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

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Abstract

Background: Liver fibrosis is now being considered as a 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 noninvasive methods in patients with diabetes mellitus and metabolic syndrome has not been assessed who might develop fibrosis during asymptomatic stage. Hence we tried to use these noninvasive methods in patients with diabetes and metabolic syndrome who are at high risk of developing NAFLD or liver fibrosis in routine clinical practice.Aim: To evaluate liver fibrosis in patients with diabetes and metabolic syndrome.Methodology: This was a single center, prospective, 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 classification.

Index terms— liver fibrosis, enhanced liver fibrosis, non alcoholic fatty liver disease, cirrhosis, NAFLD fibrosis score.

1 I. Introduction

iver fibrosis or hepatic fibrosis is a reversible process, results due to chronic tissue damage characterized by excessive accumulation of extracellular matrix (ECM). 1 It is the first stage of liver scarring and slowly builds up and take over most of the liver diminishing the normal activities of the liver. If not treated or reversed may lead to cirrhosis the final stage of fibrosis. 2 The most common causes for cirrhosis are viral infections such as hepatitis C, alcohol abuse, nonalcoholic fatty liver disease (NAFLD), Non-alcoholic steatohepatitis (NASH), the extreme form of NAFLD is recognised to be the major cause. 3 Liver fibrosis progresses to cirrhosis based on the etiology of liver diseases accelerated by environmental and genetic factors. 4 Oxidative stress is well documented cause for liver fibrogenesis clinically. 5 The process is initiated by cell injury with activation of hepatic stellate cells (HSC) producing ECM. 6 It is a dynamic process with many changes in the cell physiology of liver.

Treatment for liver fibrosis is not standard globally, mainly due to proper diagnostic issues and lack of understanding of its pathophysiology which is mainly derived from in vitro studies. Reversal of liver fibrosis has been observed in patients after successful treatment of underlying disease. However treatment of liver fibrosis involve treating the causative mechanism or agent by use of anti-inflammatory drugs, antioxidants, growth factors, gene therapy, insulin sensitizers, antifibrotic agents and renin angiotensin inhibitors. The clinical management of patients with chronic liver disease is still not up to the mark due to lack of translation of basic research. 7 Liver biopsy is the standard for evaluating liver fibrosis with histopathological examination, it has limitation in interpreting the fibrosis stage with intra and inter observer variability, pain during the procedure and development of major complications. **??** Ultrasonography is quick and low cost method to detect increased echogenicity, but has got much operator dependency. The focus has been shifted to non-invasive methods based on biochemical

and radiological test. 9 Routinely available serum test not related directly to extracellular matrix metabolism has been evaluated for prediction of liver fibrosis. These parameters are known as indirect markers while the direct biomarkers are hyaluronic acid,tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) 10,11 The need for simple, reliable non-invasive method for assessing liver fibrosis will be much useful. With combination of biochemical parameters few studies have validated results for liver fibrosis and some studies have used serum fibrotic markers.Among these methods the AST-to-platelet ratio index (APRI) test, Forns test, and FibroTest (FT) have given some satisfactory results. 12,13,14 Patients with diabetes mellitus (DM) and Metabolic Syndrome (MS) hasa significantly higher prevalence of NAFLD compared to those without diabetes and metabolic syndrome. 15 Previous studies has suggested NAFLD may progress to cirrhosis and failure of liver. Thus identifying liver fibrosis in this population will be of significant value and early detection may help in starting the treatment and management earlier.

NAFLD fibrosis score has been validated for presence of fibrosis in NAFLD patients where biopsy can be avoided for confirmation of fibrosis. The rates of NAFLD in general population is 32% while in population with diabetes and metabolic syndrome is 90%. 16 Since NAFLD is more prevalent in patients with diabetes mellitus and metabolic syndrome with a high risk of cardiometabolic syndrome, we tried to evaluate liver fibrosis in this population.

2 II. Materials and Methods

This was a single center, prospective cross sectional observational study. Patients with diabetes mellitus and metabolic syndrome were evaluated for fatty liver by ultrasound imaging and out of 68 screened, 50 patients with fatty liver were enrolled in to the study visiting to endocrinology department of Osmania General Hospital.

Patients having type II diabetes mellitus and metabolic syndrome were included with age ? 18 years. Diabetes was confirmed with patient's medical history and fasting blood glucose. Modified National Cholesterol Education Program Adult Treatment Panel III criteria 17 was used to define Metabolic Syndrome. Patients with waist circumference (>90 cm in men and >80 cm in women), increased TGs and low HDL cholesterol, high blood pressure (>130/ 85mmHg; or on anti-hypertensive drugs), and high fasting blood glucose (FBG) (>110 mg/dL; or a known diabetic) were applied and metabolic syndrome was defined by the presence of three or more of these criteria. 18 Patients body mass index, was calculated and biochemistry assessment were done. A qualitative test to determine the presence of anti-nuclear antibody test was done to rule out any autoimmune disorders and viral screening for Hepatitis B surface antigen (HbsAg) and Hepatitis C virus (HCV) was done. Liver fibrosis assessment was done using online NAFLD fibrosis score calculator (http://nafldscore. com) and staging of fibrosis was done using BARD scoring system (http://gihep.com/calculators/hepatology/ bard/). 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.

NAFLD fibrosis score is a validated simple noninvasive scoring system comprising of easily available clinical and laboratory variables. Using the cutoff values a prediction can be made of absence or presence of liver fibrosis in patients with NAFLD and liver biopsy can be avoided. NAFLD is the common cause for chronic liver disease in general population with increasing prevalence of obesity, diabetes mellitus and metabolic syndrome. This score has been validated in patients with diabetes mellitus and metabolic syndrome with fibrosis confirmed with liver biopsy. 19 BARD score is a very simple non-invasive method for staging of liver fibrosis in patients with NAFLD that can be used in routine practice. It was introduced in 2008 and involves ALT/AST ratio, BMI and diabetic assessments. It has been validated in biopsy proven NAFLD patients.

The study has been approved by the institutional ethics committee and is registered at clinical trial registry of India (CTRI/2014/07/004725).The study was carried out in accordance with the "Ethical Guidelines for Biomedical Research on Human Participants, 2006" by the Indian Council of Medical Research and the Declaration of Helsinki, 2008.

3 a) Data Analysis

Descriptive statistics was done using Microsoft Excel 2013.

4 III. Results

All results has been expressed as means± standard deviation (S.D) in Table **??**. 50 patients were enrolled with diabetes and metabolic syndrome, mean age of the population was 50.8 ± 8.2 with 22 men and 28 women participants. The mean age of menand women was 52.1±8.2and 49.7±8.1 respectively. Mean NAFLD fibrosis score was 0.4 ±1.2. 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 cutoff value (-1.455 -0.676) and 21% in females. 62% were at low cutoff point in females as per the NALFD fibrosis score. Figure **??** and 2 shows the distribution patients as per the cut off values of NAFLD fibrosis score and assessment of liver fibrosis respectively. Viral screening for HbsAg, HCV and Anti-nuclear antibody test was negative for all patients. 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 (Figure 3).

5 IV. Discussion

Many non-invasive methods has been developed for liver fibrosis assessment following the limitations for liver biopsy. These methods can be used for primary evaluation for the population at risk or undiagnosed fibrosis in outpatient departments. 20 The popularity of these noninvasive scores is increasing for evaluation of non-significant and advanced liver fibrosis. 21 Transient elastography is a rapid non-invasive method for evaluation of liver fibrosis with high cost and limited to specialist. **??**2 Most of the non-invasive methods has been validated in population with hepatitis C and few in NASH/NAFLD. 11,23 In a exploratory study advanced fibrosis was diagnosed with high accuracy in patients with NAFLD using non-invasive parameters. 24 Direct serum markers for liver fibrosis are not done routinely in all labs, the results might not be reliable in patients characterized by fibrogenesis in organs other than liver and are relatively expensive. Radiological assessments include computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, Acoustic Radiation Force Impulse (ARFI) imaging and transient elastography which are quite costly. Ultrasound imaging is a cheap and easily available imaging technique widely used for fatty liver detection. Considering the merits and demerits imaging techniques alone, a combination of serum direct and indirect markers and imaging techniques helps is identifying liver fibrosis is patients at risk. 25 Our results shows that 90% (Figure **??**) of patients with diabetes mellitus and metabolic syndrome have some degree of liver fibrosis which are consistent with previous epidemiological studies for NAFLD, 15,26,27 however further evaluation needs to be done for classifying these patients based on the pathophysiological mechanism. These non-invasive methods can be routinely used to follow up these patients as these are highly reproducible. 11 It is recommended to use the non-invasive biomarkers along with transient elastography which increases diagnostic accuracy for liver fibrosis. Compared to liver biopsy these methods has no contraindication, less risk to the patients, has 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 will help in identifying patients for further screening, evaluation and treatment. 20 In our study, males (73%) were at high cutoff value suggesting of advance fibrosis. While in females it was only 21%, suggesting men to have more prevalence of fibrosis than women, however earlier studies which was done in type 2 diabetes patients shows more prevalence in females than males. 26 The BARD score is another noninvasive method for assessing liver fibrosis and it stages the liver fibrosis as per metavir scoring system. We used NAFLD fibrosis score and BARD score to assess liver fibrosis in this population and to identify staging of liver fibrosis as per metavir scoring system respectively suggesting 56% of this population is at either F3 or F4 stage of fibrosis.

Oxidative stress being widely considered as one of the pathophysiological mechanism, 27 patients with diabetes and metabolic syndrome are at more risk and use of these non-invasive assessments will help in early identification of patients having moderate to advanced liver fibrosis. While liver fibrosis is considered to be reversible, 28 this population should be studied further for classifying the various pathophysiological mechanism that can occur so as to follow the treatment guidelines accordingly.

There is a need to identify patients underlying with liver fibrosis as early as possibly to start the treatment early. The non-invasive methods are well validated and should be used in day to day clinical practice for population at risk. We tried to evaluate liver fibrosis in fatty liver patients with diabetes mellitus and metabolic syndrome using their routine biochemical test. The main limitation of our study is that it's a cross sectional study with less sample size, however due to various pathophysiological mechanism and reversibility of liver fibrosis this population should followed further for any complication that can happen due to decreased performance of liver.

6 V. Conclusion

Liver fibrosis is the first step in progression to liver cirrhosis with different etiologies lacking effective therapy. Liver plays an important role in detoxifying chemicals, metabolizing drugs and producing important proteins for body functions. Patients with diabetes and metabolic syndrome are at risk of developing diabetes complications and cardiovascular disease. A decline in liver function may attribute to increase risk of developing diabetic complication and other cardiometabolic disease in this population. Further studies are needed to evaluate the association of liver fibrosis and cardiometabolic disease in patients with diabetes and metabolic syndrome due to its increasing global burden.

7 VI. Acknowledgments

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[1]

Figure 1: A

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Figure 2: Figure 2 :

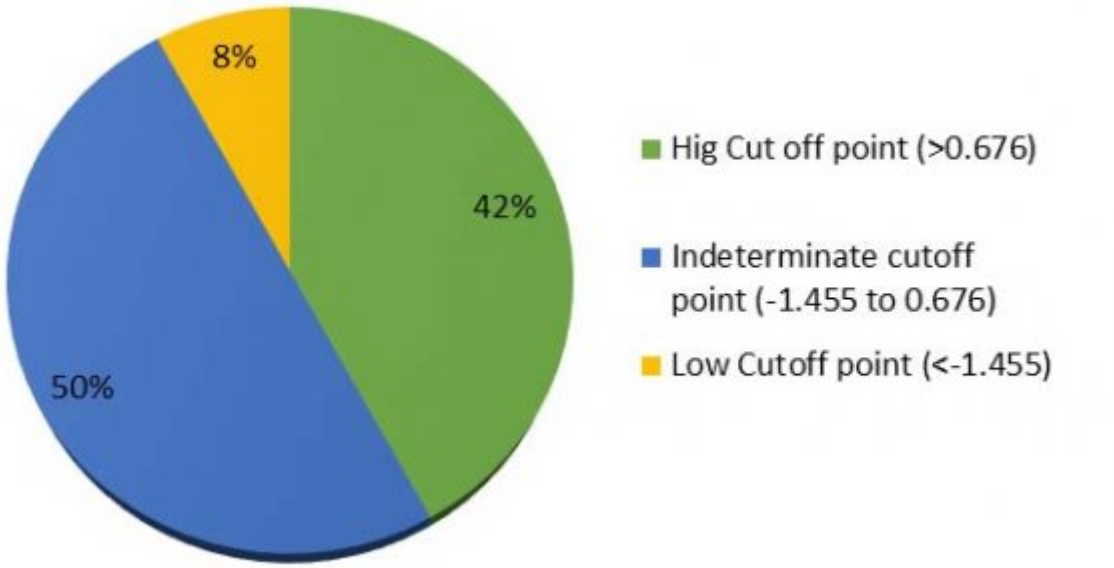

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Figure 3: Figure 3 :

[Note: Aim: To evaluate liver fibrosis in patients with diabetes and metabolic syndrome.Methodology: This was a single center, prospective, 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 classification.Results: The mean age of the patients was 50.8 ± 8.2 with 22 males and 28 female's. 90% of the population was found to have some degree of fibrosis. 56% of patients were at advance fibrosis stage as per the BARD score based on metavir classification. Conclusion: Patients with diabetes and metabolic syndrome should be constantly evaluated for liver fibrosis apart from development of diabetes and other complications to prevent any adverse effects due to waning of liver function.]

Figure 4:

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