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Transient Elastography for Follow up Liver Stiffness in Chronic Alcohol Users: A Prospective Cohort Study

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ABSTRACT

Introduction: Chronic excessive alcohol consumption is a major public health problem. Abstinence results in better liver function and regression of cirrhosis. Non-invasive method to confirm cirrhosis regression should be used to encourage sustainable abstinence. We aim to prove the usefulness of transient elastography for follow up of cirrhosis regression.

Method: Transient elastography was performed in chronic alcohol users at entry into the study, and repeated at 3 and 6 months to detect changes of liver stiffness. Other nutritional measures were also implemented alongside.

Results: Forty-one patients were included in the study. The mean liver stiffness at entry was 8.8 ± 10.9 Kpa (2.4 - 52.3). Data were compared between at entry and at month 3rd in the abstinent vs. non-abstinent group. In the abstinent group, MCV was decreased (94.5 ± 9.9 vs. 88.8 ± 9.9 , $p < 0.01$, 95% CI 2.7 - 8.9); serum albumin increased (4.0 ± 0.4 vs. 4.3 ± 0.3, $p = 0.02$, 95% CI -0.5 to -0.03); and liver stiffness tended to decrease (8.9 ± 10.7 vs. 6.1 ± 3.1, $p=0.05$). Comparison of changes at month-3 between the two groups showed only ΔMCV that was statistically significant ($p=0.004$). There was no statistical significant difference in the change of Hb, WBC, body weight, triceps skin fold, and liver stiffness, either within the group or between the two groups.

Conclusion: In the abstinent group, parameters such as MCV and albumin were improved with statistical significance, and liver stiffness also tended to decrease at 3 month. The improvement of liver stiffness and nutrition could be used as encouraging information for further abstinence.

Key words : Transient elastography, liver stiffness, chronic alcohol users

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INTRODUCTION

Chronic excessive alcohol consumption is a major public health problem. Alcoholic liver disease (ALD) is characterized by a spectrum of damage, ranging from hepatic steatosis, hepatitis, and finally developed cirrhosis, which carries an increased risk of hepatocellular carcinoma. In persons who consume more than 50 gram of alcohol per day for more than 5 years, hospital-based studies using systematic liver needle biopsy (LNB) have estimated the prevalence of 17.5% for fibrosis and 25.6% for cirrhosis[1].

A study by Naveau, et al[2] in patients with alcohol intake over 50 g/day found that advanced fibrosis was present at biopsy examination in 63% (F2 - F4 by METAVIR score) of whom 31% had cirrhosis[3].

However, it is probable that severe fibrosis and asymptomatic alcoholic cirrhosis are under-diagnosed in routine clinical practice, notably because the invasiveness and potential morbidity and mortality of liver biopsy make it poorly accepted by patients. Equally, early diagnosis would be essential to motivate patients undergoing alcohol withdrawal treatment and to implement preventive measures for cirrhosis complications. In the past few years, transient elastography has been used as a non- invasive tool for the assessment of liver fibrosis by measuring liver stiffness instead. Transient elastography is performed with an ultrasound transducer probe mounted on the axis of a vibrator. A vibration transmitted from the vibrator toward the tissue induces an elastic shear wave that propagates through the tissue. These propagations are followed by pulse-echo ultrasound acquisitions and their velocity is measured, which is related directly to tissue stiffness.

Liver biopsy does not represent the overall pathology of the liver due to small specimens compared with total liver mass, whereas transient elastography examines 1/500 of the liver volume vs. 1/50000 for liver biopsy[4].

In recent studies comparing transient elastography with liver biopsy in the diagnosis of liver fibrosis in chronic liver disease from multiple etiologies, it has been found that transient elastography performs well in identifying liver fibrosis staging[5-7].

In chronic alcohol drinking, Nguyen KE, et al[8] compared transient elastography with liver biopsy and found that liver stiffness correlated well with fibrosis ($r = 0.72$, $p < 0.014$) and AUROC from this study for F≥1, F≥2, F≥3 and F=4 is 0.84, 0.91, 0.90 and 0.92 respectively.

There was a report that alcoholic abstinence or reduction of alcohol consumption improved liver pathology and survival in all stages of alcoholic liver disease[9].

As we have a cohort of alcoholic patients to follow up prospectively, we thus aim to evaluate changing of liver stiffness as measured by transient elastography in these patients, and then comparing between those becoming abstinent and those continuing to drink, as well as comparing the changes during periods of abstinence.

PATIENTS AND METHODS

The study was conducted at Maharaj Nakorn Chiang Mai Hospital and Suanprung Hospital, between March 2010 and November 2010. The protocol was approved by the Research Ethic Committee of the Faculty of Medicine, Chiang Mai University.

We received grants from the Integrated Management for Alcohol Intervention Program (I-MAP), Ministry of Public Health, Thailand, and the Gastroenterological Association of Thailand.

Patients

In collaboration with Suanprung Hospital, where a program was conducted to track and to closely follow up discharged alcoholic neuropsychiatric patients in order to reduce readmission. We included patients aged 18 or over with a history of chronic alcohol consumption of more than 50 g/day for more than 5 years who agreed give a signed to informed consent.

Exclusion criteria were as follow: ascites, uncooperative patients, BMI > 30 kg/m^2, pregnancy, chronic liver disease from other etiology such as hepatitis B or C, and refusal to give consent.

Methods

The following data were recorded: age, gender, weight, height, body mass index (BMI), alcohol intake, duration of alcohol abuse (years), triceps skin fold, complete blood count, liver function test, liver stiffness, and abdominal ultrasound findings.

Transient elastography, abdominal ultrasonography and, blood chemistry profile were performed at entry. After hospital discharge, patients were followed up at 3 months. We evaluated alcohol consumption during the period, recorded body weight and triceps

skin fold, performed transient elastography, and collected blood for complete blood count, liver function test, and gamma-GT.

Statistical analysis

As there were no previous similar studies sample size was not determined for our study, which was thus proposed as a pilot study.

Data were presented as frequency and percentage for nominal data (gender, liver pathology by ultrasonography) were and as mean ±SD for continuous data (age, liver stiffness, blood chemistry).

Comparison of hemoglobin level, WBC, MCV, albumin, and body weight between the two groups (abstinent versus non abstinent) was made using paired student *t* - test.

Comparison of changes in triceps skin fold and liver stiffness was made using non-parametric test (Wilcoxon signed ranks test).

Comparison of hemoglobin, WBC, MCV, albumin, body weight, triceps skin fold at month-3, between the two groups (abstinent vs. non-abstinent) was made by using paired student *t* - test. Non-parametric test (Wilcoxon signed ranks test) was used to compare the difference of liver stiffness.

RESULT

Between March 2010 and November 2010, 41 patients were included in this study. There were 39 male (95.1%), and 2 female (4.9%). Ultrasonography documented liver cirrhosis in 3 patients (7.3%), fatty liver in 16 patients (39%), liver parenchymal disease in 5 patients (12.2%) and normal liver in 17 patients (41.5%).

Baseline characteristics were shown in Table 1. Mean liver stiffness was 8.8 ± 10.9 kPa (2.4 - 52.3). Following the determination of liver stiffness cut-off values for the diagnosis of liver fibrosis according to the METAVIR score by Nguyen, et al[9], we noted the number of F0 (liver stiffness < 5.8 kPa) = 26 (63.4%), F1 (5.9 -7.7) = 4 (9.8%), F2 (7.8-10.9) = 6 (14.6%), F3 (11-19.4) = 1 (2.4%), and F4 (≥19.5) = 4 (9.8%).

Table 1. Baseline characteristic at entry (n= 41)

	Mean ± SD	Median	Range
Age (years)	40.4 ± 5.6	40	28-53
Weight (kg)	56.3 ± 9.5	55	40-86
Body mass index (BMI)	21.1 ± 2.8	20.8	16.1-28.6
dose alcohol (g/day)	253.1± 151.7	243.2	64-729.6
duration (years)	17.5 ± 5.8	18	7-28
CBC			
-Hb (g/dL)	13.4 ± 1.8	13.3	9.1-18.1
-Hct (%)	41.3 ± 5.4	42	28.2-54.8
-WBC (cell/mm^3)	8287.8 ± 3560.7	7500	3100-20600
-Platelet (cell/mm^3)	228926.8 ± 126490.7	224000	59000-671000
-MCV (Fl)	95.4 ± 9.1	97	69-111
LFT			
-Total protein (g/dL)	7.3 ± 0.6	7.3	6.3-8.8
-Albumin (g/dL)	4.0 ± 0.4	4	2.6-4.7
-ALP (U/L)	79.4 ± 35.9	73	28-178
-AST (U/L)	73.2 ± 58.2	55	15-283
-ALT (U/L)	45.7 ± 35.3	33	3-160
-TB (mg/dL)	1.2 ± 1.1	0.8	0.2-5.6
-DB (mg/dL)	0.6 ± 0.6	0.4	0-3.1
Triceps skin fold (mm)	9.4 ± 4.8	7	3-20
Liver stiffness (kPa)	8.8 ± 10.9	5.4	2.4-52.3

Month-3 follow up data

Six patients were lost to follow up (14.6%) and 35 turned up for follow up (85.4%). Alcoholic status was: abstinent 15 (42.9%), non-abstinent 20 (57.1%). Overall, most patients drank less than before (19 in 20) and less frequently comparing with before entry into the study.

Liver Stiffness

Comparable parameters at month 3rd were shown in Table 2. Following Nguyen KE, et al[8] determination of liver stiffness cut-off values, we noted F0 (<5.8) = 24 (68.6%), F1 (5.9 - 7.7) = 6 (17.1%), F2 (7.8 - 10.9) = 2 (5.7%), F3 (11 - 19.4) = 1 (2.9 %), and F4 (≥19.5) = 2 (5.7%).

When we compared liver stiffness at entry and at month-3 in the abstinent and non-abstinent groups, it was interesting that in the abstinent group liver stiffness tended to decrease from the entry value (8.9 ± 10.7 vs. 6.1 ± 3.1, p=0.05).While in the non-abstinent group, there was no change of liver stiffness (8.4 ± 12.2 vs. 9.0 ± 13.8). Interestingly, the mean changes in liver stiffness in the 2 groups (2.8 ± 8.0 vs. -0.5 ± 4.3) revealed no significant difference (p=0.12).

Table 2. Characteristic data at month-3 (n=35).

	Mean ± SD	Median	Range
Weight (kg)	56.9 ± 8.7	55	44-78
CBC			
-Hb (g/dL)	14.1 ± 1.4	14.3	10.9 - 16.4
-Hct (%)	43.3 ± 4	43.9	35.3 - 50.9
-WBC (cell/mm^3)	6368.9 ± 1607.4	6100	4300-11500
-Platelet (cell/mm^3)	235914.3 ± 81376.2	248000	58000-493000
-MCV (Fl)	91.8 ± 9.3	93.6	69-110
LFT			
- Total protein (g/dL)	7.5 ± 0.5	7.6	6.4 -8.4
-Albumin (g/dL)	4.2 ± 0.4	4.3	3-4.8
-ALP (U/L)	73.7 ± 26.8	66	33-142
-AST (U/L)	72.3 ± 145	34	18-872
-ALT (U/L)	43.3 ± 45.4	27	12-243
-TB (mg/dL)	0.8 ± 0.4	0.63	0.3-2.4
-DB (mg/dL)	0.2 ± 0.1	0.13	0.03-0.81
GGT	237.3 ± 434	80	17-2180
Triceps skin fold (mm)	8.6 ± 3.9	7	4-17
Liver stiffness (kPa)	7.78 ± 10.6	4.8	2.1 - 49.6

Table 3. Comparison data of at entry and month-3 in non-abstinent group (n=20).

	At baseline	At month-3	p- value
Hb (g/dL)	13.6 ± 1.7	13.8 ± 1.5	0.67
Wbc (cell/mm^3)	8305 ± 3974.2	6030.5 ± 1002	0.02
MCV (Fl)	95.1 ± 9.4	94.1 ± 8.4	0.24
Albumin (g/dL)	4.03 ± 0.5	4.1 ± 0.4	0.51
BW (kg)	55.1 ± 7.9	55.6 ± 7.7	0.45
Triceps skin fold (mm)	9.6 ± 4.5	9.1 ± 3.9	0.41
Liver stiffness (kPa)	8.4 ± 12.2	9.0 ± 13.8	0.82

Table 4. Comparison data of at entry and month 3 in abstinent group (n=15).

	At baseline	At month-3	*p*-value
Hb (g/dL)	13.7 ± 2.1	14.5 ± 1.1	0.15
Wbc (cell/mm^3)	8186.7 ± 3582.1	6820 ± 2128.5	0.23
MCV (Fl)	94.5 ± 9.9	88.8 ± 9.9	<0.01
Albumin (g/dL)	4 ± 0.4	4.3 ± 0.3	0.03
BW (kg)	58.1 ± 9.1	58.7 ± 9.8	0.68
Triceps skin fold (mm)	8.5 ± 4.9	8 ± 3.9	0.91
Liver stiffness (kPa)	8.9 ± 10.7	6.1 ± 3.1	0.05

Table 5. Comparison data at month-3 between abstinent and non-abstinent.

	Non-abstinent	Abstinent	*p*-value
Hb (g/dL)	13.8 ± 1.5	14.5 ± 1.1	0.15
Wbc (cell/mm^3)	6030.5 ± 1002	6820 ± 2128.5	0.20
MCV (Fl)	94.1 ± 8.4	88.8 ± 9.9	0.09
Albumin (g/dL)	4.1 ± 0.4	4.3 ± 0.3	0.18
BW (kg)	55.6 ± 7.7	58.7 ± 9.8	0.31
Triceps skin fold (mm)	9.1 ± 3.9	8 ± 3.9	0.42
Liver stiffness (kPa)	9.02 ± 13.8	6.1 ± 3.1	0.16

Other nutritional parameters

Of the parameters we chose to follow, i.e. serum albumin, mean corpuscular volume (MCV) of the red blood cell, triceps skin fold, and body weight, we found that in the abstinent group MCV decreased significantly (94.5 ± 9.9 vs. 88.8 ± 9.9, $p < 0.01$, 95% CI 2.7 - 8.9) while serum albumin increased significantly (4.0 ± 0.4 vs. 4.3 ± 0.3, $p = 0.02$, 95% CI -0.5 to -0.03). There were no significant changes of triceps skin fold and body weight (Table 3).

A in the non-abstinent group, there were no changes of such parameters other than decreased of white blood cells from 8,305 ± 3,974 to 6,030 ± 1,002 (p=0.02). We have no satisfactory explanation for this change (Table 4).

Comparison of changes at month-3 (Δ between entry and month-3) in the abstinent and non-abstinent groups showed that only ΔMCV was significant (p=0.004) (Table 5).

Discussion

In our study, we found that among heavy alcohol drinkers, their nutritional status improved remarkably after 3 months of abstention.

Improvement was reflected not only from increased body weight or triceps skin fold, but also increased serum albumin and decreased MCV. Increase of serum albumin resulted from improved nutrition and/or improved liver function. Decreased MCV reflected depletion of vitamin B12 and folate that was corrected through better nutrition intake.

We also observed a trend for improvement of liver stiffness, although this was not statistically significant. The initial averaged liver stiffness was rather low, so any improvement would be hard to document. More cases with higher initial fibrosis score would be needed to demonstrate later improvement more reading.

In spite of our efforts to keep the patients in touch to remain abstinent, a significant proportion (14.6%) was lost to follow up. For the remaining only about 40% could maintain abstinence. We lost even more patients after 6 months, and some who were abstinent at month-3 later resumed drinking again. More subjects would have to be recruited for such study as ours to achieve a meaningful analysis after excluding lost cases and cases of non-compliance.

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