Transient Elastographic Values of Healthy Volunteers in a Tertiary care Hospital

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ABSTRACT

Introduction: Transient elastography is a very promising noninvasive procedure to determine liver stiffness for diagnosis of fibrosis in various chronic liver diseases. However, studies on normal values of liver stiffness in apparently healthy subjects are still few. We aimed to determine liver stiffness values in healthy Nepalese volunteers.

Methods: Transient elastography (Fibro ScanR, Echosens, Paris, France) was performed to find out liver stiffness values in 45 apparently healthy volunteers after explaining study protocol. Complete medical examination with routine laboratory tests was performed. Subjects with normal liver biochemistries and normal liver ultrasonography were taken for analysis.

Results: Mean liver stiffness value of study subjects was 4.24 ± 0.70 kPa. Liver stiffness value was found higher in males than in females (4.32±0.74 vs 4.07±0.61 kPa, respectively, P =0.26) but not statistically significant. Similarly, comparison between age and liver stiffness also showed positive correlation(r = 0.211) but not statistically significant(P = 0.164)

Conclusions: Our study showed that the mean liver stiffness value was 4.24 ± 0.70 kPa in our population and influence of age, gender and body mass index were not significant.

Keywords: *chronic liver disease; Fibro ScanR; healthy volunteers; liver stiffness valve; transient elastography.*

INTRODUCTION

Chronic liver diseases often result in fibrosis that may eventually lead to cirrhosis, a state that carries a risk of lethal complications, including hepatocellular carcinoma.[1,2] The prognosis and management of chronic liver diseases often depend strongly on the degree of liver fibrosis.[3]

These facts point out the clinical interest in quantifying hepatic fibrosis and detecting patients with cirrhosis. At present, liver biopsy is the "gold standard" method to assess the grade of liver fibrosis. However, the use of liver biopsy has several limitations: physical and mental discomfort of the patients that may lead to a high percent of refusal, non-negligible morbidity and occasional mortality.[4-6] Liver biopsy examination is difficult to repeat in generally asymptomatic patients. Furthermore, due to the limited size of liver samples and the subjective assessment made by pathologists, accuracy and reproducibility of histological grading has been questioned. Therefore, there is an increasing need for alternative noninvasive methods to estimate

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the grade of liver fibrosis.[7] Among the other potentially interesting approaches, elastography seems to be one of the most promising. Indeed, it is well known that liver stiffness is related to the degree of hepatic fibrosis, and palpation has been used from decades to establish a clinical diagnosis of hepatic fibrosis and cirrhosis.

Transient elastography (FibroScanR, Echosens, and Paris, France) is a recently described non-invasive procedure which consists of a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. The vibrator generates a completely painless vibration (with a frequency of 50 Hz and amplitude of 2 mm) which generates an elastic share wave propagating through the skin and the subcutaneous tissue to the liver. The velocity of the wave is directly related to the tissue stiffness which allows evaluating liver stiffness.[8] The basic principle of transient elastography is that the propagation velocity of a wave through a homogenous tissue is proportional to its elasticity, which is correlated with the amount of fibrosis in the liver. The FibroscanR test has the advantage of being pain-free, easy-to-learn and fast[9] and give result immediately.

In the context of growing burden of chronic liver disease in our country, we need a novel, noninvasive and bedside method like transient elastography to assess liver fibrosis by measuring liver stiffness. Unlike liver biopsy, transient elastography can be repeated without risk to patients. Since, transient elastography is a relatively new diagnostic tool and it has been tested in different chronic liver disease but there are few data regarding healthy population. There are no published studies of transient elastography on either healthy or people with chronic liver diseases in Nepalese population. So, we aimed in this study to see the transient elastographic values in apparently healthy Nepalese population.

METHODS

This was a cross sectional descriptive study done in Liver Unit, National Academy of Medical Sciences, Bir Hospital on July-August 2013.

Healthy volunteers were taken for study after explaining about study purpose and methods. Volunteers were Resident Doctors and Nursing Staffs working in Bir Hospial at the study time. Healthy Volunteers aged 18 years and above were included and those volunteers who had any liver disease or suspected of having systemic disease affecting liver like raised transaminases, fatty liver in ultrasonography and those not willing to participate in study were excluded. All volunteers gave informed consent and the study protocol was approved by the institutional review board (IRB), National Academy of Medical Sciences. Those who agreed to participate had a complete medical examination with laboratory tests on the same day. Data were collected for each volunteer: age, gender, ethnicity, occupation and vital signs. Similarly, history of liver diseases, diabetes, arterial hypertension, smoking and alcohol use were also recorded. Routine laboratory tests including complete haemogram, random blood glucose, renal function test, liver biochemistries, serum total protein, albumin and total cholesterol, serological tests for hepatitis B&C virus was also done. Likewise, ulrasonography of the abdomen done where size of liver and spleen was recorded and chest x- ray also carried out. Body mass index was calculated and classified according south Asian BMI value (Normal BMI: 18.0-22.9 kg/m^2, Overweight: 23.0-24.9 kg/m^2, Obesity: >25 kg/m2).[10]

Then FibroscanR of all volunteers were done in Centre for Liver Disease next day by the same clinician who was blinded to clinical and biochemical profiles. FibroscanR was performed on the right lobe of the liver, through intercostals spaces, with the patient lying in dorsal decubitus with the right arm in maximal abduction. The operator placed the fibroscanR transducer perpendicularly to the intercostals space, assisted by time motion ultrasound images, located the probe in a liver portion at least 6cm thick and free of large vascular structures and gallbladders and presses the probe button to commence the measurement. Ten valid measurements were performed to examine a patient with transient elastography. The median value of the ten valid measurements was considered representative of liver elasticity. The success rate was calculated as the number of valid measurements divided by the total number of measurements. Examinations with a success rate higher than 60% and interquartile range (IQR), which represents the intrinsic variability of TE, <30% of the median were considered reliable. The results were immediately obtained after performance of TE and expressed as the median value of 10 validated measurements in kilopascals (kPa), values ranging from 2.5 to 75 kPa. Only procedures with at least ten successful acquisitions and a success rate of at least 60% were considered reliable and recorded.

Descriptive statistical measures such as mean, standard deviation, median, range, etc for continuous variables and percentages for categorical variables had been reported to summarize the data distribution. Continuous variables between two groups were compared by independent t-test/ Mann-Whitney U test wherever applicable and the three groups were compared by using one way ANOVA. The associations between two independent categorical variables were assessed through the use of Chi-square test/ Fisher's exact test wherever applicable.

All statistical analyses were carried out with statistical software SPSS version 16.0. Results were considered statistically significant with p value less than 0.05.

RESULTS

A total of 51 apparently healthy volunteers were enrolled in this study. Six of them were excluded in which two volunteers had raised transaminases, two had fatty liver in ultrasonography and two had both raised transaminases and fatty liver. Of the remaining 45 volunteer subjects with normal liver biochemistries and normal liver ultrasonography were taken for subsequent analysis. Demographic profiles and vital parameters of the study subjects are given in Table 1 and laboratory parameters in Table 2. Similarly, ultrasonographic measurements of spleen and liver and fibroscan values are presented in Table 3. Among these volunteers percentage of male was higher than female (66.66% vs 33.33%) and percentage of resident doctors was higher than nursing staff (80% vs 20%). The mean age of our study subjects was 30. 13±4.96 years and according to gender was comparable (31.70 ± 3.80 vs 27.00 ± 5.62 years for men and women ,respectively, p = 0.002).

Table 1. Demographic profiles and vital parameters of the study subjects.

Characteristics	All subjects	Men	Women	P-value
Number (%)	45	30	15	
Age (yrs)	30.13 ± 4.96	31.70 ± 3.80	27.00 ± 5.62	0.002
Occupation:				
Doctor (%)	36 (80.00)	30(83.30)	6 (16.70)	
Nurse (%)	9 (20.00)	0(0.00)	9 (100.00)	
Ethnicity:				
Brahmins (%)	18(40.00)	13 (72.20)	5 (27.80)	
Chhetry (%)	9(20.00)	6 (66.70)	3 (33.30)	
Newar (%)	7(15.60)	3 (42.90)	4 (57.1)	
Others (%)	11(24.40)	8 (72.70)	3 (27.30)	0.529
SBP (mmHg)	114.67±8.68	118.00 ±8.45	108.00 ±4.14	< 0.001
DBP (mmHg)	74.00 ±6.45	75.33 ±5.71	71.33 ±7.19	0.049
Pulse (per minute)	76.91±6.38	76.87 ±5.79	77.00 ± 7.64	0.948
Weight (Kg)	63.08 ±10.59	68.38 ± 7.48	52.47 ± 7.46	< 0.001
West circumference (cm)	86.24 ±7.29	89.67 ± 4.41	79.40 ± 7.18	< 0.001
BMI (Kg/m2)	23.26 ±2.67	23.96 ± 2.29	21.85 ± 2.90	0.021

Table 2. Laboratory parameters of the study subjects.

Characteristics	All subjects	Men	Women	p-value
Blood Sugar R (mg/dl)	97.47 ± 18.46	98.07 ± 18.62	96.27 ± 18.72	0.762
Urea (mg/dl)	29.84 ± 6.75	30.83 ± 6.92	27.87 ± 6.14	0.167
Creatinine (mg/dl) [median, range]	1.08 ± 0.92 [1.00, 0.60 – 7.00]	1.01 ± 0.12 [1.00, 0.80 – 1.30]	1.21 ± 1.61 [0.80, 0.60 – 7.00]	< 0.001
Total serum bilirubin(mg/dl) [Median, range]	0.91 ± 0.33 [0.90, 0.50 – 2.40]	0.98 ± 0.38 [0.90, 0.50 – 2.40]	0.78 ± 0.11 [0.80, 0.6 – 0.90]	0.010
Direct serum bilirubin (mg/dl) [Median, range]	0.33 ± 0.12 [0.30, 0.20 – 0.80]	0.35 ± 0.14 [0.30, 0.20 -0.80]	0.29 ± 0.07 [0.30, 0.20 – 0.40]	0.1597

AST(u/l)	19.47 ± 6.68	20.90 ± 7.03	16.60 ± 4.95	0.040
ALT(u/l) [Median, range]	23.16 ± 10.95 [20.00, 7 – 55]	26.90 ± 11.17 [25.00, 7 – 55]	15.67 ± 5.31 [14.00, 9 -29]	< 0.001
ALP(u,KA)	81.93 ± 19.07	84.97 ± 20.14	75.87 ± 15.62	0.133
Albumin(gm/dl)	5.06 ± 0.43	5.13 ± 0.52	4.94 ± 0.12	0.178
Total Cholesterol(mg/dl)	181.27 ± 27.47	190.83 ± 24.65	162.13 ± 22.91	< 0.001
Hb(gm%)	14.70 ± 1.29	15.18 ± 1.14	13.75 ± 104	0.001
CBCTc(/cumm)	7015.56 ± 1786.69	7066.67 ± 1952.25	6913.33 ± 1456.45	
ESR(fl)	83.13 ± 12.75	80.53 ± 14.42	88.33 ± 6.06	0.052
Platelets (/cumm)	244000 ± 59295	236000 ± 54995	262000 ± 65488	0.162
Platelet to spleen ratio (cumm/mm)	2618.63 ± 726.95	2495.18 ± 719.67	2865.52 ± 700.03	0.108

Table 3. Ultrasonographic measurements and Fibroscan values of the study subjects.

Characteristics	All subjects	Men	Women	P-value
Liver size (cm) [Median, Range]	13.16 ± 0.88 [13.35,11.58-14.94	13.43 ± 0.86 13.42,11.76-14.94]	12.61 ± 0.67 [12.42,11.58-13.73	0.002
Spleen diameter(cm) [Median, Range]	9.50 ± 1.12 [9.44, 7.32-11.52]	9.65 ± 1.15 [9.57, 7.32-11.52]	9.20 ± 1.02 [8.88, 7.82- 11.08	0.211
Liver stiffness(kPa) [Range]	4.24 ± 0.70 [2.80 – 5.80]	4.32 ± 0.74 [2.80 - 5.80]	4.07 ± 0.61 [3.10 – 5.40]	0.260

Mean liver stiffness value of study subjects was 4.24 ± 0.70 kPa. Liver stiffness value was found higher in males than in females (4.32 ± 0.74 vs 4.07 ± 0.61 kPa, respectively, P = 0.26) but not statistically significant. We also compared BMI and liver stiffness values but no statistically significant (P = 0.377). The association between liver stiffness and different group of BMI are given in Table 4. Similarly, comparison between age and liver stiffness showed positive correlation (r = 0.211) but not statistically significant (P = 0.164). Platelet (/cu mm) to spleen size (bipolar diameter of spleen in millimeter) ratio was calculated and found 2618.63 ± 726.95. Scatter diagram between age and liver stiffness is presented in Figure 1. Similarly, scatter diagram of liver stiffness and platelets count (per cubic millimeter) in Figure 2 and spleen size (cm) in Figure 3 are shown.

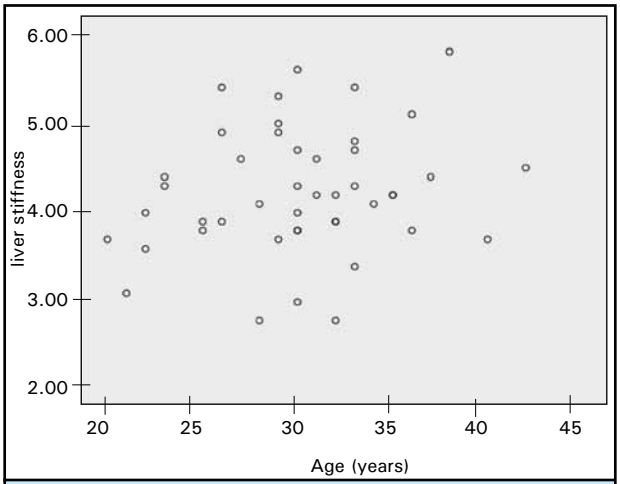

Figure 1. Scatter diagram between liver stiffness and age of the study subjects.

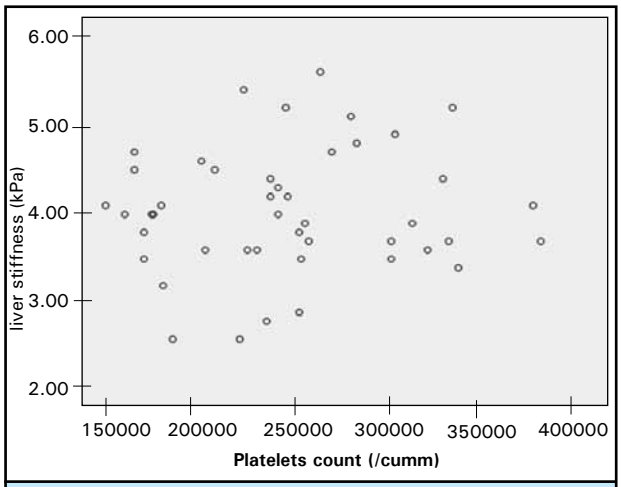

Figure 2. Scatter diagram between liver stiffness and platelet count of the study subjects.

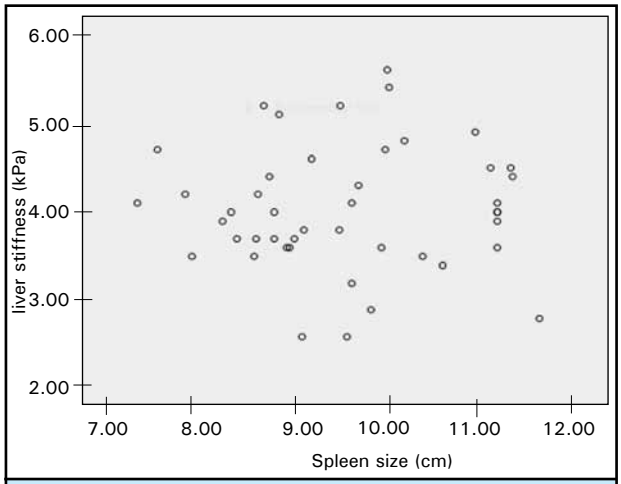

Figure 3. Scatter diagram between liver stiffness and spleen size of study subjects.

Table 4. Association between liver stiffness and different group of BMI.

BMI	n	Liver stiffness Mean ± S.D.	p-value
18 - 22.9	20	4.06 ±0.58	
23 – 24.9	14	4.41 ±1.01	
≥ 25	11	4.31 ±0.28	0.3776

DISCUSSION

Transient elastography (TE) is a recently described non-invasive procedure, which measures the transmission of an elastic share wave generated by vibration. This technique allows to evaluate liver stiffness.[8] Briefly, TE consists of an ultrasound transducer mounted on the axis of the vibrator, which produces vibration of a mild amplitude and low frequency (50 Hz), consequently inducing an elastic shear wave that propagates through the liver. Pulse-echo ultrasound follows the propagation of the shear wave and measures its velocity, which is related to liver tissue stiffness. It is reported that the velocity of elastic waves is faster in fibrotic liver than normal liver. Performance of TE takes only a few minutes, and it is well tolerated by most patients. TE is performed on the right lobe of the liver with the patient lying in dorsal decubitus with the right arm in maximal abduction. Usually, 10 valid measurements are performed and median value of the ten valid measurements is considered representative of liver elasticity. Examinations with a success rate higher than 60% are considered reliable and results expressed in kilopascals (range 2.5-75 kPa). The interquartile range (IQR), which represents the intrinsic variability of TE, <30% of the median indicates a high-quality result.[8] Transient elastography has already been validated in different liver diseases like chronic viral C hepatitis,[11-14] chronic viral B hepatitis,[1516] HCV-HIV co- infection,[17,18] liver transplant recipients,[19-22] cholestatic conditions[23] and hemochromatosis.[24]

FibroscanR is gaining popularity in various chronic liver diseases to determine status of liver in term of stiffness with different cut-off values. But data of normal values of liver stiffness is still few. We studied 45 apparently healthy volunteers with normal liver chemistries and normal liver ultrasound finding. The study subjects are few due to limitation of available resources. FibroscanR is available in single center (Center for liver diseases) and relatively inexpensive, easier to perform and safer than liver biopsy. It can also be repeated, in order to monitor changes in fibrosis during the course of treatment and can yield an immediate result after procedure. It measures liver stiffness of a value of parenchyma approximately 100 times bigger than a needle biopsy specimen so it is more representative of liver parenchyma. In this study, we found mean liver stiffness value (4.24 ± 0.70 kPa) in apparently healthy volunteers. Liver stiffness values were found higher in males than in females (4.32±0.74 vs 4.07±0.61 kPa, respectively, P =0.26) but not statistically significant which is similar to Kim SU et al[25] where they found the mean liver stiffness value of 4.6±0.5 kPa (range 3.3-5.6 kPa) in their study, which was calculated from 69 strictly selected living liver and kidney donors and liver stiffness values were not significantly different between men (4.6±0.6 kPa) and women (4.5±0.5 kPa, P =0.636). Similarly, Fung et al[26] reported a mean TE value in 28 healthy living-related liver donors of 4.6 (range, 2.0-7.1) kPa, and all subjects had TE values of <7.2 kPa, which is also similar to our finding. In a study, Roulot et al,[27] examined a large cohort of apparently healthy subjects with no evidence of liver diseases to establish normal liver stiffness values and mean liver stiffness was 5.49±1.59 kPa. Liver stiffness valves

were higher in men than in women [5.81 ± 1.54 kPa (range 3.8-8.0 kPa) in men vs 5.23 ± 1.59 kPa (range 3.3- 7.8 kPa) in women, P< 0.002 in contrast to our finding they found it statistically significant.

Similarly, Colombo et al,[28] found mean liver stiffness value of 4.9 kPa (95% confidence interval, 4.6 – 5.1 kPa) in 327 voluntary blood donors and liver stiffness values were not significantly different genders which is similar to our finding. Likewise, Sirli et al,[29] in their study of 144 normal subjects in Romania found liver stiffness value of 4.8 ± 1.3 kPa (range 2.3 – 8.8 kPa) which is comparable to ours. But they found that liver stiffness valves of men 5.1 ± 1.2 kPa and women 4.6 ± 1.2 kPa which was significantly different in terms of gender P < 0.01 where our finding was not significant. Corpechot et al,[30] in their study of liver stiffness value in healthy men and women found that liver stiffness values were higher in men than in women (5.2 ± 0.7 vs 4.5 ± 1 kPa, P<0.01) which is in contrast to our finding. In our study, comparison of age and liver stiffness showed positive correlation (r = 0.211) but was not statistically significant (P = 0.164). Roulot et al,[25] found liver stiffness values tended to be higher with age but not significant statistically (P = 0.06) which is similar to ours and Kim SU et al,[27] has similar result for age (P = 0.851). Similarly, in this study the association between liver stiffness and different group of BMI was also not significant statistically (P = 0.377). Similar results were reported by Kim SU et al,[27] but Roulot et al,[25] who found liver stiffness values were higher in subjects with metabolic syndrome than in those without (6.5 ± 1.64 vs 5.33 ± 1.51 kPa , P<0.0001). It is well known that liver stiffness is related to the degree of hepatic fibrosis, and gradually portal hypertension would be evident, spleen diameter increases and platelet count decreases. As platelets count and spleen size are thought to reflect the clinical consequences of portal hypertension. In a study, Berzigotti A et al,[31] reported that patients with clinically significant portal hypertension had a higher prevalence of worse liver function (higher bilirubin, lower albumin), lower platelet count and larger spleen size as compared with patients without clinically significant portal hypertension. They reported the platelets count (137 ± 64 × 109 / l in training set and 116 ± 52 × 109 / l in validation set), spleen size (13.1 ± 3.0 cm in training set and 15.5 ± 2.9 in validation set) and platelets to spleen ratio (1156 ± 704 in training set and 817 ± 443 in validation set) which correlate with liver stiffness values 25.2 ± 16.6 kPa in training set and 27.4 ± 12.1 kPa in validation set. They concluded these values from patients with compensated cirrhosis in contrast to our values. In our study where we found platelet count (244000 ± 59295/cumm) and spleen size (9.50 ± 1.12 cm), platelets to spleen ratio (2618.63 ± 726.67) and liver stiffness value 4.24 ± 0.70 kPa which does not correlate with it, as these values are from apparently healthy volunteers.

This study is the first of its kind in Nepalese population, so is expected to serve a benchmark for future research in this field. The major limitation of our study is its small sample size in comparison to different studies discussed here but still this gave us a baseline value of liver stiffness in our population. It is recommended that future studies are required with larger sample size and in subjects of various demographic backgrounds.

CONCLUSIONS

We examined liver stiffness value of relatively small group of healthy subjects and found mean liver stiffness value of 4.24 ± 0.70 kPa {male(4.32 ± 0.74 kPa) and female (4.07 ± 0.61 kPa)}. The influence of age, gender and body mass index on liver stiffness value was not significant.

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