Original Article

CORRELATION OF HEPATIC ENZYMES WITH ULTRASOUND LIVER FINDINGS IN NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

Objective: To evaluate the association between hepatic enzymes and Non-Alcoholic Fatty Liver disease (NAFLD).

Material and Methods: This cross-sectional study was conducted at Fauji Foundation Hospital (FFH) Rawalpindi from July 2019- July 2020.Our study included 200 patients randomly selected from outpatient department of FFH Rawalpindi, who fulfilled the inclusion and exclusion criteria. The subjects were split into 3 categories based on ultrasonography diagnosed Non- Alcoholic Fatty Liver Disease as grade I, II and III. The consent of the participants was taken and data was collected through a proper questionnaire. The liver enzymes and the body mass index (BMI) were recorded for all the participants. Data analysis was done using SPSS version 21.

Results: Our study showed highly significant (p<0.001) results between the grades of NAFLD and alanine aminotransferase (ALT) with the mean SD for grade I (41.03±11.92) being the lowest followed by grade II (54.17±18.0) the highest for grade III (66.48±15.93). Serum gamma glutamyl transferase (GGT) also showed significant correlation (p<0.001) with the different grades of NAFLD, the mean being (45.76) for grade I, (69.13) for grade II and (91.36) for grade III. Serum aspartate transaminase (AST p<0.01), alkaline phosphatase (ALP p<0.05) and ALT/AST ratio (p<0.001). Also showed a significant relationship with the grades of NAFLD. A significant relationship of BMI with the grades of fatty liver were also seen, the higher the grade the higher the BMI (p<0.001). The results of our study also showed that increasing the degree of NAFLD had a direct positive correlation with the increased BMI and liver enzymes (ALT, AST, ALP and GGT) (p<0.01).

Conclusion: Our study concludes that higher levels of serum liver enzymes and BMI can be used as predictive markers for determining the degree of NAFLD.

Key Words: Non-Alcoholic fatty liver disease, Liver enzymes, Body mass index, Ultrasonography.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) prevalence is significantly increasing since the last 20-30 years. In western countries it is one of the biggest cause of fatty liver disease. Latest researches have now proved that NAFLD is spreading equally worldwide [1]. The prevalence in the Western world is around 15-40% and in Asian countries the prevalence ranges from 9-40% [2, 3]. It is characterized by the accumulation of fat in the hepatocytes exceeding 5-10% of the liver weight in the absence of excessive alcohol consumption. NAFLD refers to liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis leading to hepatocellular carcinoma (HCC) [1, 4]. NAFLD is usually diagnosed incidentally in asymptomatic patients during routine clinical/laboratory assessment when abnormally elevated liver enzymes are noted [5, 6]. “Thus, World Gastroenterology Organization guidelines prescribe a hierarchical resource-sensitive approach”. The hepatic enzymes i.e. ALT, AST, ALP, GGT and other liver injury markers can be used as substitute measures of NAFLD [5-8].

Chang *et al*. proved that increasing levels of ALT, even within the reference range, was an independent predictor of incident NAFLD.[9] NAFLD is closely related to insulin resistance (IR), obesity, metabolic syndrome (MS), and diabetes which can be the initiatives for laboratory estimation of liver enzymes and considering a diagnosis of NAFLD [6].

Multiple researchers in their studies showed a strong association of ALT with NAFLD. The reasons being hepatic IR, central obesity, high triglycerides (TG), low high density lipoproteins (HDL) and increased levels of fasting plasma glucose (FPG) which are the metabolic syndrome components [10-13].

Masoom *et al*. in 2015 in their study proved that ALT levels were high in fatty liver diagnosed patients[3]. Alvina in 2016 showed that ALT, AST and GGT are indicators of degree of NAFLD[14]

A number of studies have been carried out to see the relationship of Gamma GT with NAFLD. Hepatocyte apoptosis is an important and invasive

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predictor of liver injury and fibrosis in non-alcoholic fatty liver disease (NAFLD). Tahan, V *et al* in 2008 studied that increased gamma-glutamyl trans peptidase (GGT) level is frequently observed in NAFLD. Hepatocyte growth factor (HGF) stimulates fibrogenesis and is correlated with GGT [15]. Other workers have reported that high levels of GGT are associated with fatty liver, insulin resistance, type 2 diabetes, obesity, and other metabolic risk factors. There is growing evidence that the liver, which is the primary source of circulating GGT, is a key target organ for the development of the metabolic syndrome. An elevation of GGT is seemingly closely related to hepatic steatosis [16-19]; the latter in turn is strongly associated with the metabolic syndrome [20-22]. The mechanisms whereby elevated GGT is related to hepatic steatosis have not been determined, but several possibilities have been proposed by Ortega *et al* [23]. For example, fatty liver could cause hepatocellular damage that would simulate the synthesis of GGT. Alternatively, excess fat in the liver could enhance oxidative stress, leading to overconsumption of glutathione (GSH) with a compensatory increase in GGT synthesis. Finally, a higher GGT production could be secondary to a low-grade hepatic inflammation induced by hepatic steatosis.

In chronic liver disease the relationship of high ratio of AST/ALT with fibrosis as identified may be a reflection of defective removal of AST by the liver sinusoidal cells[24]. Patients of NAFLD that do not have fibrosis typically have less than 1 ratio of AST/ALT, but as the severity of the disease advances to fibrosis and subsequent progression of the disease to cirrhosis the ratio tends to go above 1[25]. Several studies have shown a correlation between advanced fibrosis on liver biopsy and a greater than 1 ratio of AST/ALT indicating that this ratio may be a useful clinical tool for predicting or excluding advanced fibrosis in patients with NASH[26].

The most common cost effective and easily available method used to evaluate patients with increased levels of liver enzymes or for the screening of asymptomatic patients is Ultrasonography (USG). USG, can, with reasonable sensitivity and specificity be used to identify moderate to severe grades of NAFLD with limited accuracy for detecting mild grade of NAFLD which is really operator dependent [27]. However, biopsy of the liver still remains the gold standard procedure for the diagnosis of NAFLD but this invasive procedure has its own risks. Therefore, a lot of researchers have worked on the noninvasive diagnostic evaluations of NAFLD especially the hepatic enzymes and USG [1, 28-31].

In Pakistan one of the most important mortality related cause of liver disease is NAFLD. The percentage of deaths due to cirrhosis and chronic liver diseases caused by NAFLD is around 21% and the percentage of deaths following hepatocellular carcinoma is 11·8% [32].

The rise in the prevalence of obesity & metabolic syndrome could be the reason for high occurrence of NAFLD that leads to the progression of end stage liver diseases. There is not too much data available on NAFLD from Pakistan. In the rural areas the prevalence is lower (9-27%) as compared to urban areas (21-42%) mostly because of lifestyle & disease status[33, 34]. The main contributing factors associated with high prevalence of NAFLD worldwide is metabolic syndrome & its components, the cases being predominant in women [32, 35-37].

In Pakistan the biggest threat for health management system is the emergence of NAFLD. In the light of the above the authors planned to carry out a study to see the correlation of liver enzymes with NAFLD and its accuracy to predict NAFLD.

MATERIAL AND METHODS

The subjects of this study were NAFLD patients selected from Medical & Liver out patients department of Fauji Foundation Hospital Rawalpindi from July 2019-July 2020 after approval from ethical review committee of the institute. All our patients were females as it is a family hospital. The age range of the patients was from 25-70yrs.

Exclusion criteria included patients suffering from other causes of fatty liver like alcoholics, diabetics, hyperlipidemics, hypertensives, patients with hepatitis B, C virus, recent cases of pregnancy and all those who did not give consent to be part of the study. Those that gave consent and were diagnosed with NAFLD by USG machine model Xario Toshiba were included in our study. Grading of NAFLD was done as grade I, II & III.

RESULTS

Grade I (mild):- Echogenicity of liver parenchyma is increased with normal echogenicity of vascular wall & diaphragm.

Grade II (moderate):- Echogenic walls of the portal vein branches are obscured by infiltration of fat.

Grade III (severe):- Diaphragmatic outline is obscured by liver parenchyma echogenicity.[14, 27, 38]

Liver function tests were done after collection of 5ml of blood sample in plain tubes. Sample

centrifuged at 4000 rpm for 5mins, serum separated & analyzed for ALT, AST, ALP & GGT on auto-analyzer Dimensions RxL. By using the formula kg/m^2 the BMI of the patients was evaluated. Reference values of liver enzymes used were as follows:

ALT: Females- 10-35 U/L
AST: Adults- 5-40 U/L
ALP: Adults- 65-306 U/L
GGT: Female- 5-50 U/L

The data collected was analyzed by SPSS version 21. The descriptive data was shown as mean ± SD. The comparison of the concentration of hepatic enzymes between the different grades of NAFLD was done using one-way ANOVA.

Correlation of NAFLD with hepatic enzymes was done using Pearson's Correlation co-efficient. Linear regression models were constructed to analyze the associated risk factors. Statistical significance was expressed as p<0.05.

RESULTS

Two hundred subjects were included in the study. The mean age of the patients was 50.91±8.76, youngest being 34 and eldest 73 years. The evaluation of liver enzymes and BMI was done according to the grades of NAFLD. Grade I included 96 participants; grade II had 79 while grade III included 25 participants. Significant relationship was seen between the liver enzymes and grades of NAFLD as seen in Table-1.

Highest mean of ALT was seen in grade III of fatty liver (66.48±15.93) while in grade II it was (54.17±18.0) and in grade I (41.03±11.92) (p<0.001). Highly significant results were seen between the different grades of NAFLD and GGT. In grade I GGT levels were (45.76±17.07), in grade II (69.13±25.18) and in grade III (91.36±13.56) (p<0.001). A significant relationship of AST was seen with the fatty liver grades the highest mean being (60.04±15.36) and lowest being (41.03±11.92) (p<0.01). ALP levels were statistically significant p<0.05.

A significant correlation of the mean ratio of AST/ALT with NAFLD grades was seen. The lowest ratio of 0.970 was in grade I and highest ratio of 1.34 in grade III (p<0.001). We also evaluated the BMI of these patients which was found to be statistically higher with the mean of 28.5±5.09 in grade I, 30.67±4.23 in grade II and in grade III it was 30.92±4.70 (p<0.01).

Our study showed positive correlation and positive linear regressions of hepatic enzymes and BMI that depended on the grading of NAFLD. ALT and GGT showed the strongest positive correlation (r .510 & r .618, p<0.001). Correlation of AST was also highly significant (r .213, p<0.01), while ALP similarly showed a significant positive correlation (p<0.005). A significant positive association of NAFLD with BMI was seen (p<0.01). Table-2 showing the correlation of hepatic enzymes with NAFLD grading and linear regression models can be seen in Figure-1.

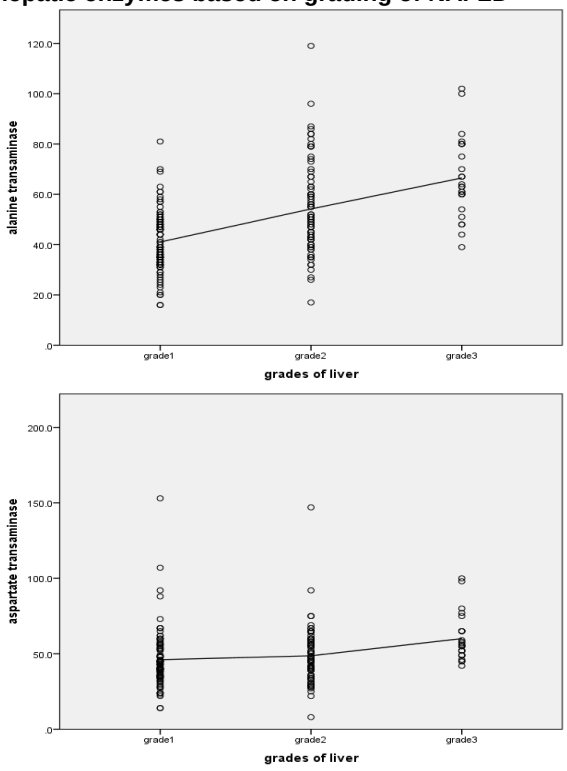
Table-1: Comparison of different variables with NAFLD grades

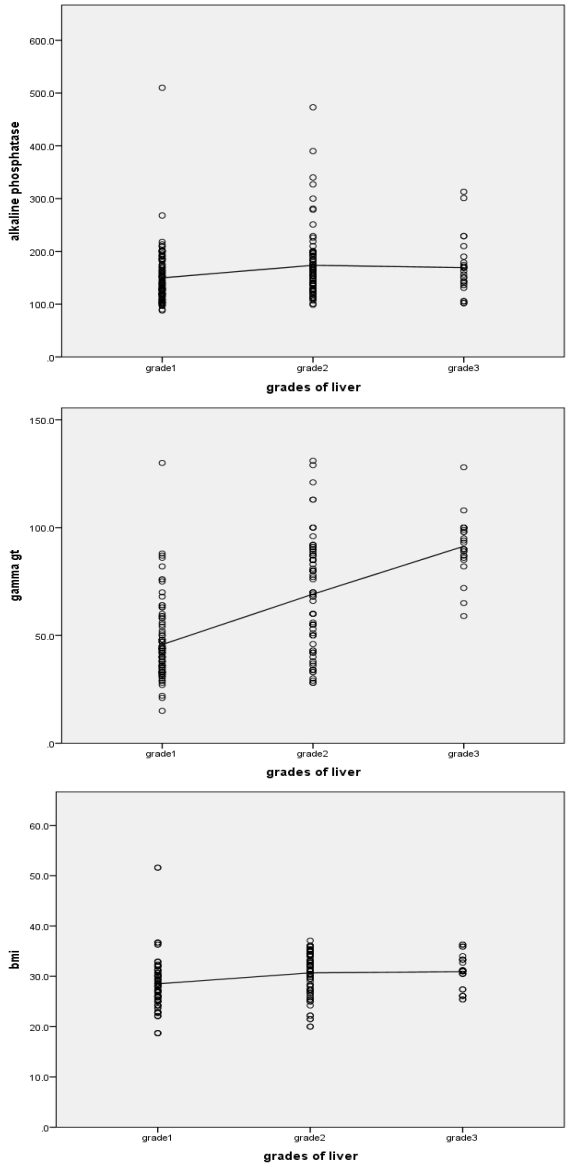
Variables	NAFLD Grade I n=96	NAFLD Grade II n=79	NAFLD Grade III n=25	*p*-value
ALT (U/L)	41.0 ± 11.92	54.17 ± 18.00	66.48 ± 15.93	0.000
AST (U/L)	46.08 ± 18.68	48.65 ± 18.17	60.04 ± 15.36	0.003
ALP (U/L)	149.91 ± 51.99	173.69 ± 64.85	169.24 ± 54.10	0.021
GGT(U/L)	45.76 ± 17.07	69.13 ± 25.18	91.36 ± 13.56	0.000
AST/ ALT	0.97 ± 0.336	1.26 ± 0.907	1.34 ± 0.252	0.000
BMI (kg/m^2)	28.5 ± 5.09	30.67 ± 4.23	30.92 ± 4.70	0.003

Table-2: Correlation of different variables with NAFLD.

Variables	R	R^2	*P*
ALT	.510	.260	<0.001
AST	.213	.045	<0.01
ALP	.164	.027	<0.05
GGT	.618	.382	<0.001
BMI	.219	.048	<0.01

Figure-1: Linear regression models showing the levels of hepatic enzymes based on grading of NAFLD





DISCUSSION

The disease NAFLD is usually silent having no clinical signs and symptoms. Multiple studies have been carried out to see the correlation of NAFLD with lipid profile but less have focused on the relationship of NAFLD with hepatic enzymes, which are the most routinely done tests by the clinicians. Elevated hepatic enzyme concentrations may indicate the presence of excessive fat deposits in the liver, which are indirectly associated with obesity and deposits of visceral fat, now considered as part of the metabolic syndrome, which is a multiplex of serious health conditions.

Our study focused on the laboratory results of hepatic enzymes and their relationship with NAFLD. For early stage diagnosis of NAFLD this blend of liver function tests and USG grading can be very facilitating thus the expensive & invasive methods can be avoided.

This study showed a significant relationship between the hepatic enzymes and NAFLD grading. Ultrasonography can be used for the preliminary diagnosis of NAFLD. It is simplest and cost-effective method for NAFLD identification. In our study the association between the hepatic enzymes and the degree of NAFLD was highly significant with ALT (p<0.001), AST (p=0.003), ALP (p=0.021), GGT (p<0.001), AST/ALT ratio (p<0.001) and BMI (p=0.003) respectively.

Chang *et al*. proved that increasing levels of ALT, even within the reference range, was an independent predictor of incident NAFLD.[9] NAFLD is closely related to insulin resistance (IR), obesity, metabolic syndrome (MS), and diabetes which can be the initiatives for laboratory estimation of liver enzymes and considering a diagnosis of NAFLD[6].

Multiple researchers in their studies showed a strong association of ALT with NAFLD. The reasons being hepatic IR, central obesity, high triglycerides (TG), low high density lipoproteins (HDL) and increased levels of fasting plasma glucose (FPG) which are the metabolic syndrome components[10-13].

Masoom *et al*. in 2015 in their study also proved that ALT levels were high in fatty liver diagnosed patients[3]. Mansour-Ghanaei 2019 proved in his study that the relationship among the levels of hepatic enzymes and NAFLD grading was highly significant: p<0.001 for ALT & AST while for ALP p=0.42 and for GGT p<0.05[39].

Chien-Min K, Cheng-Chuan L in 2017 explained in their study that hepatic enzymes, BMI, TG & FPG were highly associated the NAFLD & positively correlated in respect grading of fatty liver infiltration. Their ALT mean was highest in grade III NAFLD and lowest in grade I (p<0.001), GGT mean in grade III was highest & lowest in grade I (p<0.05), the levels of AST being the highest in grade III of NAFLD and lowest in grade I (p<0.01). AST/ALT ratio was also highly significant at p<0.001[4].

Another similar study carried out in 2017 by Waseem, Puri M also showed a significant association of ALT (p<0.01), GGT (p<0.001), ALP (p<0.01) & BMI (p<0.001) with the different grades of NAFLD[40].

Behzadmehr R, Ebadati D and Tasneem AA, Luck NH, Majid Z in two different studies in 2017 also showed similar results showing significant correlation (p<0.001) between hepatic enzymes and NAFLD grading. BMI & AST/ALT ratio were also highly comparable in relation to the grades of fatty liver (p<0.001) and that the ratio of AST/ALT more than 1 was more indicative towards fibrosis[41, 42].

A significant positive correlation and linear regression of liver enzymes, ALT (p<0.001), AST (p<0.01), ALP (p<0.05), GGT (p<0.001) and BMI (p<0.01) with different grades of NAFLD was seen respectively. Similar results were shown by Chien-Min K, Cheng-Chuan L and Chen ZW, *et al* with p<0.05[4, 43].

Furthermore, liver biopsy which is the ultimate test to diagnose fatty liver in regard to staging/grading and evaluating the progression of NAFLD to NASH. This technique is invasive, complications and errors may occur especially the associated mortality in apparently healthy individuals. Therefore, USG is more frequently used to diagnose NAFLD [1, 4, 28, 44].

The limitation of this study was small sample size and using USG for the diagnosis of NAFLD which was not confirmed histologically by liver biopsy. Further studies regarding the non-invasive predictors of NAFLD should include lipid profile, insulin resistance, FPG along with hepatic enzymes to timely evaluate and predict the severity of NAFLD so that treatment and prevention of the disease is started early and progression of the disease be avoided.[11-13, 29, 45].

CONCLUSION

Our study concludes that higher levels of serum liver enzymes and BMI are independent predictive markers for determining the degree of NAFLD.

AUTHOR CONTRIBUTION

Mehnaz Khattak: Literature review, study design, data collection, result analysis, drafting & proof reading

Jawwad Anis Khan: Proof reading, questionaire design

Sami Saeed: Drafting, revising criticaly, final approval

Anisa Kalsoom: Data collection & analysis

Hasan Ikram: Data collection

Umme Farwa: Critical review

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