BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Sonographic Measurement of the Thickness of Subcutaneous Tissue and Hepatic Echo-Intensity Attenuation Rate in Non-alcoholic Fatty Liver Disease

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Received: 24 September 2019

Accepted: 16 January 2020

Keywords:
subcutaneous tissue thickness, hepatic echo-intensity attenuation rate, non-alcoholic fatty liver disease, sonography

ABSTRACT

The most common cause of the chronic liver disease is non-alcoholic fatty liver disease (NAFLD). This study was designed to compare a mean subcutaneous tissue thickness (SCTT) and hepatic echo-intensity attenuation rate (HEIAR) among NAFLD grades. Sonography was carried out on 628 consecutive subjects. The distance between the skin surface and the liver capsule was measured and was labelled the SCTT. Also, the ultrasound of HEIAR was retrospectively quantified on an image archiving. HEIAR was calculated as the difference between mean intensity of echo for two regions of interest (ROIs) in near- and far-fields divided by the distance between these two ROIs multiply by frequency of the probe. Of the 628, 235 subjects were diagnosed with NAFLD. The age range was 45 – 75 years with mean 54.5 ± 6.7 years. There was a significant difference of mean SCTT among NAFLD grades ($p<0.001$), 65.4% of subjects with SCTT measured ≥ 2.1 cm had NAFLD versus 34.6% of subjects had no NAFLD. Similarly, the differences of mean HEIAR among NAFLD grades were reported to be statistically significant ($p<0.001$). All of the subjects with HEIAR of 1. 7dB/cm MHz and over had NAFLD. HEIAR is a useful indicator for non-invasive quantitative assessment of NAFLD where sonographically measured HEIAR equal to or over than 1.7 dB/cm MHz makes identifying NAFLD is probably (sensitivity is 59% and specificity is 89%). HEIAR is a useful indicator for non-invasive quantitative assessment of NAFLD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide[1]. It is also the most common cause for the chronic elevation of the liver enzymes in United States nowadays[2]. Histologically, NAFLD is defined as excessive fat accumulation in the liver tissues over 5% of the wet liver weight due to causes other than alcohol intake[3, 4]. Dyslipidaemia is the most common condition that can lead to fatty liver disease. An abnormal circulating lipoprotein concentration has reflected the disturbances in the homeostasis of the major lipid components of TG, lipoproteins, TC, and cholesterol esters. Lipids conveyed in the blood plasma are composed of lipoprotein complexes. After eating, fat-food and TC are deposited into the intestine cells and then connected with newly resultant chylomicrons. With energy increases, the glucose is transformed into fatty acids. The latter is further utilized to build up TG. TG is stored in the form of fat droplets in the hepatocytes or merged with VLDL and then excreted into the bloodstream. In this manner, the TG content of these molecules is piecemeal decreased by the action of the lipoprotein lipase that leads to LDL with comparative increases in the cholesterol content. LDL is transported and deposited into the liver by linking the LDL to the LDL receptor. Hence, excess deposition of TG in hepatocytes is considered the hall-mark of NAFLD[5]. It roughly affects 20 – 40 % of Western population[6]. In Asia, it was initially uncommon but with the increase in obesity and diabetes mellitus (DM)[7], it would also be on the increase with affecting 12 – 37 % of general population[8 – 15]. NAFLD encompasses a wide spectrum of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) that leads to fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC)[16]. Nevertheless, NAFLD is still considered as a benign disease unless it develops into steatohepatitis and fibrosis[17]. Its association with insulin resistance and obesity has been well reported where a previous study showed that NAFLD was strongly correlated with hypertriglyceridaemia, type 2 DM and obesity[18]. Furthermore, fatty liver changes are likely to be as the hepatic manifestation of the metabolic syndrome[13]. Interestingly, Targher, Marra & Marchesini G (2008)[19] indicated that NAFLD is not only a risk factor for chronic liver disease but it is also considered an independent risk factor for developing cardiovascular disease (CVD).

Currently, ultrasound is widely used for detection NAFLD because it is a non-invasive machine, safe (with no radiation hazard), available and less expensive than other radiological modalities such as magnetic resonance imaging and computed tomography[20]. There are sonographic features could indicate to fatty liver changes, two of the idealistic features are an increased hepatic echo-intensity attenuation rate (HEIAR) of the liver parenchyma and also increased subcutaneous tissue thickness (SCTT). Therefore, the present study was designed to define a cut-off value of the hepatic echo-intensity attenuation rate above which NAFLD is likely. We also sought to compare the SCTT in subjects with and without NAFLD.

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MATERIALS AND METHODS

A prospective cross-sectional study was carried out among Malaysian adults with age ranges between 45 to 75 years who underwent screening programme for the period from 15 August 2015 until 15 January 2016 at Golden Horses Health Sanctuary (GHHS) located in Seri Kembangan, Klang Valley, Malaysia. Ethical from Ethics Committee for Research Involving Human Subject (JKEUPM) with number UPM/TNCPI/RMC/1.4.18.1(JKEUPM)/F2 was obtained prior to conducting of this study. Each respondent was informed about the study verbally and in writing according to Good Clinical Practice, after that, informed consent was obtained from all respondents before the commencement of this study.

Males who have drunk alcohol over 140 g/week and females over 70 g/week, were hepatitis B or C viruses carrier, previous liver insults or surgery, pregnancies, taken corticosteroid or lipid-lowering medications were excluded from the study. The subjects were randomly selected using a systematic sampling method. Liver ultrasound was performed on 628 consecutive subjects by a single radiologist with experience over 10 years using Philips (HD 15) medium-range machine with a convex-array probe (3.5 MHz). A standard approach has been used in image acquisition. The subjects have been recommended not to eat any food by mouth for 8 hours prior to the examination; if the fluid is needed, only plain water should be taken. The subject lied in the supine position with his/her right arm elevated above the head. The coupling agent (gel) was applied to the right upper abdomen. The radiologist started the examination with a longitudinal scan. Afterwards, the transverse scan and intercostal scan along the mid-axillary line were achieved. The distance between the skin surface and the liver capsule was measured and labelled as the SCTT. Therefore, an attempt was made to reduce compression of subcutaneous tissue by the probe.

The normal liver parenchyma is homogenous in echotexture with reflectively (echogenicity) equal to or slightly greater than that of the renal cortex and spleen. Therefore, fatty liver changes were qualitatively assessed based on the increase in reflectively of liver parenchyma compared to the right renal cortex and spleen[21, 22]. The determination cut-off value of HEIAR to define fatty liver changes was based on the mean of the hepatic echo-intensity attenuation rate among NAFLD grade I. NAFLD grades were also qualitatively assessed based on reflectively of intrahepatic vessels walls and diaphragm (Figure 1). When there is no increased in reflectively of the liver parenchyma compared to the renal cortex or spleen, it is described as grade 0 or normal. When there is slightly increased in reflectively of the liver parenchyma, it is described as grade I or mild. When there is increased in reflectively of the liver parenchyma with loss visualization of portal vascular walls, it is described as grade II or moderate. When there is markedly increased in reflectively of the liver parenchyma with poor or no visualization of the posterior portion of the diaphragm, it is described as grade III or severe [22-25].

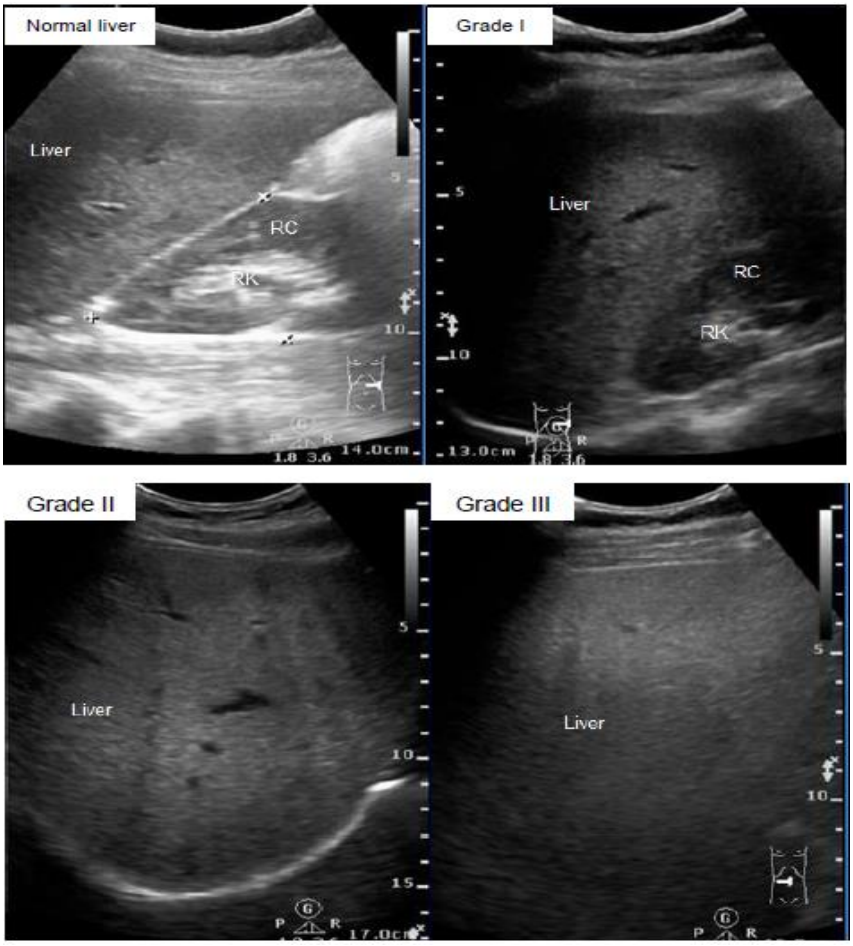

Figure 1 Various grades of diffuse fatty liver disease as compared with the normal liver (the pictures were taken from the study population)

In meanwhile, the ultrasound HEIAR was retrospectively quantified on an image archiving. On the liver image, the observer selected two ROIs of 5 mm square in the liver homogenous area along the ultrasound beam in the near-field (depth 3 – 5 cm) and far-field of the liver, respectively, avoiding vessels and artefacts. The distance between the two ROIs were also measured (Figure 2).

HEIAR was calculated according to the equation below:

HEIAR = $(lnEn\text{-}lnEf)/(\Delta d \times f)$; where

lnEn and *lnEf* are the mean intensity of echo in near-field and far-field of the liver, respectively.

Δd is the distance between two liver ROIs.

f is the ultrasound frequency of transducer and was used 3.5 MHz in this study.

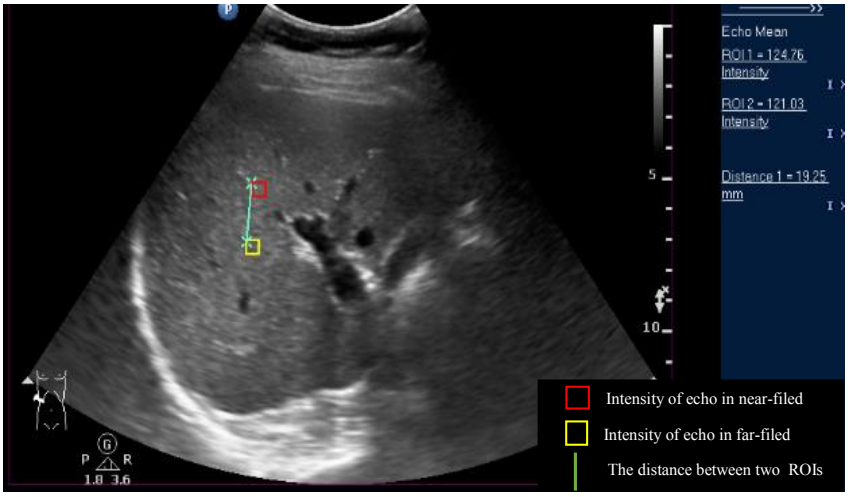

Figure 2 Hepatic echo-intensity attenuation rate on ultrasound. Image shows the liver intercostal view with the drawing of two ROIs in near-field and far-field at the homogenous area in the liver parenchyma. The distance was measured from the top corner of the near-field ROI into the top corner of far-field ROI

Statistical Analysis

Data analysis was performed using Statistical Package for Social Science (SPSS) program version 22.0. First, descriptive analysis was carried out to calculate the percentages of each factor among the study population. Chi-square test was performed to determine the association between categorical variables. In addition, sensitivity and specificity were calculated based on crosstab from the descriptive statistic. Analysis of variance (ANOVA) was achieved to compare a mean among more than three groups with normally distributed data. A p-value of < 0.05 was considered statistically significant.

RESULTS

Of the 628 consecutive subjects with a mean age of 54.5 ± 6.7 years who underwent a screening programme and met the inclusion criteria in this study. Table 1 shows characteristics of the study population based on the distribution of age, gender, ethnicity, presence of disease and its grades. Of 235 (37.4%) subjects diagnosed with NAFLD and 393 (62.6%) subjects were not found to have NAFLD. Of those with NAFLD, there were 9.6% of subjects with a mild grade of fatty liver, 23.7% with a moderate grade and 4.1% with severe grade. The females had a higher percentage than males in our study population and overwhelming Chinese in race reflecting the urban population from which is derived from.

Table 1 Basic socio-demographic characteristics of study population (*n* = 628)

Variables	*n* (%)	mean ± SD
Age	–	54.54 ± 6.69
Gender		
Male	302 (48.1)	–
Female	326 (51.9)	–
Race		
Malay	92 (14.6)	–
Chinese	518 (82.5)	–
Indian	18 (2.9)	–
NAFLD		
Yes	235 (37.4)	–
No	393 (62.6)	–
NAFLD grades		
Grade I (mild)	60 (9.6)	–
Grade II (moderate)	149 (23.7)	–
Grade III (severe)	26 (4.1)	–

NAFLD: Non-alcoholic Fatty Liver Disease

Based on one way ANOVA test, Table 2 shows the differences of means SCTT and HEIAR among NAFLD grades. The mean SCTT was 1.8 ± 0.4 cm in grade 0 (normal), 2.1 ± 0.5 cm in grade I (mild), 2.2 ± 0.5 cm in grade II (moderate) and 2.6 ± 0.7 cm in grade III (severe). This indicates that differences in mean SCTT among NAFLD grades were noted to be significant (p <0.001). According to HEIAR, the results also revealed that mean HEIAR was 0.8 ± 0.7 cm in grade 0 (normal), 1.7 ± 1.3 cm in grade I, 2.2 ± 1.3 in grade II and 3.0 ± 1.5 cm in grade III. This indicates that there are significant differences in mean HEIAR among NAFLD grades (p <0.001)

Table 2 Differences of means HEIAR and SCTT among NAFLD grades (*n* = 628)

variables	NAFLD grades				F-statistics (df)	*p*-value
	Grade 0 (*n* = 393)	Grade I (*n* = 60)	Grade II (*n* = 149)	Grade III (*n* = 26)		
HEIAR (dB/cm.MHz)	0.8 ± 0.7	1.7 ± 1.3	2.2 ± 1.3	3.0 ± 1.5	9.277 (2)	< 0.001
SCTT (cm)	1.8 ± 0.4	2.1 ± 0.5	2.2 ± 0.5	2.6 ± 0.7	9.133 (2)	< 0.001

HEIAR: Hepatic echo intensity attenuation rate; dB: decibel, cm: centimetre; SCTT: Subcutaneous Tissue Thickness

According to the Chi-square test, Table 3 shows an association between SCTT and HEIAR with NAFLD. As grade I is considered initial stage of NAFLD, so that we adopted mean of the SCTT in grade I (2.1 cm) as a cut-off value to likely diagnose NAFLD where there were 65.4% (149/228) of subjects with SCTT measured ≥ 2.1 cm had NAFLD versus 34.6% (79/228) of subjects without NAFLD with sensitivity 52% and specificity 86%. Among subjects with SCTT < 2.1 cm, there were 21.5% (86/400) of subjects with NAFLD versus 78.5% (314/400) with no NAFLD.

Table 3 Chi-Square of HEIAR and SCTT with NAFLD

Variables	NAFLD status		X^2 (df)	*P*-value
	Yes, *n* (%)	No, *n* (%)		
HEIAR			405.7 (1)	<0.001
(≥1.7 dB/cm. MHz), (*n* = 175)	175 (100.0)	0 (0.0)		
(<1.7 dB/cm. MHz), (*n* = 453)	60 (13.2)	393 (86.7)		
SCTT			119.2 (1)	<0.001
(≥2.1 cm), (*n* = 228)	149 (65.4)	79 (34.6)		
(<2.1 cm), (*n* = 400)	86 (21.5)	314 (78.5)		

Thus, Figure 3 illustrates the thinning of SCTT (less than 2.1 cm) in subject with normal liver whereas Figure 4 illustrates the thickening of SCTT (more than 2.1 cm) in a patient with NAFLD. Moreover, the mean HEIAR in grade I (1.7 dB/cm. MHz) has been depended for detecting NAFLD, where 175 out of 175 (100.0%) subjects with HEIAR of 1.7 dB/cm. MHz or above had NAFLD with sensitivity 59% and specificity 89%. In contrast, only 60 out of 453 (13.2%) subjects with NAFLD had HEIAR less than 1.7 dB/cm.MHz.

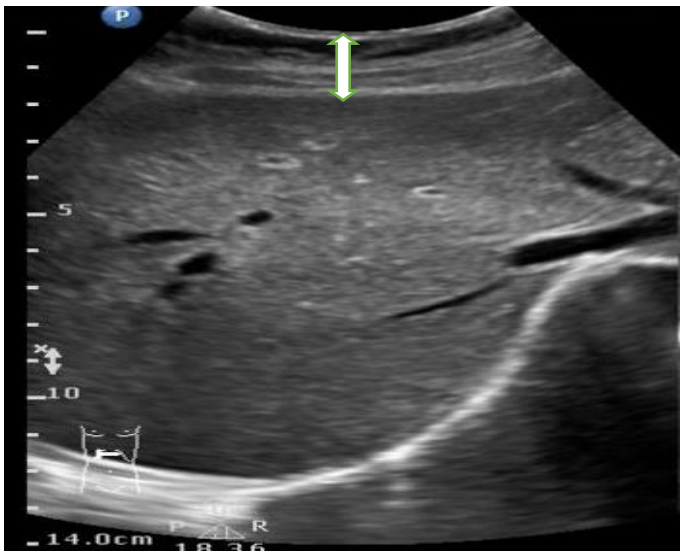

Figure 3 Normal liver sonography demonstrates a subcutaneous tissue thickness (arrow) of less than 2.1 cm

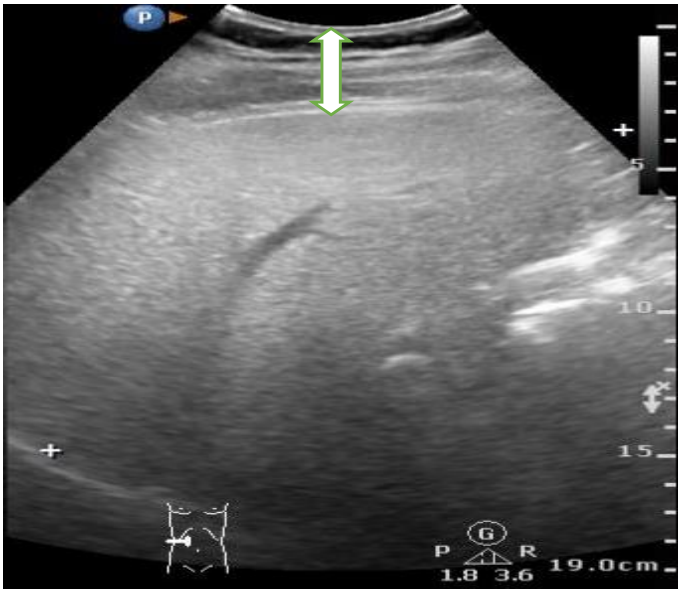

Figure 4 Sonography in of NAFLD patient demonstrates a subcutaneous tissue thickness (arrow) of more than 2.1 cm

DISCUSSION

Although ultrasound is valuable to diagnose NAFLD, the liver biopsy is still considered as the reference tool for the detection, quantifying and grading of NAFLD as well as its ability to differentiate between NAFLD and nonalcoholic steatohepatitis (NASH)[25, 26]. However, sampling error may occur because the fat infiltration is sometimes unequally distributed in hepatocytes[27]. Moreover, the biopsy is an invasive tool and has some risks which lead to serious complications. In this study, qualitative and quantitative ultrasound methods were used for assessment of fatty liver disease. The qualitative method describes the fatty liver disease based on increasing in reflectively of the liver parenchyma compared to the renal cortex[28].

In contrary, the quantitative ultrasound method of HEIAR is an additional method that can be applied to the detection of NAFLD. In the present study, we present a method to quantify fatty infiltration in hepatocytes using ultrasound HEIAR. The ultrasound HEIAR is an objective, computer-calculated index. This idea is not new innovative but it is identical to concepts addressed in previously published studies with some amendments of practical points. Although Fujii et al. (2002)[29] and Itoh et al. (1988)[30] indicated that sonographically measured the attenuation coefficient would be used for ultrasound quantitative assessment of the grading of fatty liver changes. The researchers needed specific systems to quantify the attenuation coefficient and these are hard to use in the factual clinical area. In our study, ultrasound evaluated the hepatic attenuation because it demonstrates a 256-level grayscale brightness on screens which is no highly accurate but could be useful. Although Webb et al. (2009)[26] stated that the hepatorenal index was beneficial for quantification of hepatic steatosis, the various disease processes can, unfortunately, alter the echogenicity of the renal cortex. Moreover, the activated of time-gain compensation (TGC) activated as a default function using by most sonographers is considered a confounding factor to compensate for the echogenicity of deeper attenuated areas. Therefore, in the present study, we thwarted the activation of TGC because it is an inverse objective to measure the ultrasound attenuation.

In light of that, Sonographic quantitative assessment was used to quantify the mean of HEIAR among NAFLD grades as well as adoption these means in grade I as cut-off values to likely identify NAFLD. Our study reported a high difference of HEIAR among NAFLD grades. Importantly, mean HEIAR in grade I was 1.7 dB/cm.MHz, thereby we found that the prevalence of NAFLD was 100% among patients who had HEIAR equal to or greater than 1.7 dB/cm.MHz. Hence, sonographically measured HEIAR equal to or over than 1.7 dB/cm.MHz makes the diagnosis of NAFLD probably. Incompatible with our study, Zhang et al. (2012)[31] confirmed that the difference of HEIAR between NAFLD and non-NAFLD was strongly significant. On equal importance, Kwon et al. (2013)[32] assessed cut-off values of the ultrasound attenuation index for estimation severe hepatic steatosis using two probes 4 MHz and 8 MHz. The researchers reported that optimal ultrasound attenuation index cut-off value of 31.0 at 8 MHz is beneficial to approach for non-invasive diagnosis of severe hepatic steatosis.

Furthermore, this study has also compared the means of SCTT among NAFLD grades where we depend on the mean in grade I as cut-off values to likely identify NAFLD. As expected, our results revealed a close correlation between SCTT and NAFLD grades. In addition, most of the healthy subjects had less than mean SCTT in grade I (less than 2.1 cm). Our study is partially consistent with a study done by Riley & Bruno (2005)[33], which reported that the diagnosis of NAFLD among subjects with SCTT measuring sonographically less than 2.0 cm is unlikely.

CONCLUSION

Sonographically measured SCTT is not strongly approached to diagnose NAFLD. Nevertheless, HEIAR is a useful indicator for non-invasive quantitative assessment of NAFLD.

ACKNOWLEDGMENTS

The authors would like to acknowledge the help of Dr Norafida Bahari, a radiologist from the Department of Imaging, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. The authors are also thankful and grateful to all of the administrators and medical personnel who have willingly helped out with their abilities in Golden Horses Health Sanctuary, Klang Valley.

CONFLICT OF INTEREST

The authors declare that they have co competing interests in publishing this article.

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