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Orignal Article

Association of Sonographic Grading of Fatty Liver Disease with Liver Function Tests and CT Hounsfield

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ABSTRACT

Fatty Liver Disease (FLD) is described as the accumulation of triglycerides within cytoplasmic vesicles of hepatocytes exceeding 5 percent of total liver weight. It is generally of two types: Alcoholic or Non-alcoholic FLD (NAFLD). It has a tendency to progress and cause steatohepatitis, fibrosis, cryptogenic cirrhosis, hepatocellular carcinoma, chronic liver disease, metabolic syndrome, polycystic ovarian syndrome and adenocarcinomas. It is associated with obesity, diabetes mellitus, high triglycerides and low HDL levels. **Objective: T**o find association of Sonographic Grading of Fatty Liver Disease with Liver Function Tests and CT Hounsfield units. The evaluation of the significance of Ultrasound and LFTs over Computed Tomography is the aim of this study for the diagnosis of Fatty Liver Disease. **Method:**104 patients were undergone CT exams, Ultrasound exams and LFT tests for this this study (mean age: 38 years). Their hepatic (right lobe and left lobe) and Splenic Hounsfield units were obtained, Ultrasonographic grades were specified and LFTs were recorded. Crosstabulations, multiple comparisons and ANOVA was done separately on the results obtained. **Results:** In a cross-tabulation between Lobes of Liver, Hounsfield Units and Fatty Liver Grades through ultrasonography, a significant association is seen. The means of total bilirubin in three groups of Fatty Liver (Grade I, Grade II, Grade III) are statistically insignificant. The means of ALT, AST and Alkaline Phosphatase in three groups of Fatty Liver (Grade I, Grade II, Grade III) are statistically significant **Conclusion:** It is concluded that Ultrasound is effective in diagnosing this disease in all grades of FattyLiver Disease along with Liver Function Tests.

INTRODUCTION

Fatty Liver Disease (FLD) is described as the accumulation of triglycerides within cytoplasmic vesicles of hepatocytes exceeding 5 percent of total liver weight. It is considered to be insignificant clinically in normal circumstances [1], however, it has been described as a silent killer in recent studies [2]. It is generally of two types: Alcoholic or Non-alcoholic fatty liver disease.Non-alcoholic fatty liver disease (NAFLD) which is also known as Metabolic Associated fatty liver disease (MAFLD)[3] and is referred to the condition of triglyceride accumulation on liver when no other causes for secondary hepatic fat accumulation are present such as hypothyroidism or alcohol intake [4]. It is further subdivided into NAFLD in which there is no inflammation of liver and Non-alcoholic steatohepatitis (NASH) in which hepatic inflammation is present [4]. NAFLD is commonly seen in under-developed countries. 30% of general population in United States, 12-24% in Asia [2], 25-26% in Europe is affected by this disease, making a worldwide prevalence of around 20% in general population [4]. FLD has a tendency to progress and cause steatohepatitis, fibrosis, cryptogenic cirrhosis, hepatocellular carcinoma and may also be the leading cause of chronic liver disease [1,3-5], metabolic syndrome, polycystic ovarian syndrome and certain adenocarcinomas [3]. It is associated with a number of complications or metabolic risk factors such as obesity, diabetes mellitus,

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high triglycerides and low HDL levels [2,5]. It is generally seemed that men are usually at risk of experiencing NAFLD than women, although, the risk increases with age [2]. Diagnosing this malady, liver biopsy is considered to be a gold standard technique. It has also been observed that the modalities of magnetic resonance imaging, computed tomography (CT) and ultrasonography are generally used for this purpose, however, this study only deals with the comparison of CT and ultrasonography as magnetic resonance imaging is not a common procedure in developing countries as it is expensive [4]. Ultrasonography is done by producing waves with the help of transducer placed against the desired structure of body [6]. Liver ultrasonography is considered to be the first-line modality for the diagnosis of NAFLD [7]. Normal parenchyma of liver on ultrasound is isoechoic or slightly more echogenic to kidney and spleen. However, in case of fatty liver, the echogenicity of liver parenchyma is increased prominently. Moreover, the fat does not allow the sound beam to penetrate deeper into the liver tissue, leading to poor visualization of intrahepatic vessels, bile ducts, diaphragm and other pathologies of liver. The sensitivity of ultrasound in detecting mild to moderate FLD is 80-89% and specificity is 87-90%, while it has been seen that ultrasonography remains relatively insensitive in the detection of mild FLD [8]. In addition to that, the severity of the FLDcan also be evaluated with the help of ultrasound based on the degree of attenuation of beam and the loss of echoes from portal vein walls [7,8]. Ultrasonography holds a special significance in the detection of NAFLD as it can diagnose the disease in asymptomatic patients and is relatively simple, cheap and have minimum side effects [9]. The characteristics of ultrasonography allows to detect attenuation of image, diffuse echogenicity and uniform heterogenous liver, thick subcutaneous depth in a bedside scan, the accessibility and ease of use of ultrasound compliments the ultrasound modality for its use in the diagnoses of FLD, though the reliability of this modality strongly satisfies the clinician when the steatosis is greater than 33%. In conclusion, ultrasonography would definitely confirm the presence of no-alcoholic FLD if features such as attenuation of image within 4-5 cm of depth, diffusely echogenic liver within the first 2-3 cm of depth, uniform heterogenous liver, greater than 2 cm subcutaneous depth and no visible edges of liver are present [10]. CT utilizes X-rays to diagnose pathologies within the patient's body. The interpretation of a CT scan is dependent upon the Hounsfield units (HU). Through the use of the attenuation coefficients of water and air, different body parts have been assigned their CT numbers on the basis of their density [11]. This way, CT can represent liver fat content by measuring Liver attenuation [12]. Normally, the comparison of hepatic and splenic attenuation is done for the accuracy of measurement. The attenuation of spleen is 8-10 HUs less than liver in normal people. In a patient of FLD, an unenhanced CT would demonstrate liver with the attenuation of less than 40 HUs or when compared with the spleen, there would be a difference of greater than 10 HUs. In recent studies, CT is considered useful in diagnosing FLD of greater than 30% with the help of liver to spleen attenuation ratios, with a sensitivity of 73-100% and a specificity of 95-100% [13]. CT scan is considered to be 100% specific in diagnosing moderate to severe FLD, when liver to spleen attenuation ratio is less than 0.8 [12]. However, Unenhanced CT scan does not hold significance if the degree of fatty liver is low. This is because a considerable amount of overlap of Hounsfield units of normal and abnormal liver is seen, thus, representing that the density measured by CT may not be sensitive enough to predict fat content of liver [14]. In simple words, the Hounsfield unit attenuation of liver is usually higher than spleen on CT scans but when this ratio is reversed, it connotes the presence of a fatty liver [15]. Liver profile or LFTs usually include alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and bilirubin. ALT and AST are generally the indicators of an injury to hepatic cells on a molecular level. ALP, however, is associated with hepatocellular injury, as well as biliary movements and any obstruction in the pathway of bile may lead to an increase in the levels of ALP. Bilirubin, on the other hand, is important in distinguishing the causes of Jaundice, precisely differentiate the causes of pre-hepatic, hepatic and post-hepatic jaundice on the basis of conjugated and unconjugated bilirubin [16]. NAFLD is usually associated with metabolic syndrome and, therefore, clinicians recommend LFTs and Liver fat scores for the calculation of non-invasive scores. Although LFTs are normal in almost 50 percent of NAFLD cases, but there is a great risk of LFTs, especially ALT to derail towards the upper levels from the normal range due to this disease. The screening of the liver has a marked significance in the diagnosis of NAFLD [17]. By screening, patients with NAFLD are often identified by asymptomatic elevation of liver enzymes, most frequently ALT which has been used as a substitute marker for NAFLD [18]. Although CT has obliged clinicians and radiologists to understand the human body better and diagnose the maladies, it could also prove to be fatal due to ionizing radiation. On the other hand, ultrasonography does not use such radiations, thus it is justifiable to use ultrasonography. It should be necessary for the clinicians to seek help through LFTs.

METHODS

A total of 104 patients were included in this study (mean

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age: 38 years), 58 patients were female and 46 patients were male. Siemens 64 slice dual source in one center and Toshiba Aquilion 64 slice was used in the other center to scan patients in supine position. Both centers had the same Ultrasound Toshiba Xario Machine with 3.5 MHz probe and Cobas Roche 6000 series analyzer for LFTs. Unenhanced CT scan with 80 to 140 kV and100 to 300 mAs was done and the 5 mm thickness slices were taken. The random selection points were taken in Liver and Spleen to calculate the Hounsfield units. Ultrasound was done by different physicians and patients were scanned in supine decubitus positions. The grades of Fatty Liver were specified by the physicians.

RESULTS

In a total of 104 patients, the mean value of 'total bilirubin' calculated among total patients of FLD was 0.90 with a standard deviation of 1.82. Specifically, the mean value in 58 patients with Grade I FLD came out to be 0.72 with a standard deviation of 1.41, mean value in 38 patients with Grade II FLD came out to be 1.15 with a standard deviation of 2.45 and the mean value in 8 patients with Grade III FLD came out to be 0.97 with a standard deviation of 0.36 (Table 1). The mean value of 'ALT' calculated was 42.79 with a standard deviation of 27.76 9 (Table 2). Specifically, the mean value in 58 patients with Grade I FLD came out to be 27.15 with a standard deviation of 12.14, mean value in 38 patients with Grade II FLD came out to be 53.71 with a standard deviation of 10.43 and the mean value in 8 patients with Grade III FLD came out to be 104.37 with a standard deviation of 50.63. The mean value of AST calculated was 46.46 with a standard deviation of 31.22. Specifically, the mean value in 58 patients with Grade I FLD came out to be 30.63 with a standard deviation of 13.49, mean value in 38 patients with Grade II FLD came out to be 54.78 with a standard deviation of 17.80 and the mean value in 8 patients with Grade III FLD came out to be 121.6 with a standard deviation of 47.7. The mean value of Alkaline Phosphatase was 193.97 with a standard deviation of 248.01. Specifically, the mean value in 58 patients with Grade I FLD came out to be 122.22 with a standard deviation of 51.11, mean value in 38 patients with Grade II FLD came out to be 288.31 with a standard deviation of 365.08 and the mean value in 8 patients with Grade III FLD came out to be 266.00 with a standard deviation of 287.03 9 (Table 3).

Count		Fatty liver grades			Total
		Grade I	Grade II	Grade III	
Right lobe	< 25	0	3	5	8
	25 ---39	9	25	2	36
	> 39	49	9	1	59
Total		**58**	**37**	**8**	**103**
Left lobe	< 20	0	1	5	6
	20----39	13	31	1	45
	> 39	45	6	2	53
Total		**58**	**38**	**8**	**104**

Table 1: Crosstabulation Between Liver lobes Hounsfield Units and Fatty Liver Grades

		Fatty liver grades			Total
		Grade I	Grade II	Grade III	
SGPT (ALT)	< 40	49	1	0	50
	40---65	9	31	1	41
	> 65	0	6	7	13
Total		**58**	**38**	**8**	**104**
SGOT (AST)	< 45	52	13	1	66
	45---80	6	23	0	29
	> 80	0	2	7	9
Total		**58**	**38**	**8**	**104**
Alkaline Phosphatase	< 200	56	18	5	79
	200---900	2	18	2	22
	> 900	0	2	1	3
Total		**58**	**38**	**8**	**104**

Table 2: Crosstabulation between values of SGPT (ALT), SGOT (AST), ALP and Fatty Liver Grades

		Right Lobe				Left Lobe			
		<25	25-39	>39	Total	<20	20-39	>39	Total
SGPT (ALT)	< 40	0	7	43	50	0	11	39	50
	40-65	3	23	14	40	1	28	12	41
	>65	5	6	2	13	5	6	2	13
Total		8	36	59	103	6	45	53	104
SGOT (AST)	<45	1	17	48	66	0	23	43	66
	45-80	2	16	10	28	1	20	8	29
	>80	5	3	1	9	5	2	2	9
Total		8	36	59	103	6	45	53	104
ALP	<200	4	22	52	78	3	26	50	79
	200-900	3	12	7	22	2	17	3	22
	>900	1	2	0	3	1	2	0	3
Total		8	36	59	103	6	45	53	104

Table 3: Crosstabulation between values of SGPT (ALT), SGOT (AST), ALP values and Liver Lobes Hounsfield Units

ANOVA		Right Lobe		Left Lobe	
		F	Sig.	F	Sig.
Total Bilirubin	Between Groups	0.538	0.586	0.255	0.775
SGPT (ALT)	Between Groups	18.385	0	11.563	0
SGOT (AST)	Between Groups	20.867	0	22.915	0
Alkaline Phosphatase	Between Groups	3.631	0.03	4.521	0.013

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ANOVA			
		F	Sig.
Total Bilirubin	Between Groups	0.651	0.523
SGPT (ALT)	Between Groups	81.544	0
SGOT (AST)	Between Groups	82.762	0
Alkaline Phosphatase	Between Groups	6.055	0.003

Table 4: Descriptive Fatty Liver grades and LFTs

The means of total bilirubin in three groups of FAD (Grade I, Grade II, Grade III) are statistically insignificant as the p-value = 0.523 (> α = 0.05). The means of ALT, AST and Alkaline Phosphatase in three groups of FLD (Grade I, Grade II, Grade III) are statistically significant as the p-value obtained was 0.00, 0.00 and 0.03 (> α = 0.05), respectively (Table 4).

DISCUSSION

The abnormal accumulation of triglycerides within cytoplasmic vesicles of hepatocytes is identified as FLD. There are two major types, Alcoholic and NAFLD. Non-alcoholic is further classified as Non-alcoholic Fatty Liver (NAFL) and Non-alcoholic steatohepatitis (NASH) on the basis of hepatic inflammation. The worldwide prevalence of the NAFLD is around 20% of the total population. NAFLD is ordinarily asymptomatic or have findings that usually does not specify the gravity or severity of the disease, even so it can cause right upper quadrant pain, lethargy, malaise or feeling of fullness. Furthermore, NAFLD may lead to CLD, fibrosis, cirrhosis, HCC and metabolic syndrome. It is associated to complications such as obesity and diabetes mellitus. Imaging techniques especially ultrasonography and Computed tomography has been given considerate significance in diagnosing NAFLD in recent studies. The first study regrading grading of FLD through the use of Ultrasonography and CT was presented by John CS et al. in the year 1985. They found the accuracy of Ultrasonography 85%, sensitivity 100% and specificity 56%. The relationship of Ultrasonography and CT for the diagnosis of FLD, especially Grade I and Grade II FLD, came out to be significantly productive similar to our study [18]. Cody J. Boyce et al. investigated the incidence of FLD in asymptomatic patients in 2010 by the use of Hounsfield numbers of CT. They inducted 3,357 patients out of which 45.9% (1,542) patients were suffering from mild FLD and 6.2% (208) patients were diagnosed with moderate-to-severe FLD. They concluded that unenhanced CT examination worked as a reliable and non-invasive procedure for the detection and study the progression of asymptomatic FLD [1]. Irrespective of this, our study discussed that CT is irrelevant in majority of FLD cases as Ultrasound is a reliable modality. In 2011 Hernaez R et al. [19] led a met-investigation on 49 investigations and reported sensitivity and specificity as of USG 84.8% and 93.6%, respectively for identification of moderate-to-severe FLD when compared with histology. Most recent investigations contrasting USG and histopathology have affirmed that it is an appropriate non-obtrusive instrument for assessment of FLD and mild to moderate grades does not require biopsy which is a conclusion similar to our study. From 2012 to 2014, Steven C. Lin et al [5]. performed a prospective, cross-sectional analysis of 204 subjects who underwent MRI exams and Quantitative ultrasonography in a cohort study. The parameters of Quantitative ultrasound and backscatter coefficient were calculated. They concluded that Quantitative ultrasound measurements using backscatter coefficient analysis and taking MRI-Proton Density Fat Fraction as reference, can precisely diagnose FLD and grading can be done. However, in our study, simple Ultrasonography also proved to be beneficial enough for the accurate diagnosis of FLD. Another study concluded the same results as our study was brought out by Rehman J. et al [20]. in 2015 which employed 30 patients for each group based on grades of FLD that were obtained through Ultrasonography. They calculated CT Hounsfield units of Liver and Spleen and found a significant difference for each grade of FLD and between Liver and Spleen. They concluded that Ultrasound was a reliable as the first imaging modality for the diagnosis of Fatty Liver. In 2019, Muhammad Yousaf et al [12]. conducted a cross-sectional analytical study on 227 subjects and compared Ultrasonography grades of FLD with CT Hounsfield numbers. They reported significant p-values when CT Hounsfield units were compared with all three grades of Fatty Liver obtained through Ultrasonography. They concluded that Ultrasonography came out to be well-grounded and dependable modality for the diagnosis of NAFLD. Some studies have also compared the Liver profile with the FLD and acknowledged high ALT and AST levels in patients with FLD and but they did not specify the grades of FLD. Our study is the first to acknowledge Ultrasound grades, CT Hounsfield units in Right Lobe of Liver, Left Lobe of Liver and Spleen and Liver Function Tests and their comparison in a single patient criterion.

CONCLUSION

Computed tomography is considered as the necessary requirement for the accurate diagnosis of this disease. However, in reference to this study, it is concluded that CT is not the requirement but in fact, is just harmful to the patient, when Ultrasound is effective in diagnosing this disease in all grades along with Liver Function Tests as it is

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non-invasive, easily and widely available and have no detrimental effects in long term.

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