fatty liver and enrolled in to the study. NAFLD fibrosis score was used to assess liver fibrosis and BARD score was used for staging of fibrosis as per metavir classificationThe mean age of the patients was 50.8 ± 8.2 with 22 males and 28 females. 90% of the population was found to have some degree of fibrosis. 56% of the patients were at advance fibrosis stage as per the BARD score.Patients with diabetes and metabolic syndrome should be constantly evaluated for liver fibrosis apart from development of diabetes and other complications and to prevent any adverse effects due to waning of liver functions.

Keywords: liver fibrosis, enhanced liver fibrosis, non-alcoholic fatty liver disease, cirrhosis, NAFLD fibrosis score, BARD score.

INTRODUCTION

Liver fibrosis is a reversible process, due to chronic tissue damage characterized by excessive accumulation of extracellular matrix. It is the first stage of liver scarring, this scar tissue slowly builds up and takes over most of the liver, diminishing the normal activities of liver[1]. If untreated liver fibrosis may lead to cirrhosis which is the final stage of liver fibrosis[2]. The onset of liver fibrosis is usually insidious and mostly related to morbidity and mortality after development of cirrhosis. Liver fibrosis has been associated with diabetics, metabolic syndrome, cardiovascular problems and portal hypertension. Obesity is found in 35-100% of liver fibrosis patients and diabetics in 5-55%[3]. The non-alcoholic fatty liver diseased patient is an obese middle aged individual with diabetics.

Liver fibrosis is a common consequence of almost all chronic liver diseases. Asian countries have a higher prevalence of type II diabetes and fatty liver as well as increased rates of hyperinsulinemia and insulin resistance[4]. Epidemiological studies suggest prevalence of Liver Fibrosis in around 9% to 32% of general population in India with higher prevalence in those with overweight or obesity and those with diabetes or prediabetes. The prevalence of Liver Fibrosis has increased over the past two decades to become the commonest disease in Indians. Indians have a high prevalence of insulin resistance and the metabolic syndrome[5]. Liver fibrosis actually represents an emerging disease of clinical interest.The advanced liver fibrosis may lead to development of cirrhosis, hepatocellular carcinoma, portal hypertension, ascites and end stage liver disease. Assessing fibrosis with coexistence disease condition may prevent further progression of fibrosis and advanced liver diseases and also control other diseases progression.

Treatment strategies for liver fibrosis aim to improve insulin sensitivity, modify underlying metabolic risk factors, or to protect the liver from further damage by reducing oxidative stress. Multiple pharmacological interventions have been attempted with variable success. Insulin sensitizing agents such as metformin, thiazolidinedione's and lipid lowering agents have yielded promising results. The removal of the causative agent is the most effective intervention in the treatment of liver fibrosis.

**Author for Correspondence: safiullahghori@gmail.com*

Thus, identifying the presence of liver fibrosis in patients with diabetes and metabolic syndrome is of major important in management of liver fibrosis. This study aims to assess liver fibrosis in type 2 diabetic and metabolic syndrome patients.

MATERIAL AND METHODS

This study was a single center, prospective cross sectional observational study. Patients with diabetes and metabolic syndrome were evaluated for fatty liver by ultrasound imaging and out of 68 screened, 50 patients with fatty liver were enrolled in the study visiting to endocrinology department of Osmania General Hospital. At enrollment patient's case details were obtained in CRF. The clinical profile consisted of age, initial diagnosis, social habits, life style and medication used. The patients were enrolled based on the inclusion criteria and exclusion criteria. The inclusion criteria was patient's age should be above 18 years and patients must have type 2 diabetics and metabolic syndrome. Exclusion criteria were patients with NHYA class III-IV and patients suffering with neurological disease was avoided. This study was conducted for a total period of 6 months (November 2015 to April 2016) out which enrolment of patients was completed in 2 months and study duration was 5 months. This study was approved by the institutional ethics committee and is registered at clinical trial registry of India (CTRI/2014/07/004725).

Physical examination

Diabetes was confirmed with patient's medical history and fasting blood glucose. Modified national cholesterol education program adult treatment panel III[6] was used to define metabolic syndrome. The criteria involved is patients with waist circumference ≥ 94cm for men and ≥ 80cm for women. Increased TGs and low HDL cholesterol. High blood pressure (>130/85 mmHg or treatment of previously diagnosed hypertension). Raised fasting blood glucose (FBG) ≥ 110 mg/dL, known diabetic. Metabolic syndrome was defined by the presence of three or more of these criteria[7] out of which central obesity is mandatory variable.

Anthropometric measurements

Physical examination weight, height, and body mass index waist circumference were measured. BMI was calculated as body weight (kg) divided by the square of height (m2) (BMI=$\frac{weight\ in\ kg}{height\ in\ m^2}$). Waist circumference was measured, during expiration, at the narrowest point between the lower rib and the iliac crest. Overweight and obesity were defined according to the International Obesity Task Force criteria[8].

Biochemical Estimations

Serum lipid profile

Low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol and triglycerides were measured by using common standard laboratory techniques (LDL-C, HDL-C, CHOL [plus 2nd generation]) and TG assay.

Hematological parameters

Fasting blood glucose, hemoglobin, platelet count and HBA1c weremeasured according to international guidelines[9].

Liver Function Tests

Serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), gamma-glutamyl transferase (GGT), serum bilirubin and total protein were measured by EASL Clinical Practice Guidelines.

Blood Pressure Measurements

Blood pressure monitoring was obtained according to Guidelines of the International Society of Hypertension. Blood pressure readings are recorded, around three readings are obtained at 2-5 minute intervals and average reading of second and third systolic blood pressure and diastolic blood pressure is recorded and further used in the analyses[10].

Noninvasive diagnosis of liver fibrosis

The NAFLD Fibrosis score

NAFLD score is calculated through a formula which includes six variables: age, presence of diabetes, BMI, AST/ALT ratio, platelet count, and albumin[11]. NAFLD fibrosis score was calculated using online calculator (http://www.nafldscore.com).

The BARD score

The BARD score includes the following 3 variables: body mass index [BMI], aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ratio, and presences of diabetes for calculation. The BARD score was calculated using online calculator (http://gihep.com/calculators/hepatology/bard).

RESULTS AND DISCUSSION

Physical examination

The mean age of the population was 50.8 ±1.15 with 22 men and 28 women participants. The mean age of men and women was 52.1±1.76 and 49.7±1.53 respectively. The mean height and weight of the population was 156±1.076 and 67.2± 1.43 respectively. The mean BMI of total population was 27.5±0.48 (Table-1).

Blood pressure measurement

The mean systolic BP of total population was 132.9±2.91 and mean diastolic BPof total population was 81.3±1.57 (Table-2).

Serum Lipid Profile

The mean LDL of total population was 103.8±5.01, HDL mean of total population was 42.5±1.25. The mean cholesterol of total population was 176.3±5.32 and mean triglyceride of total population was 151.9±9.77 (Table-3).

Hematological parameters

The mean FBS of total population was 160±9.75 and mean platelet count of total population was 3,0462000±0.125. The mean haemoglobinof total population was 12.0±0.26, HBA1c meanof total population was 8.27±0.26 and the mean creatinine of total population was 1.01±0.06 (Table-4).

Liver functions test

The mean SGOT of total population was 24.±1.37 and mean SGPT of total population was 36.0±2.44. The mean GGT and bilirubin of total population was 44.4±4.33 and

Table 1: Physical Examination.

Variable	Mean	SEM
Age	50.8400000	1.158239339
Age (Male)	52.18181818	1.76256941
Age (Female)	49.790000	1.535000
Height cm	156.0200000	1.076081326
Weight Kg	67.2600000	1.437631272
BMI	27.5960000	0.481026724

Table 2: Blood Pressure Examination.

Variable	Mean	SEM
Systolic BP	132.9800000	2.912392943
Diastolic BP	81.3800000	1.571919404

Table 3: Serum Lipid Profile Examination.

Variable	Mean	SEM
LDL mg/dL	103.8540000	5.019541576
HDL mg/dL	42.5480000	1.252407445
Total Cholesterol mg/dL	176.3240000	5.321503209
Triglyceride mg/dL	151.9040000	9.772595152

Table 4: Hematological parameter examination.

Variable	Mean	SEM
FBS mg/dL	160.7200000	9.755502477
Platelet Count Lacs/Cmm	3,0462000	0.125724315
Haemoglobin g/dL	12.0480000	0.265533579
HBA1c	8.2760000	0.267483511
Creatinine mg/dL	1.0190000	0.061570766

Table 5: Liver Functions Test.

Variable	Mean	SEM
SGOT__U_L_	24.4600000	1.373878764
SGPT__U_L_	36.0200000	2.441225855
GGT__U_L_	44.4200000	4.331855426
Bilirubin mg/dL	0.4658000	0.033893097
Total Protein g/dL	7.6880000	0.060382455
Albumin g/dL	4.0924000	0.049992293
A:G Ratio	1.1504000	0.029371595

Table 6: NAFLD Fibrosis Score.

Variable	Mean	SEM
Fibrosis score	0.3651000	0.1663

Table 7: BARD Score

Variable	Mean	SEM
BARD score	1.7000000	0.1

0.465±0.033 respectively. The mean of total protein was 7.68±0.06 and mean of albuminof total population was 4.09±0.499. The mean A: G ratio of total population was 1.50±0.029 (Table-5).

Non-invasive Methods

NAFLD Fibrosis Score

The Mean NAFLD fibrosis scoreof total population was 0.4 ±1.2 (Table-9). The high cut off value (>0.676) as per NAFLD fibrosis score was 73% and 17% in males and females respectively, while 27% in males were at indeterminate cut-off value (-1.455 0.676) and 21% in females. 62% were at low cut-off point in females as per the NALFD fibrosis score. Figure 23 shows the distribution patients as per the cut off values of NAFLD fibrosis score (Table-6).

BARD Score

The mean BARD score of total population was 1.70±0.1 (Table-11).56% of patients were at advance fibrosis stage i.e., F3 or F4 while 44% were having fibrosis score of F0-F2 as evaluated by BARD score and scoring (Table-7). A Bard score of 2 to 4 is associated with F3 or F4 stages of fibrosis and a score of less than 2 was considered as strong negative predictive value of advanced fibrosis F0 or F2 as per metavir scoring system.

DISCUSSION

Assessment of liver fibrosis risk has become the accepted method for prevention of further progression of diseases and had approach for better treatment. Many non-invasive methods have been developed for liver fibrosis assessment following the limitation of liver biopsy[12].

First and most fundamentally, the method described was aimed at assessing liver fibrosis by estimation of total liver fibrosis risk. Knowledge of liver fibrosis together with diabetic and metabolic syndrome issues reinforces the need for precise and early diagnosis and treatment of liver fibrosis. By assessing the liver fibrosis risk we hope to convey estimation of risk to the person and also better reflection of the health service implication of liver fibrosis risk factors.

The results shows that 90% of patients with diabetes and metabolic have some degree of liver fibrosis which are consistent with previous epidemiological studies for NAFLD[13,14,15]. However further evaluation needs to be done for classifying these patients based on the pathophysiological mechanism. It is recommended to use the non-invasive biomarkers along with transient elastography which increase diagnostic accuracy for liver fibrosis. Compared to liver biopsy these methods have no contraindications, less risk to the patients, have high applicability and reproducibility with a demerit of accurately staging liver fibrosis, non-specific surrogates of liver. These non-invasive methods with proper physical examination helps in identifying patients for further screening, evaluation and treatment[16]. In our study, males (73%) were at high cut off value suggesting advanced fibrosis. While in females it was only 21%, signifying men to have more prevalence of fibrosis than women. However earlier studies which were done in type 2 diabetic patients shows more prevalence in females than males[17]. The BARD score is another non-invasive method for assessing liver fibrosis as per metavir scoring system. NAFLD fibrosis score and BARD scoring was used to asses liver fibrosis suggesting 56% of the population at either F3 or F4 stage of fibrosis.

CONCLUSION

In conclusion, the findings support the hypothesis that NAFLD is associated with a moderately increased risk for

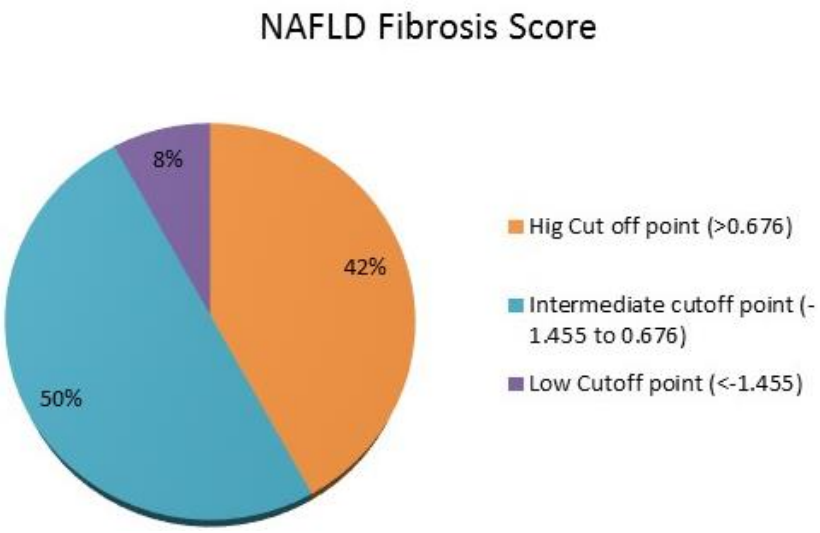

Figure 1: Distribution of NAFLD fibrosis score.

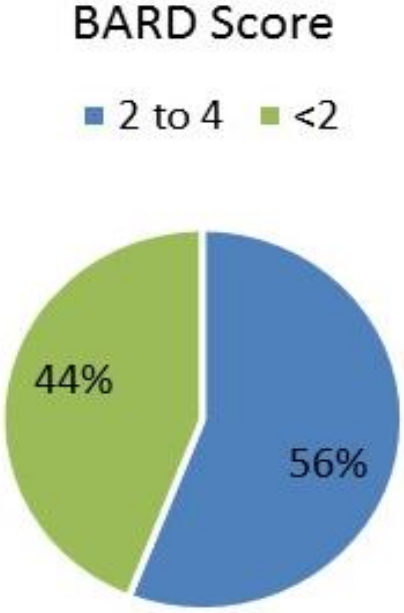

Figure 2: Distribution of BARD score.

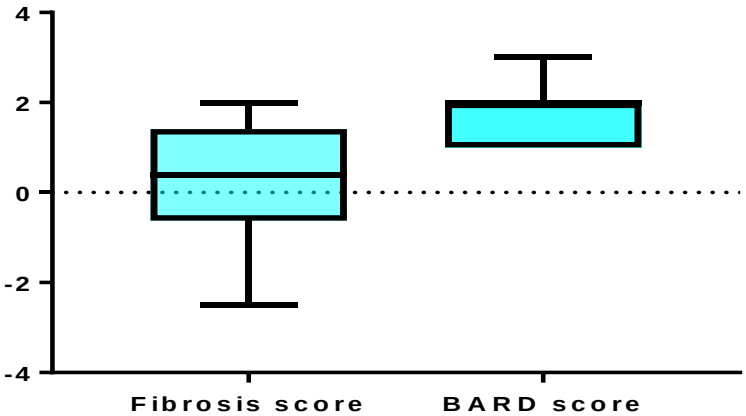

Figure 3: Box and Whiskers plot of NAFLD score and BARD score.

future liver fibrosis among type 2 diabetic individuals and the metabolic syndrome. Future research of multi centred study in larger cohorts of patients is needed to understand the association of liver fibrosis with diabetic and metabolic syndromeand how potential treatment of liver fibrosis will decrease the risk of type 2 diabetics and metabolic syndrome. Development of new therapeutic strategies will definitely lead to prevention and treatment of liver fibrosis.

ACKNOWLEDGEMENTS

The authors are thankful to the Management of Osmania General Hospital,Afzalgunj,Hyderabad,Telangana for providing the required research facilities.

REFERENCES

1. Friedman S. Liver fibrosis – from bench to bedside. Journal of Hepatology. 2003;38:38-53.
2. WANLESS I. Pathogenesis of cirrhosis. Journal of Gastroenterology and Hepatology. 2004;19(s7):S369-S371.
3. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003:37:917-23.
4. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 2005; 42: 44–52.
5. Marchesini, G., Brizi, M., Bianchi, G., Tomassetti, S., Bugianesi, E., Lenzi, M., et al. (2001) Nonalcoholic Fatty Liver Disease, a Feature of the Metabolic Syndrome. Diabetes, 50, 1844-1850.
6. Ahmed et al., 2010.Hyperglycemia decreases mitochondrial function: the regulatory role of mitochondrial biogenesis.
7. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112(17): 2735-52.
8. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Criteria. The metabolic syndrome: a new worldwide definition. Lancet. 2005; 366: 1059–1062.
9. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227–242.
10. World health organisation-international society of hypertension (WHO/ISH) hypertension guidelinesClinical and Experimental Hypertension (New York, N.Y. : 1993) [2004, 26(7-8):747-752.
11. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–854 14.
12. Castera L, Pinzani M. Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango? Gut. 2010; 59: 861–866.
13. Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, et al. Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT) J Assoc Physicians India. 2013; 61: 448–53
14. Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. World Journal of Gastroenterology : WJG. 2014; 20 (25): 8082-8091. doi: 10.3748/wjg.v20.i25.8082.
15. V. Mohan, et al., Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome, Diab. Res. Clin. Pract. 2009; doi:10.1016/j.diabres.2008; 11.039.
16. Castera L, Pinzani M. Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango? Gut. 2010; 59: 861–866.
17. Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, et al. Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT) J Assoc Physicians India. 2013; 61: 448–53.