Noninvasive assessment of liver fibrosis in Nonalcoholic Fatty Liver Disease in Nepal

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Abstract

Background and Aims: Nonalcoholic Fatty Liver Disease (NAFLD) progresses to liver fibrosis and ultimately cirrhosis and its complications. Grading of liver fibrosis 2D SWE (Shear Wave Elastography) is a noninvasive study of liver fibrosis and stiffness. We compared different fibrosis scores (NAFLD fibrosis score, FIB 4 score, APRI score) and ultra-sonogram identified fatty liver with 2 d shear wave elastography score.

Methods: A hospital based prospective observational study was conducted from May 2019 for ten months period in the Gastroenterology and Liver Unit, NAMS, Nepal. Seventy patients with known fatty liver and its severity were identified by Ultrasonogram criteria were enrolled, who met the exclusion criteria. All patients underwent 2D shear wave elastography. Patients were evaluated for effects of obesity, diabetes mellitus, thyroid related disease and dyslipidemias on NAFLD. Tests were done to calculate different fibrosis scores (NAFLD Fibrosis, FIB4, APRI, AST/ALT ratio) and compared with 2d shear wave score.

Results: Baseline Characteristics among 70 patients 39(55.7%) were male and 31(44.3%) were female with mean age of the patients 44.3 years. Most of the patients were overweight with mean BMI of 28.2, kg/m2among them 51(72.9%) patients were more than 25.kg/m2Most of the patients 41.4% had diabetes mellitus, 77.1% had hypertension, 30% had hypothyroidism and were 25.9% had metabolic syndrome. Majority of patients on ultrasound gradings were mild 64.28%, 25.72% were moderate and only 10 % were in severe groups. In comparison ultra-sonogram with 2 d shear wave elastography, mild grade mean fibrosis 7.07 kpa, for moderate grade mean fibrosis 8.22 kpa and for severe grade mean fibrosis was 18.16 kpa.

Conclusion: In patients with NAFLD, measurement of liver stiffness by 2d shear wave elastography has positively correlated with fib-4 score and non-inferior to NAFLD fibrosis score. The mean value of elastography increases significantly with the severity of steatosis on ultrasonography.

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Introduction

The definition of Non-alcoholic fatty liver disease (NAFLD), (1) evidence of hepatic steatosis (HS), either by imaging or histology, and (2) lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders. [1]

NAFLD actually represents the most common chronic liver disorder, with a global prevalence of about 24%. Current data estimate that NAFLD affects 30% of the United States, 30% of the South American, 27% of the Asian.[2] In Nepal, The magnitude of problem of NAFLD is unknown, there are only few studies related to NAFLD. Among them the prevalence of NAFLD in diabetes mellitus in Nepal were 79.62%. [3]

NAFLD is the most common form of liver disease and a leading cause of morbidity and mortality in both developed and developing countries.[2] NAFLD progresses to liver fibrosis and ultimately cirrhosis and its complication. So early diagnosis and timely treatment of fibrosis is important to prevent cirrhosis related complications, mortality and healthcare cost. Cardiovascular disease is the leading cause of death in people with NAFLD.[1]

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Ultrasound is the simplest diagnostic method, providing the best diagnostic results when steatosis affects more than 30% of the liver but it is poorly correlated with NASH.4 Fibrosis assessment of NAFLD is necessary. Different noninvasive assessment of fibrosis are widely available like serum biomarkers and imaging-based techniques. The most promising and widely applied techniques are liver stiffness measurement (LSM) by transient elastography and 2d shear wave elastography. Transient elastography is a non-imaging elastographic technique, while 2d- SWE its combines imaging with elastography.

METHODS

The study was conducted from May 2019 for ten months period in the Gastroenterology and Liver Unit, NAMS, Nepal. The study was designed as a hospital based prospective observational study. 70 patients with fatty liver in ultrasonography (USG) who met the criteria were recruited for the study.

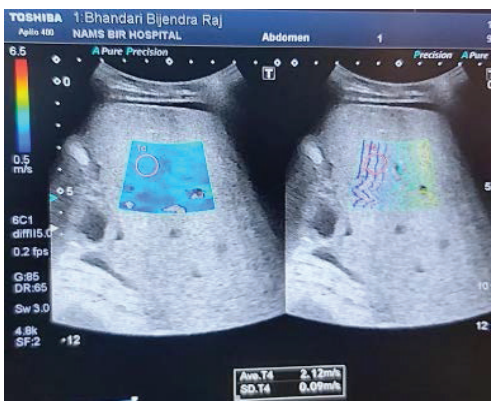

Fig : 1. 2 d Shear wave elastography

Criteria for the enrollment is the presence of steatosis within the liver with the absence of excessive alcohol consumption defined as ongoing or recent alcohol consumption more than 20 g/day for women and 30 g/day for men. Common secondary causes of fatty liver are like drugs, chronic hepatitis B, chronic hepatitis C, Iron overload and wilson disease etc were excluded from the study. Complete general and systemic examination including anthropometry was done. Routine blood investigations were done. Fatty liver and its severity was assessed by USG.

All patients with fatty liver were evaluated by Toshiba Aplio 400 2d SWE. Measurement of 2d SWE were done, according to guideline published by of the European Federated Societies of Ultrasound in Medicine and Biology (EFSUMB), World Federation of Ultrasound in Medicine and Biology (WFUMB), The Society of Radiologists in Medicine (SRU). This technique is a combination of a radiation force induced into the tissues by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence. A region of interest of variable depth and diameter is then defined within the visualized liver. Elasticity is displayed using a color coded image, superimposed on a B-mode image: in red – stiffer tissues and in blue – softer tissues .5 At the same time, a quantitative estimation of LS is performed. LS value in the region of interest (whose size can be modified by the operator), is displayed on the screen, expressed either in kPa, or in m/s.

NAFLD Fibrosis score was calculated from the values obtained by using formula 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl).

NAFLD Score < -1.455 = F0-F2, NAFLD Score -1.455 – 0.675 = indeterminate score, NAFLD Score > 0.675 = F3-F4.6 FIB 4 score was also calculated by using standard formula including variables of age, AST, ALT and platelets. Using a lower cutof value of 1.45, a FIB4 score<1.45 had a negative predictive value of 90% for advanced fibrosis. In contrast a FIB4 >3.25 would have a 97% specificity and a positive predictive value of 65% of advanced fibrosis. AST/ALT ratio and level of platelets were correlated with the severity of fibrosis score.[7]NAFLD fibrosis score, and FIB4 score and APRI score was calculated by using the standard formula from website and was compared with 2D SWE.

Table 1

Base line Characteristics	Total (n=70)
Male	39(55.7%)
Female	31(44.3%)
Age(IQR)	44.3±12.1
BMI (IQR)	28.2±4.9
BMI >25	51(72.9%)
DM	29(41.4%)
HTN	54(77.1%)
Hypothyroidism	21(30%)
HDL (IQR)	45±12.3
LDL (IQR)	96.±35.2
TG (IQR)mean	213.3±146
AST (IQR)	64.5±117.1
ALT (IQR)	63.3±80.3
GGT (IQR)	70±75
Platelets (IQR)	231.4±91.5
Metabolic Syndrome	18(25.9%)
AST/ALT ratio	32(45.7%)

Results:

Among 70 patients 39(55.7%) were male and 31(44.3%) were female with mean age of the patients were 44.3. Most of the patients were overweight with mean BMI of 28.2, kg/m^2 among them51(72.9%) patients were more than 25.kg/m^{2}Most of the patients 41.4% were diabetes mellitus, 77.1% were hypertension, 30% were hypothyroidism and metabolic syndrome were 25.9% as defined by Adult Treatment Panel III clinical definition of Mets. Other variables are given in table 1.

In the quantitative ultrasound classification system devised by Saadeh et al., steatosis can be categorized as follows : grade 1 (mild)—mild, diffuse increase in hepatic echogenicity, the hepatic vessels and diaphragm having a normal aspect; grade 2 (moderate)—moderate, diffuse increase in hepatic echogenicity, the hepatic vessels and diaphragm having a blurred aspect; grade 3 (marked)—marked increase in hepatic echogenicity, the hepatic vessels, diaphragm, and posterior liver not being visible.8 Among 70 patients majority of patients were mild 64.28%, 25.72% were moderate and only 10 % were in severe groups. Given in fig.2

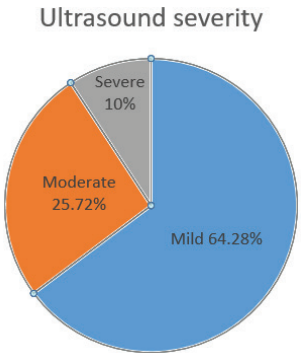

Fig. 2

Table 2 Descriptive data				
	Ultrasonogram grade	Mean	Std. Deviation	p-value
FIB-4 Score	mild	1.25	0.57	0.000
	moderate	1.40	1.09	
	severe	5.52	3.45	
NFS Score	mild	-2.07	1.56	0.020
	moderate	-1.94	1.89	
	severe	0.16	1.01	
APRI Score	mild	0.45	0.22	0.000
	moderate	0.93	1.47	
	severe	2.60	2.10	
2D SWE Mean	mild	7.07	1.68	0.000
	moderate	8.22	1.91	
	severe	18.16	11.98	
2D SWE Median	mild	6.96	1.80	0.000
	moderate	8.16	1.73	
	severe	17.94	11.76	

We correlated with FIB -4, NAFLD fibrosis score and APRI score with severity with ultrasound grade, as severity of grading increases with each of value increase given on table 2.

2 d shear wave elastography in mild fibrosis mean 7.07 kpa, for moderate fibrosis 8.22 kpa. and for severe fibrosis 18.16 kpa. It has significant value with moderate and severe grade of ultrasonography value. The optimal normal cutoff values of 2d SWE for diagnosing liver fibrosis by Herman et al. Metavir fibrosis stage 0,1,2= 7.15 kpa, for fibrosis stage 2-3 =9.15 kpa , and for fibrosis stage 3-4 =11 kpa or more .[9]

Table:3 correlations with fib 4, Nafld Score and 2 D SWE mean.				
	FIB-4 Score	NFS Score	2D SWE Mean	BMI
FIB-4 Score	1	.486**	0.221	-0.218
NFS Score	.486**	1	.377**	.355**
2D SWE Mean	0.221	.377**	1	0.205

The FIB 4 score is positively correlated with 2d SWE and Nafld score with mean value of 2d SWE. The Pearson correlation coefficient values are given in table 3.

Discussion:

In the context of the increasing prevalence of NAFLD in Nepal and worldwide, we evaluated alternative to liver biopsy for the noninvasive staging of liver fibrosis. Due to invasive procedure of liver biopsy, it has associated with rare but serious complications, and it can only a sample a small portion of liver parenchyma, making susceptible to sampling variation.

A comparative study to assess the clinical use of liver stiffness measurement (LSM) evaluated by supersonic shear imaging (SSI), Fibro Scan, and acoustic radiation force impulse (ARFI) among 291 NAFLD patients, in France university hospital, concluded that 2D-SWE by Supersonic Imagine SSI provides high value for the diagnosis of liver fibrosis in NAFLD patients.[10] Similarly in the comperative study by Furlan et al, 2d Shear wave elastography, Transient elastography, and MR elastography for the diagnosis of fibrosis in patients with biopsy proven NAFLD has exhibited comparable and excellent diagnostic accuracy for advanced fibrosis and comparable but lower accuracy for significant fibrosis.11 Castera L. et al in their study had concluded that liver stiffness measurements by transient elastography are uninterpretable in obese patients and in patients with ascites. [12] A study from Japan has compared various risk scores and elastography (MR as well as TE) against liver histology which showed that NFS and FIB-4 were better than other indices such as APRI, and AST/ALT ratio and as good as MRE for predicting advanced fibrosis in patients with biopsy-proven NAFLD.[13]

In this study most of the patients were overweight and there LSM was evaluated by 2d SWE technique. We correlated 2d shear wave elastography mean value with fib 4, Nafld score, which correlated positively with each other.

Conclusion:

Liver stiffness assessment by different clinical and laboratory based examinations including different fibrosis scores (Fib-4, NAFLD and APRI scores) were correlated with mean value of 2d shear wave elastography showing positive results. The mean value of shear wave elastography was higher fibrosis score and high grade of steatosis by ultrasonography.

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