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Original Article

Radiology Section

Assessment of Portal Venous and Hepatic Artery Haemodynamic Variation in Non-Alcoholic Fatty Liver Disease (NAFLD) Patients

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ABSTRACT

Introduction: Non-Alcoholic Fatty Liver Disease (NAFLD) has various spectrums of liver diseases like isolated fatty liver, steatohepatitis and cirrhosis usually progressing in a linear fashion. In this process they are known to cause certain haemodynamic changes in the portal flow and hepatic artery flow.

Aim: The aim of the study was to study these haemodynamic changes in patients with NAFLD and to correlate it with the disease severity.

Materials and Methods: Ninety patients diagnosed to have NAFLD based on ultrasound abdomen (30 each in grade1, grade2 and grade3 NAFLD) and 30 controls (Normal liver on ultrasound abdomen) were subjected to portal vein and hepatic artery Doppler study. Peak maximum velocity (Vmax), Peak minimum velocity (Vmin), Mean flow velocity (MFV), and Vein pulsality index (VPI) of the portal vein and hepatic artery resistivity index (HARI) of the hepatic artery were the doppler parameters which were assessed. Liver span was also assessed both for the fatty liver and controls.

Results: The mean Vmax, Vmin, MFV and VPI of the portal vein in patients with NAFLD was 12.23±1.74cm/sec, 9.31±1.45cm/sec, 10.76±1.48cm/sec, and 0.24±0.04 as compared to 14.05±2.43cm/sec, 10.01±2.27cm/sec, 12.23±2.47cm/sec, 0.3±0.08 in controls respectively. All these differences were statistically significant except for Vmin. The Mean HARI in patients with fatty liver was 0.65±0.06 when compared to controls of 0.75±0.06 (p=0.001). HARI (r-value of -0.517) had a better negative correlation followed by VPI (r-value of -0.44) and Vmax (r-value of -0.293) with the severity of NAFLD. MFV had a very weak negative correlation (r-value of -0.182) with the severity of NAFLD.

Conclusion: The Vmax, MFV, VPI and HARI were significantly less when compared to controls suggesting a reduced portal flow and an increased hepatic arterial flow in patients with NAFLD. Among the parameters, HARI correlated better with the severity of NAFLD followed by VPI.

Keywords: Hepatic artery resistivity index, Portal doppler, Portal vein pulsality index

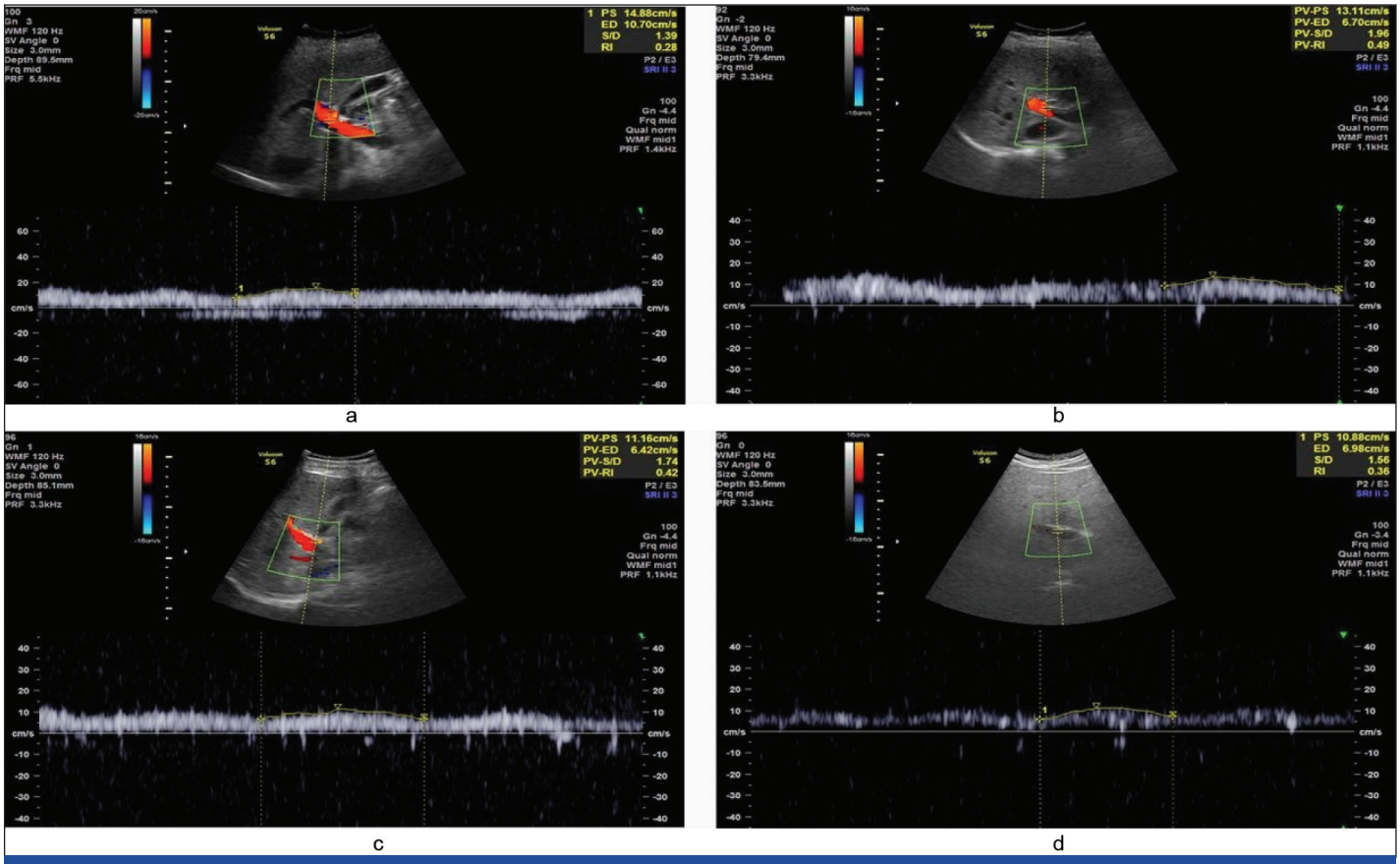
INTRODUCTION

The Non-alcoholic Fatty Liver Disease (NAFLD) currently affects one fourth to one third of world's general population and is on the rise with increasing prevalence of diabetes and obesity [1-3]. It has become a global burden with people developing complications like steatohepatitis, cirrhosis and eventually hepatocellular carcinoma. Currently it is the third common indication for liver transplant and is expected to be the first in the year 2020. India being the diabetic capital of the world is particularly at increased risk of incidence of NAFLD and the prevalence ranges from 16.6% to as high as 39% [4-6]. Various studies done to assess the vascular dynamics of liver in patients with fatty liver disease have shown that with increasing severity of NAFLD there are significant changes in the haemodynamics of the hepatic circulation which can determine the prognosis of the condition [7,8]. Literature regarding this from India is limited and so it was decided to conduct a study among patients with NAFLD who were attending one of the tertiary care centre in Pondicherry, Tamil Nadu, India.

MATERIALS AND METHODS

It was a prospective case control study done at Aarupadai Veedu Medical College and Hospital in Pondicherry between September 2015 and February 2016 after obtaining the institutional ethical committee clearance. The ultrasound abdomen was performed by a single radiologist with seven years of institutional experience in the field of ultrasound abdomen using GE Voluson S6 machine with a low frequency transducer (3.5MHz) with the patients on four hours of fasting. Consecutive patients diagnosed to have fatty liver disease (When the echogenecity of the liver was increased than that of the renal cortex) based on ultrasound abdomen attending the general medicine out patient department were considered as cases eligible for the study. Patients taking alcohol of >20g/day, hepatitis B infection, Hepatitis C infection, patients already diagnosed to have chronic liver disease were excluded from the study. Severity of the fatty liver was then graded based on the USG findings into grade 1 (mild) if the echogenicity was slightly increased, with normal visualization of the diaphragm and the intrahepatic vessel borders, grade 2 (moderate) if the echogenicity was moderately increased, with slightly impaired visualization of the diaphragm or intrahepatic vessels and grade 3 (severe) if the echogenicity was markedly increased with poor visualization of the diaphragm, the intrahepatic vessels and the posterior portion of the right lobe [9]. Healthy volunteers with normal appearing liver on ultrasound abdomen were taken as the controls.

Thirty consecutive patients in each of the grades of the NAFLD and 30 controls were then finally included in the study. Patients consuming alcohol more than 20g/day, critically ill patients, haemodynamically unstable patients, patients not willing for the study and patients with morbid obesity posting difficulty in doppler measurement, were excluded from the study. Portal venous Doppler indices namely peak maximum velocity (Vmax) [Table/Fig-1], and peak minimum velocity (Vmin), Mean Flow Velocity (MFV), portal Vein Pulsatility Index (VPI), along with hepatic artery resistivity index (HARI) were measured. The Portal VPI was calculated using



[Table/Fig-1]: Spectral dropper ultrasound pictures showing maximum peak velocity of 14.8 cm/s, 13.1 cm/s, 11.16 cm/s and 10.8 cm/sec in the portal vein of patients without fatty liver (a), Grade 1 (b), Grade 2 (c), and Grade 3 (d) fatty liver respectively.

the formula; VPI= (Vmax-Vmin)/ Vmax [10,11]. The portal vein measurements were all done in the left lateral decubitus position with breath held in inspiration and the measurements were taken at the level of the main portal vein before the bifurcation [12]. The hepatic artery indices were measured at the level of porta hepatis with patient lying in the supine position [12]. Liver span was also measured in all the subjects. Later observations of the measured indices were analysed using suitable statistical methods and were correlated with the severity of grading of the NAFLD.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 23 software (Trial Version). Numerical variables are expressed as mean ± standard deviation and categorical variables as percent (%). ANOVA test was used to compare the doppler indices and liver span between the controls and patients with fatty liver and a p-value ≤ 0.05 was considered to be statistically significant. Spearman test was used to find out whether the doppler parameters correlated with the severity of the NAFLD. To find out whether the age and gender were associated with severity of fatty liver, correlation test and chi square tests were used respectively.

RESULTS

In this study the mean age of the patients with fatty liver was 41 and the controls was 42.4. Among the controls, 16 were females and 14 were males and among the cases 46 were females and 44 were males. There was no statistically significant difference between the cases and controls with respect to the age and sex. The mean Vmax, Vmin, MFV, VPI, HARI and liver span of the controls and patients with fatty liver were shown in the [Table/Fig-2]. It was found that differences in all the indices except the Vmin were statistically significant between the controls and patients with fatty liver. The Vmax, Vmin, Portal vein pulsality index was found to be significantly lesser in the fatty liver group when compared to the controls. The HARI was also significantly less in the fatty liver group when compared to the controls. The mean liver span in controls was 14.07 ±0.77 and it was found to be significantly higher (15.63±0.67) in the fatty liver group.

The mean Vmax, MFV, VPI, HARI and the liverspan according to the grading of fatty liver is shown in the [Table/Fig-3]. Using spearman test it was found that Vmax, MFV, VPI and HARI negatively correlated and the liver span positively correlated with the severity of the NAFLD. i.e., the Vmax, MFV, VPI and HARI decreases and the liverspan increases as the severity of the fatty liver increases. In our study age and the sex of the patient didn't show any association with the severity of the fatty liver.

Doppler Indices	Controls (n=30)	Patients with Fatty liver (n=90)	p-value
Vmax (cm/sec)	14.05 ± 2.43	12.23 ± 1.74	0.001
Vmin (cm/sec)	10.01 ± 2.27	9.31 ± 1.45	0.158
MFV (cm/sec)	12.23 ± 2.47	10.76 ± 1.48	0.001
VPI (cm/sec)	0.30 ± 0.08	0.24 ± 0.04	0.001
HARI	0.75 ± 0.06	0.65 ± 0.06	0.001
Liverspan	14.07 ± 0.77	15.63 ± 0.67	0.001

[Table/Fig-2]: The comparison of mean doppler indices in controls and patients with fatty liver.

Doppler indices	Grade I (n=30)	Grade II (n=30)	Grade III (n=30)	r-value	p-value
Vmax (cm/sec)	12.93±2.35	12.2±1.46	11.57±0.83	-0.293	0.005
MFV (cm/sec)	11.25±1.97	10.67±1.28	10.37±0.87	-0.182	0.086
VPI (cm/sec)	0.26±0.04	0.25±0.04	0.21±0.04	-0.449	0.0001
HARI	0.69±0.0.04	0.66±0.05	0.613±0.05	-0.517	0.0001
Liverspan	15.04±0.43	15.8±0.41	16.06±0.66	+0.611	0.0001

[Table/Fig-3]: Shows comparison of the doppler indices with grades of fatty liver subjects.

DISCUSSION

NAFLD came into existence in 1980's when Ludwig and his colleagues observed changes similar to alcoholic hepatitis in a group of patients without history of alcohol intake, wherein they

introduced the term; Non-Alcoholic Steatohepatitis (NASH) [13]. Later the concept of NAFLD was well established with more understanding of its pathophysiology. Ever since its introduction the incidence of NAFLD is on the rise with increasing incidence of diabetes and obesity which are considered the most important and common risk factors for this condition. The spectrum of the disease is similar to alcoholic liver disease and includes Isolated Fatty Liver (IFL), NASH, cirrhosis, and eventually Hepatocellular Carcinoma (HCC) which corresponds to the severity and the duration of the disease [14,15].

Though histopathology is considered the gold standard for the diagnosis of NAFLD, it is not practically possible to do biopsy for the huge population of NAFLD, considering its deadly complications. Hence imaging modalities (Ultrasonogram, Computed Tomography, Magnetic Resonance Imaging) are now becoming a reasonable and acceptable option for diagnosing NAFLD. It has been shown in some studies that, as the disease progresses from isolated fatty liver to non-alcoholic statohepatitis to cirrhosis the haemodynamics in the portal vein also changes as the resistance to the blood flow in these vessels increases secondary to changes happening in the liver (Inflammation, inflammation with or without fibrosis, fibrosis) and also these changes respond after treatment [16-19]. Certain studies have also shown that as a compensatory mechanism the flow in the hepatic artery increases and the HARI in these patients decreases as the severity of the fatty liver increases [18-20]. Only very few studies have correlated the portal venous and hepatic artery indices with the different grades of severity of the NAFLD and hence this study was done firstly to find out whether there is significant haemodynamic changes in the portal vein and hepatic artery in patients with NAFLD when compared to the controls and secondly whether the haemodynamic changes correlates with the severity of the NAFLD which was assessed by USG grading [17,21,22].

In this study it was found that the velocity of the portal flow (Vmax and MFV) and the portal VPI were less in patients with fatty liver when compared to the controls and it also correlated with the severity of the fatty liver. However, though not very strong, only HARI (r-value of -0.517) and VPI (r-value of -0.449) had a better correlation with the grading of the severity of NAFLD when compared to Vmax (r-value of -0.293) and MFV (r-value of -0.182). Our findings of Vmax, MFV, VPI and Vmin was very similar to the studies by Erdogmus B et al., and Balci et al., [17,23], and most of the others emphasizes the hypothesis that the fatty infiltration of the liver causes increased resistance to the flow of portal vein thereby reducing the portal blood flow to the liver [21,22,24]. It was found that the HARI also decreases as the severity of the fatty liver increases suggesting an increased hepatic artery blood flow which could explain the compensatory mechanism happening due to a reduced portal flow. But it is hard to explain this hypothesis pathophysiologically since the fatty infiltration of the liver while reducing the portal flow due to increased resistance should also reduce the hepatic artery flow because after the entry into the liver anatomically both these vessels are very similar travelling in the portal triad and supply the same area of the liver but in a different proportion. This is controversial [23], however, it is possible that artery being structurally different from a vein might undergo some secondary changes in the form of vasodilatation or hypertrophy so that it can increase its blood supply and various feedback mechanisms and chemical mediators might play a role in this regard and might need further exploration. Few of the previous studies which evaluated HARI in patients with fatty liver have also found that it reduces as the severity of fatty liver increases thereby increasing the hepatic artery blood flow [17,21,22]. A study by Mohammad Kazem Tarzamni et al., have also shown that hepatic artery resistance index improves after treatment of NAFLD [19].

The liver span of fatty liver was found to be significantly higher when compared to the controls and it positively correlated with the severity of the fatty liver. The possible explanation would be as the severity of the fatty infiltration increases there is more deposition of fat in the liver, causing an increase in the liver span. This study results show that the liver size does not seem to start reducing even with grade 3 fatty liver and hence it is possible that in patients with severe fatty liver and a normal or a reduced liver span, one need to be careful and these patients must be adequately evaluated to rule out the possibility of early cirrhosis. However, literature regarding the liver span in various grades of NAFLD could not be found and hence confirmation of our observation needs further larger studies in this regard.

LIMITATION

The major limitation of the study is that a biopsy was not performed both to confirm the diagnosis of fatty liver and next to grade the severity of the condition, because we know that the gold standard for diagnosis of NAFLD is biopsy and the grading of severity of fatty liver is accurate only with biopsy and grading based on ultrasound is inferior to a biopsy. Further studies which look into the exact pathophysiology of these haemodynamic changes like the possible feedback mechanism and the mediators, which might be involved in the proposed decrease in the portal flow and increase in the hepatic arterial blood flow, are required to better understand these changes. These portal doppler parameters might become important for the prognosis of patients with fatty liver in future because when a cutoff value for any of these parameters alone or in combination (composite model) if detects early cirrhosis with a good sensitivity and specificity, then it will be a better noninvasive and cost effective method for prognostication of this condition.

CONCLUSION

There are significant haemodynamic changes seen in the portal vein and the hepatic artery in patients with fatty liver and these changes correlated with the grading of the severity of the fatty liver. The Vmax, MFV and VPI of the portal vein was decreased significantly in subjects with fatty liver suggesting a reduced portal flow while the HARI was found to be significantly lesser in fatty liver suggesting an increased hepatic artery blood flow.

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