Research Article

The Significance of Reporting Increased Liver Echogenicity in Nonalcoholic Fatty Liver Patients

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Abstract

Purpose: Many ultrasound performers underappreciate the Sonographic sign of "increased liver echogenicity" they do not mention it sometimes on their report, and this could be because it is common and usual sequel for obesity. The aim of this study was to report on the diagnosis of new cases of Type II diabetes mellitus/Pre diabetes and dyslipidemia among patients who on ultrasound scan were found to have liver hyper echogenicity .Also to study liver echogenicity impact on different factors like HbA1c, ALT, AST, serum Cholesterol level, serum Triglyceride level, Body Mass Index MBI, liver size. **Patients and Methods**: This cross sectional study took place in the department of Radiology and Gastroenterology of a major public hospital between October 2020 and June 2021.Patients was referred to the ultrasound clinic for various indications. .Adult nonalcoholic patients who were not known to have DM, dyslipidemia or any chronic liver diseases and showed increase liver echogenicity on ultrasound were referred to the gastroenterology clinic for further evaluation, mainly to exclude any undiagnosed chronic liver disease and to confirm the diagnosis of fatty liver. Liver hyperechogenecity was categorized into three grades according to severity of fatty infiltration by visual estimation using a known grading system All patients had three main investigations; HbA1C, LFT and lipid profile. Data collected included; age, gender, body mass index (BMI), HbA1c, ALT, AST, Cholesterol, Total bilirubin, Triglyceride, liver size, liver hyperechogenecity grades **Results**: Among 320 patients were examined by ultrasound only 60 patients met the inclusion criteria and were recruited. The mean (SD) for age and BMI were 45.0(12.0) years and 32.5 (5.8) Kg/m^2, respectively. 37 patients (61.7%) were females. Furthermore, 57 patients (95%) were either overweight or obese, and 34 patients (56.7%) had a grade II and III liver echogenicity. 36 patients (60.0%) had either a borderline or high liver span. The numbers and percentages of patients who were found to have a newly diagnosed diabetes/prediabetes and dyslipidemia(after ultrasound and lab investigations) were 33.3%, 63.1%respectively, and 21.7% of patients were found to have both (diabetes/Prediabetes) and dyslipidemia. There is statistically significant relation of grade of liver echogenicity (degree of fatty infiltration) and HbA1C (P 0.001), Triglyceride (P 0.004), ALT (P 0.03), and AST (P 0.079), but not total cholesterol (P 0.620)., however in logistic regression analysis. BMI, TG and ALT were significantly related to liver echogenicity. While gender, age, cholesterol, AST, bilirubin HbA1C and liver size were not significant factors. **Conclusion**: Reporting "increased liver echogenicity" found to be essential in early detecting and controlling metabolic risk factor (dyslipidemia and insulin resistance) of non-alcoholic fatty liver disease. Obesity followed by hypertriglyceridemia are on the top of leading causative factors of NAFLD

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Keywords: Fatty liver; NAFLD; Abdominal ultrasound; Liver hyperechogenecity; Non Alcoholic fatty liver disease; Diabetes mellitus.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common disorder with an incidence of about 23.5% in the United States. [1] It refers to a group of conditions where there is accumulation of excess fat in the liver of people who drink little or no alcohol. [2,3] Fatty liver is the most common form of NAFLD and it is not a serious condition [4,3] where fat accumulates in the hepatocytes (steatosis). This process alone is not harmful and does not indicate liver damage. However, if fat accumulation induces liver cell inflammation (steatohepatitis) and then fibrosis, scarring and later on cirrhosis, this serious condition is called non-alcoholic steatohepatitis (NASH). [3,4] Which interferes with ability of the liver to function properly? Additionally, patients who progress to liver cirrhosis and some cases of hepatocellular carcinoma (HCC) may eventually require a liver transplant. [3]

While the majority of NAFLD patients are asymptomatic [3] the condition may progress and patients may develop a metabolic syndrome that is characterized by increase in BMI to the overweight or the obese range, the development of diabetes mellitus (DM), or pre-diabetes, dyslipidemia and hypertension. [3,4]

Fatty liver can be recognized on ultrasound as increase echogenicity of liver in comparison with nearby kidney. [5]

The current gastroenterology recommendations suggest that a patient with increase liver echogenicity should have three main investigations [2,4] hemoglobin A1C (HbA1C) to rule out DM as a risk factor , Liver function test (LFT) to assess the effect of steatosis on liver function, and Lipid profile to detect dyslipidemia as a risk factor.

The main aim of this study is reporting the frequencies of the diagnosis of new cases of Type II diabetes mellitus / Pre diabetes and dyslipidemia in patients with increase liver echogenicity on ultrasound which is not related to causes other than fatty infiltration.

Material and Methods

This cross sectional study was conducted in the departments of Radiology and gastroenterology of a major public hospital between October 2020 and June 2021.

Around 320 Patients were referred to the ultrasound clinic for various indications from different clinics. .

Detailed liver ultrasound scan was performed for all patients by only one boarded radiologist, using ultrasound machine Philips Affinity 50 G/curvilinear probe C6-2 of abdomen. The depth, focus, and gain were changed accordingly to improve image quality. The echogenicity of liver was assessed and compared to the nearby kidney which is normally equal or slightly darker than adjacent normal kidney. [5] (Figure 10).

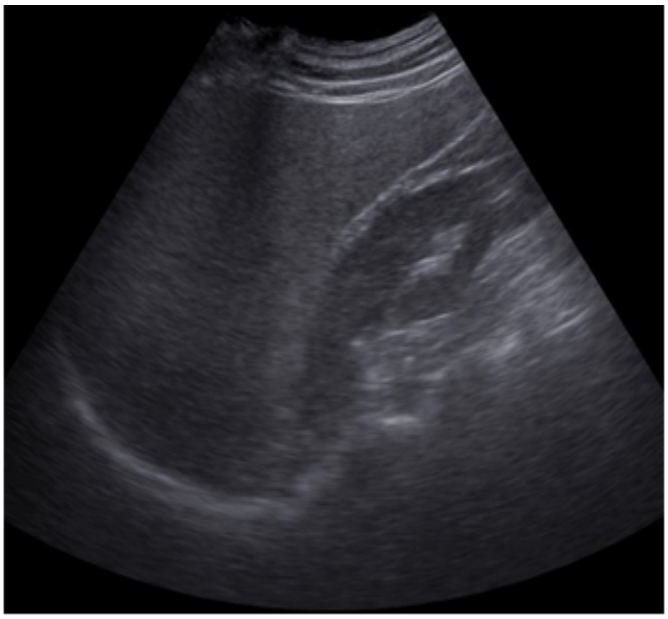

Figure 1: Increase liver echogenicity in comparison with Rt kidney.

The increase in liver echogenicity was categorized into three grades. [2] (Figure 2): Grade I: Only increase in echogenicity of liver. Grade II: increase echogenicity that obliterates portal vessels branches wall in liver. Grade III: Increase echogenicity of liver that obliterates the diaphragm.

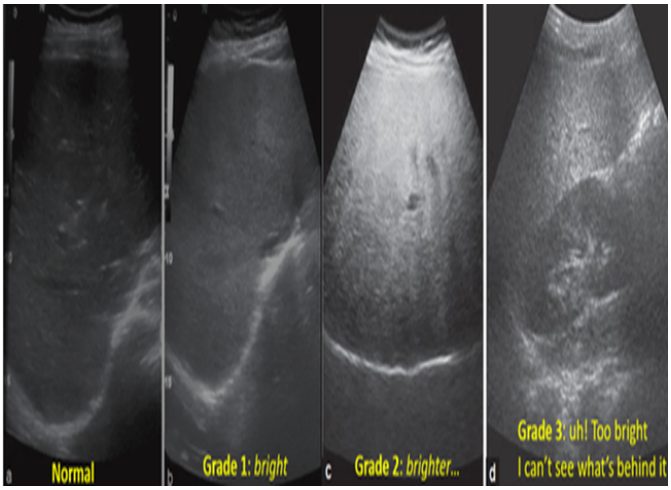

Figure 2: Grading of ultrasound. [6]

The size of liver was measured in midclavicular plane with maximal diagonal approach. When it is more than 16 cm it was considered as hepatomegaly according to Wolfgang Kratzer et al study 2003. [7] (Figure 3) and (Figure 4)

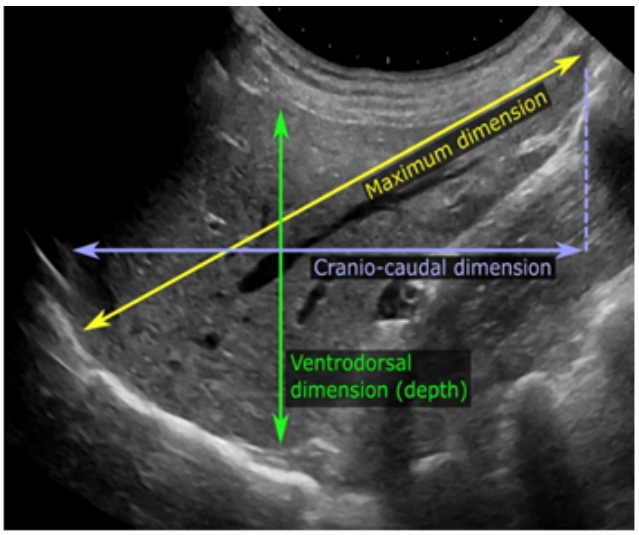

Figure 3: Different measurements of liver size in midclavicular plane. [8]

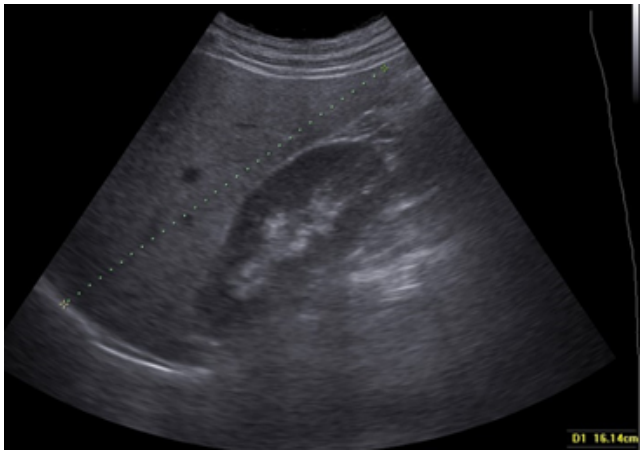

Figure 4: Maximum mid clavicular measurement.

Adult nonalcoholic patients who were not known to have DM, dyslipidemia or any chronic liver diseases and showed increase liver echogenicity on ultrasound were referred to the gastroenterology clinic for further evaluation, The main goal was to exclude any chronic liver illness like hepatitis, glycogen storage diseases, hemochromatosis, liver cirrhosis etc. , and to confirm the diagnosis of NAFLD.

all recruited patients underwent three lab investigations ; hemoglobin A1C (Hb A1C), Liver function tests (LFT) namely ALT and AST, in addition to lipid profile; namely total cholesterol and triglycerides in keeping with the American association of study of liver disease AASLD 2020, [2,4] and the "American College of Gastroenterology ACG" 2020 recommendations. [3]

Other investigations were performed accordingly to selected patients to exclude chronic liver disease. Like; Thyroid Function Test (TFT), erythrocytes sedimentation rate (ESR), antinuclear antibodies (ANA), Hepatitis B surface antigen (HBS Ag), Hepatitis C antibodies (HBC Abs), C - reactive protein (CRP), and Serum ferritin. Patients who proved to have chronic liver diseases even after lab investigations were excluded.

The laboratory normal reference values were considered as well as American society of DM, Mackinac laboratory, the guidelines of DM and dyslipidemia diagnosis and management of "American association of cardiology AAC" , "American Association of Clinical Endocrinologist AACE" and "American Diabetes Association ADA " 2020. [9,10]

Among 320 patients were examined by ultrasound only 60 patients fulfilled the inclusion and exclusion criteria which were listed in (Table 1).

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Non alcoholic	Alcoholic
Not known to have DM or Pre diabetes at time of our ultrasound study	Known to have DM or pre diabetics before our ultrasound exam.(Lab diagnosis)
Not known to have Dyslipidemia at time of our ultrasound study	Known to have dyslipidemia before our ultrasound exam. (Lab diagnosis)
No chronic liver disease at all .,like hepatitis, glycogen storage disease ,hemochromatosis,, chemotherapy	Diagnosed to have chronic liver disease before or after our ultrasound study.
Above 18 year old	Less than 18 year old
Patient welling to participate in the study	Patient refused to participate.in the study
Hyper echoic liver by ultrasound	Normal or decrease liver echogenicity
No space occupying lesion on ultrasound in liver.	Any space occupying lesion on ultrasound in liver

Data collected included; age, gender, body mass index (BMI), HbA1c, ALT, AST, Cholesterol, Total bilirubin, Triglyceride ,liver size, liver hyperechogenecity grades.

A convenience sampling method was adopted for this study. For statistical analysis, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY was used. Continuous data were expressed as mean, SD, range, minimum and maximum values and categorical variables were shown as numbers and frequencies. To facilitate comparisons; age, BMI, liver echogenicity, liver size and the laboratory results were all regroups. To study the correlations between the grade of liver

echogenicity and the various variable, Chi square test was used, P value of <0.05 was considered statistically significant.

Stepwise Logistic regression analysis (forward) was performed using SPSS 16 to detect the factors related to liver echogenicity (dependent factor). Group two and three were added together. The independent factors included BMI, ALT, and TG, gender, age, cholesterol, AST, bilirubin, HBA1C and liver size.

The study was approved by "Mutah University faculty of medicine ethics committee" (reference number 12032021), also verbal consent was obtained from all participants prior to their enrollment in the study.

Results

Sixty patients fulfilled the inclusion criteria. The mean (SD) for age and BMI were 45.0(12.0) years and 32.5 (5.8) Kg/m^2, respectively. In addition, 23 patients (38.3%) were males and 37(61.7%)) were females. Furthermore, 57 patients (95%) of them were either overweight or obese, and 34 patients (56.7%) had a grade II and III liver echogenicity. While 24 patients (40%) had a normal liver Span. 36 patients (60.0%) had a either borderline or high liver span. Data analysis showed that 35 patients (58.3%) and 20 patients (33.3%) were found to have high total cholesterol and Triglycerides respectively. Additionally, 20 patients (33.4%) were found to have either diabetes or prediabetes. In addition; while total bilirubin results were normal in all patient, some of the liver enzymes were deranged in at least 35%of the patients. The results show that none of the recruited patients had autoimmune, infectious or chronic liver diseases. (Table 1) a shows the descriptive statistics of the study population and the various study variables.

Data analysis regarding the correlations between the grade of liver echogenicity on ultrasound scan and the various patients characteristics and laboratory results showed that age and BMI were correlated with the grade of liver echogenicity, where older the age and the higher BMI correlated with higher grade of liver echogenicity (P<0.05). Furthermore, Liver size was correlated positively with the grade of liver echogenicity (P=0.001) (Table 2).

Table 2: Descriptive statistics of the study population, ultrasound and laboratory variables.

Variable	Mean(SD)	Range (minimum – maximum)
Age (years)	45.0(12.0)	49.0(19.0-68.0)
Body mass index (Kg/m^2)	32.5(5.8)	21.4(22.7-44.1)
Liver span (cm)	16.6(2.8)	11.0(12.0-23.1)
Total cholesterol (mg/dl)	207.8(40.4)	182.0(130.0-312.0)
Triglycerides (mg/dl)	175.4(60.6)	247(73.0-320)
Hemoglobin A1C (%)	5.9(0.9)	4.7(4.7-9.4)
Total bilirubin (mg/dl)	0.57(0.20)	0.8(0.02-1.0)
Alanine transaminase (U/L)	32.1(18.0)	112(13.0-125.0)
Aspartate transaminase (U/L)	25.7(12.0)	51.0(12.0-63.0)

Variable	Category	No.	Percentage%
Age groups (years)	20 - 34 years	14	23.3
	35-49 years	26	43.3
	50-70 years	20	33.3
Gender	Males	23	38.3
	Females	37	61.7
Body mass index groups (Kg/m2)	Normal weight	3	5
	Over weight	23	38.3
	Obese	34	56.7
Liver echogenicity grades	I	26	43.3
	II	30	50
	III	4	6.7
Liver span groups (cm)	Normal liver size	24	40
	Borderline liver size	2	3.3

	High liver size	34	56.7
Total cholesterol groups(mg/dl))	Normal (< 200)	25	41.7
	Abnormal (> or = 200)	35	58.3
Triglycerides groups (mg/dl))	Normal (<150)	21	35
	Borderline (150-200)	19	31.7
	Abnormal (>200)	20	33.3
HbA1c (%)	Normal (< 6)	40	66.7
	Prediabetes (6-6.5)	7	11.7
	Diabetic (>6.5)	13	21.7
Alanine transaminase (U/L)	Normal (Up to 31)	39	65
	Elevated (> 31)	21	35
Aspartate transaminase (U/L)	Normal (Up to 31)	47	78.3
	Elevated (>31)	13	21.7

Regarding lipid profiles, the results showed that while the correlation between total cholesterol and the grade of liver echogenicity was not statistically significant, there was a trend toward higher liver echogenicity grade with higher total cholesterol value. In addition, higher levels of triglycerides were associated with higher grades of liver echogenicity (P=0.004) (Table 3).

Table 3: Association between grade of liver echogenicity and the various patient's characteristics and laboratory results.

Variable		Grade of liver echogenicity			X^2	P-value
		Grade I N(%)	Grade II N(%)	Grade III N(%)		
Age groups (years)	20 - 34	5(35.7)	9(64.3)	0(0.0)	9.796	0.044
	35-49	12(46.2)	14(53.8)	0(0.0)		
	50-70	9(45.0)	7(35.0)	4(20.0)		
Body mass index groups	Normal weight	3(100.0)	0(0.0)	0(0.0)	18.372	0.001
	Over weight	16(69.6)	7(30.4)	0(0.0)		
	Obese	7(20.6)	23(67.6)	4(11.8)		
Liver size(span)	Normal	17(20.8)	7(29.2)	0(0.0)	17.989	0.001
	Borderline	2(100.0)	0(0.0)	0(0.0)		
	High	7(20.6)	23(67.6)	4(11.8)		
Total cholesterol	Normal	9(36.0)	14(56.0)	2(8.0)	0.955	0.620
	High	17(48.6)	16(45.7)	2(5.7)		
Triglycerides	Normal	14(66.7)	5(23.8)	2(9.5)	15.263	0.004
	Borderline	3(15.8)	16(84.2)	0(0.0)		
	High	9(45.0)	9(45.0)	2(10.0)		
Haemoglobin A1C	Normal	19(47.5)	19(47.5)	2(5.0)	18.584	0.001
	Prediabetes	2(28.6)	3(42.9)	2(28.6)		
	Diabetic	5(38.5)	8(61.5)	0(0.0)		
ALT	Normal (Up to 31)	20(51.3)	15(38.5)	4(10.3)	6.746	0.034
	Abnormal (>31)	6(28.6)	15(71.4)	0(0.0)		

AST	Normal (Up to 31)	23(48.9)	20(42.6)	4(8.5)	5.084	0.079
	Abnormal (>31)	3(23.1)	30(50.0)	4(6.7)		

Data analysis regarding HbA1C values showed that patients with insulin resistance (prediabetes and diabetic) were more likely to have higher grades of liver echogenicity, and the difference was statistically (P=0.001).

Regarding LFT, the results showed a statistically significant correlation between abnormal results of both (ALT and AST) and the grade of liver echogenicity (P<0.05).

(Table 4) shows the summary of the significant factors related to liver echogenicity of the stepwise logistic regression analysis. BMI, TG and ALT were significantly related to liver echogenicity. While gender, age, cholesterol, AST, bilirubin HBA1C and liver size were not significant factors.

(Table 5) showed variables used in equation.

Table 4: Stepwise logistic regression analysis of the factors related to liver echogenicity.

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a	BMI	0.27	0.071	14.611	1	0	1.31
	Constant	-8.326	2.225	14.001	1	0	0
Step 2b	BMI	0.272	0.075	13.118	1	0	1.312
	ALT	0.068	0.032	4.665	1	0.031	1.071
	Constant	-10.518	2.634	15.941	1	0	0
Step 3c	BMI	0.317	0.088	12.902	1	0	1.372
	TG	0.013	0.007	3.662	1	0.056	1.013
	ALT	0.068	0.032	4.536	1	0.033	1.071
	Constant	-14.332	3.81	14.153	1	0	0

Table 5: Variables in the Equation.

		95% C.I.for EXP(B)	
		Lower	Upper
Step 1a	BMI	1.141	1.504
	Constant		
Step 2b	BMI	1.133	1.520
	ALT	1.006	1.139
	Constant		
Step 3c	BMI	1.155	1.631
	TG	1.000	1.027
	ALT	1.005	1.140
	Constant		

Discussion

There are different noninvasive modalities of imaging fatty liver disease, like; ultrasound, CT, MRI and Magnetic Resonance Spectroscopy (MRS) The most accurate noninvasive method is MRS, however Liver biopsy and histologic analysis is considered the diagnostic reference standard for the assessment of fatty liver. [11] In this article we will discuss only the role and significance of ultrasound in NAFLD.

Ultrasound is a safe, noninvasive relatively cheap modality of imaging which is available in almost all the radiological centers and many of clinics, on the other hand, ultrasound is operator dependent, [11] this means; the ability of catching the abnormalities depends upon how professional and trained the ultrasound performer is.

Can we use the ultrasound to diagnose new cases of insulin resistance, dyslipidemia and abnormal liver enzymes in NAFLD patients based on increase echogenicity of liver on ultrasound? Is it important to report the change in liver echogenicity when we notice it during ultrasound scan? What is the impact of liver echogenicity upon HbA1C, ALT, AST, liver size, BMI? We tried to answer these questions on our research.

Sample characteristics

The female patients represent 61.7% in our sample this agree with the fact that female always had a considerably higher prevalence of obesity than men. [12] Which considered the main risk factor for NAFLD, [3] NAFLD is more common in female. Than in male [13]

95% of patients in our sample were with high BMI, 43% overweight, 47% obese, despite a much lower obesity prevalence among Jordanian adults 33.4% in 2016.according to "State of Food Security and Nutrition in the World "2019. [12,14]

our high results of obesity among NAFLD was close to the results of other research like [13] meta-analysis collected from 22 countries where the obesity prevalence in NAFLD around 51.34% [13] ; also had incidence of obesity among NAFLD about 51%. [15]

In general our results of high BMI among our sample match with almost most of research that consider obesity as a main risk factor for NAFLD, [3,4,16,17] however some researchers found that patient with normal BMI may develop NAFLD [18] 10% of our patients were with normal BMI.

Sonographic and Lab results

60% of our sample have liver span of more than 15.5 cm in oblique midclavicular trans abdominal scan, as NAFLD proved in literature to be associated with hepatomegaly in majority of cases 75%, [16] Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. [19]

The incidence of dyslipidemia among our patients with hyper echoic liver is 63.1%, this result is slightly lower in comparison with other studies like (69.2%), (69.1%), [13] The lower percentage may explained by the nature of the sample that excluded any patients with known dyslipidemia

The incidence of abnormal glucose level (DM /pre DM) among our patients who showed hyper echoic liver on ultrasound is 33.3%. Around 21.7% have lab results were diagnostic of DM which is also higher than the incidence of DM II in Jordanian adults 9.9% (control) according to the "International Diabetic Federation 2020". [20]The incidence in our research is almost around the results of other research results like (22.5%), [21] in a meta-analysis (22%), [13] (2 folds the incidence in total population) [22] (2 folds the total population incidence), [23] (around 25%) 2020. [24]

So the results of our study is in agreement with all previously mentioned studies that showed a higher prevalence of all risk factor of NAFLD,

1-95% was with high BMI

2-63.1% has dyslipidemia

3-33% have abnormal glucose level (DM/pre DM) and 21.7% with DM.

Our Data analysis using P value showed that The liver echogenicity grades on ultrasound correlates with age ,liver span, BMI, HBA1C, ALT, AST and TG but not cholesterol while multivariable logistic regression analysis. Showed that only BMI, TG and ALT were significantly related to liver echogenicity. While gender, age, cholesterol, AST, HB A1C and liver size were not significant factors.

The correlation of liver echogenicity grading with different metabolic risk factors was not widely studied, research (Liver echogenicity: relation to systemic blood pressure and other components of the metabolic syndrome) 2005, revealed that Liver echogenicity correlated significantly with BMI (r=0.527, p=0.001), serum triglycerides (r=0.472, p=0.003) and, to a lesser degree, with serum total cholesterol (r=0.305, p=0.066). [25]

We believe that reporting (increased liver echogenicity) may increase the uptake of screening tests which may help identify early conditions such as diabetes, prediabetes and dyslipidemia. Also reduces the costs, since NAFLD is a very costly disease for the healthcare system, with estimated annual direct medical costs exceeding $100 billion in the United States alone. [15]

The Sonographic fatty liver grading system succeed in categorizing the severity of the NAFLD "The Ultrasonography allow for reliable and accurate detection of moderate-severe fatty liver" [26] The performance of US B-mode imaging for the detection of mild steatosis (fat content > 5%) is low, with reported sensitivity of 60.9%-65% . [19]

Conclusion

Reporting increased liver echogenicity is valuable in the early detection of metabolic syndromes that are associated with it, these include diabetes and dyslipidemia. Early detection of metabolic syndrome is likely to reduce long term complications and health care costs.

- The leading causative effect of NAFLD is obesity followed by hypertriglyceridemia
- The Sonographic fatty liver grading system succeed in categorizing the severity of the NAFLD

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