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Association of Serum Fetuin-A and Fatty Liver Index as an Indicator of Hepatic Steatosis in Chronic HCV Patients

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Abstract

Hepatocytes that have an excess accumulation of triglycerides experience hepatic steatosis. Alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD) are the two main diseases linked to hepatic steatosis. Moreover, the pathogenesis of hepatic steatosis includes various factors like metabolic, dietary, as well as HCV infection. The liver primarily produces fetuin A, a multifunctional plasma glycoprotein. Increased Fetuin A was related to obesity and its associated complications, including T2DM, metabolic syndrome, and NAFLD. The objective of this research was to see if the fatty liver index (FLI) and serum Fetuin A could be used as an early predictor for hepatic steatosis in patients with chronic HCV. This research included 90 persons who were divided into 3 groups: Group I: comprised 30 patients with NAFLD (steatosis) who were free of other chronic liver diseases. Group II: comprised 30 patients with hepatic steatosis and chronic HCV. Group III: a control group of 30 healthy people. All individuals experienced demographic, clinical, laboratory tests (Fetuin A level) and abdominal ultrasound; Fatty Liver Index (FLI) was calculated. Fetuin A levels in group II were significantly higher than in groups I and III, and significantly greater in group I than in group III. Both groups I and II exhibited a highly significant rise in the Fatty Liver Index (FLI) when compared to group III, but groups I and II exhibited no significant difference. Fetuin A has a good diagnostic value with high sensitivity and specificity in differentiating between steatosis in NAFLD and HCV related steatosis. It can be employed as a simple, non-invasive test in predicting HCV-related steatosis.

Keywords: NAFLD, AFLD, Fatty liver index, HCV, Fetuin A.

1. Introduction

The term "non-alcoholic fatty liver disease" (NAFLD) refers to a wide range of pathological diseases, from simple steatosis to cirrhosis, non-alcoholic steatohepatitis (NASH), and hepatocellular carcinoma **[1].** The accumulation of

pathological amounts of fat within the liver, mainly triglycerides exceeding 5% of the liver weight, is known as NAFLD and is the most prevalent liver condition in developed nations **[2].** It is one of the manifestations of metabolic syndrome, which also includes hypertension, dyslipidemia, type 2 diabetes, and obesity **[3].** The gold standard in NASH diagnosis and distinguishing between NASH and simple steatosis is through a liver biopsy. The risk of complications during a biopsy, on the other hand, is minor but not negligible **[4].**

Ultrasonography is widely used as a first screening for fatty liver because it is cheap, non-invasive, and easily accessible **[5]**, and it has a 94% sensitivity and an 84% specificity to detect liver steatosis **[6].**

Hepatic steatosis, T2D, insulin resistance (IR), and cardiovascular illness are all linked to 20% to 30% of chronic HCV infections. Nevertheless, it is challenging to understand the mechanisms that lead to hepatic steatosis in HCV-positive individuals owing to the potential coexistence of numerous variables **[7].**

The fatty Liver Index (FLI) is a simple and suitable indicator for hepatic steatosis. Measurements of the waist circumference, BMI, serum triglycerides, and γ-glutamyl transferase are used to estimate it.

A value of the fatty liver index greater than or equal to 30 rules in fatty liver, whereas a value of less than 30 rules it out, with a sensitivity 86% and a specificity of 87%. It may act as a surrogate indicator for metabolic syndrome and hepatic steatosis **[8].**

The liver synthesizes and secretes fetuin-A in large quantities. It's also known as “alpha-2-Heremans-Schmid glycoprotein”. It can be present throughout the body in the extracellular space. Fetuin-A is a multifunctional protein which engages in numerous cellular pathways, like insulin resistance, inflammation, and the metabolism of calcium and bone. Metabolic syndrome (Met S) and T2D are two conditions where the genes that encode fetuin-A are implicated **[9].**

In obesity and its associated consequences, like T2DM, metabolic syndrome, and NAFLD, epidemiologic studies consistently observe higher circulating FetA **[10].** The glycoprotein was hypothesized as a molecular connection among obesity, NAFLD, insulin resistance (IR), and MetS since it was linked to insulin receptor activity inhibition, resulting in a breakdown in pathways of insulin cascades **[11].**

2. Patients and Methods

This prospective case-control research involved 90 subjects from both sexes. They aged between (18- and 60) years and attended the Hepatology, Gastroenterology, and Infectious Diseases departments at Al-Azhar University Hospital. **The study groups have been divided into:**

- **Group I**: 30 patients with hepatic steatosis and no other chronic liver disorders. Their ages are between (21-57) years with a mean 39.93 ± 10.16, they are 4 males and 26 females.
- **Group II**: 30 patients with hepatic steatosis on top of chronic HCV. Their ages are between (22-60) years with a mean 43.47 ± 9.99, they are 16 females and 14 males.
- **Group III**: a healthy control group of 30 people. Their ages are between (21-55) years with a mean 38.87 ± 11.06, they are 17 females and 13 males.

2.1 Ethical Consideration

After an explanation of the study's objectives and benefits, each patient provided written informed consent to participate in this study. The study protocol has been accepted by the Al-Azhar University Faculty of Medicine for Girls' Research Ethics Committee.

2.2 Inclusion Criteria

Adult patients of both sexes with NAFLD (steatosis) and patients with steatosis on top of chronic hepatitis C.

2.3 Exclusion Criteria

Patients with diabetes mellitus, alcohol consumption, malignancy, liver cirrhosis, viral hepatitis except for HCV, autoimmune hepatitis, obese patients (BMI>30), those taking lipid-lowering medication, corticosteroid, renal dysfunction, and pregnancy.

2.4 All individuals underwent the following

1- Take a complete history.

2- A clinical evaluation includes measurements of body weight, height, and waist circumference.

2.5 Laboratory Investigation

- Complete blood count.
- Tests of liver function (SGPT-SGOT-GGT- Total and direct bilirubin- sALB-PT-INR).
- Kidney function tests (Bl.Urea – sCr).
- Fasting blood sugar, HbA1c.
- Lipid profile (sCholestrol- sTG – HDL - LDL).
- Viral markers (HBsAg and HCV Ab).
- Serum Fetuin A by ELISA.

2.6 Pelviabdominal Ultrasound.

2.7 Calculation of

- Fatty liver index: FLI = (e (0.953×ln (TG) + 0.139×BMI + 0.718×ln (GGT) + 0.053×WC15.745))/ (1+e (0.953× ln (TG) + 0.139×BMI + 0.718× ln (GGT) + 0.053×WC-15.745)) × 100 [12].
- The fibrosis index is based on four factors (FIB-4): (age (years) × AST (U/L)]/ (number of platelets (109/L) × ALT (U/L) (1/2)] **[13].**
- Aminotransferase to platelet ratio index (APRI) by the formula [AST/upper limit of normal × 100)/platelet count] **[14].**
- Body mass index BMI (mass Kg/height m2**) [15].**

2.8 Statistical Analysis

The Statistical Package for Social Science (IBM SPSS) version 23 has been employed to collect, revise, code, and enter the data. The quantitative data has been shown as median and inter-quartile range (IQR) for non-parametric data and mean, standard deviations, and ranges for parametric data. Also, percentages and numbers were shown for the qualitative variables. Employing qualitative data, groups have been compared using the Chi-square test. When comparing quantitative data from more than two groups with a parametric distribution, a One-Way ANOVA test was performed, and when the result was significant, a post hoc analysis employing the LSD test was performed. The association between two quantitative parameters within the same group has been evaluated using the Spearman correlation coefficients. The quantitative form of the ROC curve has been employed to calculate the Fetuin-A level's sensitivity, specificity, NPV, PPV, best cutoff point, and area under the curve (AUC). The accepted margin of error was set at 5% with a 95% confidence interval. As a result, P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

3. Results

We found that there have been no statistically significant differences among the studied groups concerning sex and age, while there have been statistically significant differences in terms of BMI between the three studied groups with a p-value < 0.001, and the post-hoc analysis revealed that there has been a significant

rise in BMI in group I than in group II and a highly significant rise in group II and the group I than in group III, as shown in table (1).

Also, the examined groups differed significantly in terms of TG, LDL, and cholesterol, but not HDL, as shown in Table .2.

Post Hoc analysis shows that:

- Serum cholesterol increased significantly in groups I and II than in group III, but not in group I than in group II.
- There had been a more highly significant rise in TG in group I than in groups II and III, but there had been no difference in group II than in group III.
- When groups II and I were compared to groups III, LDL increased significantly, but not in group I in comparison with group II.

There have been no statistically significant differences among the studied groups in terms of APRI and FIB-4 scores Table .3. Also, there have been highly statistically significant differences among the groups that were studied regarding FLI and Fetuin-A Table .4.

Post Hoc analysis shows that:

- There have been no statistically significant differences among groups I and II, but there has been a highly significant rise in FLI in both groups I and II in comparison with group III.

Fetuin A levels were significantly higher in group II than in groups I and III, and significantly higher in group I than in group III.

- Also, there was no statistically significant difference among the three studied groups as regard ALT, AST, Alb, BIL T, GGT, INR and Total Protein as in Table 5.
- As regards pelvic abdominal ultrasound there was a bright liver with an average size of (36.7%) in group I and (86.7%) in group II with a highly significant difference.
- There was bright hepatomegaly in (63.3%) of group I and (13.3%) in group II with a highly significant difference as in Table 6.

Table (1): Comparison of the demographic data and BMI among studied groups.

		Group I	**Group II**	**Group III**	**Test value**	**P- value**	**Sig.**
		No.= 30	**No.= 30**	**No.= 30**			
Age (years)	Mean ± SD	39.93 ± 10.16	43.47 ± 9.99	38.87 ± 11.06	1.604•	0.207	NS
	Range	21 – 57	22 – 60	21 – 55			
Sex	Females	26 (86.7%)	16 (53.3%)	17 (56.7%)	0.271	0.873	NS
	Males	4 (13.3%)	14 (46.7%)	13 (43.3%)			
BMI (Kg/m^2)	Mean ± SD	27.82 ± 1.77	26.72 ± 2.52	25.01 ± 1.85	14.034•	**<0.001**	**HS**
	Range	22.8 – 29.9	20.9 – 29.7	22.8 – 29.3			

Post Hoc Analysis

Parameters	**P 1** **Group I vs. Group II**	**P 2** **Group I vs. Group III**	**P 3** **Group II vs. Group III**
BMI (KG/M2)	**0.043 (S)**	**0.000 (HS)**	**0.02 (S)**

Table (2): Comparison of the lipid profile among studied groups

		Group I	Group II	Group III	Test value	P- value	Sig.
		No.= 30	No.= 30	No.= 30			
CHOL (mg/dl)	Mean ± SD	205.03 ± 39.79	192.33 ± 33.26	166.47 ± 30.52	9.602•	0.000	HS
	Range	130 – 308	134 – 260	99 – 200			
TG (mg/dl)	Mean ± SD	122.48 ± 38.26	94.80 ± 25.20	89.65 ± 28.32	9.673•	0.000	HS
	Range	51.2 – 190	46 – 141	46 – 150			
HDL (mg/dl)	Mean ± SD	44.21 ± 8.93	46.65 ± 9.53	46.55 ± 8.91	0.690•	0.504	NS
	Range	30.2 – 63.5	22 – 62.9	30.1 – 65.9			
LDL (mg/dl)	Mean ± SD	115.93 ± 19.06	121.80 ± 24.15	98.87 ± 10.22	12.152•	0.000	HS
	Range	91 – 167	79 – 180	74 – 118			
			Post Hoc Analysis				
	P1 Group I vs. Group II		P2 Group I vs. Group III		P3 Group II vs. Group III		
CHOL	0.160 (NS)		0.000 (HS)		0.005 (S)		
TG	0.001 (HS)		0.000 (HS)		0.523 (NS)		
LDL	0.228 (NS)		0.001 (HS)		0.000 (HS)		

Table (3): Comparison of APRI and FIB-4 scores among studied groups.

		Group I	Group II	Group III	Test value	P- value	Sig.
		No.= 30	No.= 30	No.= 30			
APRI	Mean ± SD	0.21 ± 0.10	0.26 ± 0.11	0.24 ± 0.08	2.106•	0.128	NS
	Range	0.07 – 0.47	0.11 – 0.62	0.11 – 0.42			
FIB-4	Mean ± SD	0.69 ± 0.29	0.89 ± 0.36	0.77 ± 0.31	2913•	0.060	NS
	Range	0.25 – 1.41	0.4 – 1.5	0.02 – 1.34			

Table (4): Comparison of FLI and Fetuin-Fetuin-AA level among studied groups.

		Group I	Group II	Group III	Test value	P-value	Sig.
		No.= 30	No.= 30	No.= 30			
FLI	Mean ± SD	51.06 ± 16.93	45.93 ± 18.40	25.43 ± 10.82	22.302•	0.000	HS
	Range	14 – 82	15 – 75	6 – 54			
Fetuin A (mg/l)	Median (IQR)	1494 (915 – 2016)	2439 (1883 – 2705)	197.5 (96 – 301)	67.957≠	0.000	HS
	Range	589 – 2760	1440 – 3800	77 – 400			
Post Hoc Analysis							
Parameters	P1 Group I vs. Group II		P2 Group I vs. Group III		P3 Group II vs. Group III		
FLI	0.210 (NS)		<0.001 (HS)		<0.001 (HS)		
Fetuin A	<0.001 (HS)		<0.001 (HS)		<0.001 (HS)		

Table (5): Comparison of liver function tests among studied groups.

		Group I	Group II	Group III	Test value	P-value	Sig.
		No.= 30	**No.= 30**	**No.= 30**			
ALT (U/l)	Mean ± SD	20.45 ± 8.27	22.70 ± 9.04	19.70 ± 6.99	1.103•	0.336	NS
	Range	7 – 36	5 – 38	10 – 39			
AST (U/l)	Mean ± SD	20.78 ± 7.25	24.65 ± 7.71	21.72 ± 6.08	2.456•	0.092	NS
	Range	10 – 36	13 – 40	9 – 38			
Alb (g/dl)	Median (IQR)	4.2 (3.9 – 4.3)	4.3 (4.1 – 4.6)	4.35 (4.1 – 4.5)	2.488≠	0.089	NS
	Range	3.7 – 4.8	3.9 – 5	3.9 – 39			
BIL T (mg/dl)	Mean ± SD	0.45 ± 0.19	0.55 ± 0.16	0.48 ± 0.15	2.836•	0.064	NS
	Range	0.2 – 0.9	0.25 – 0.9	0.2 – 0.8			
GGT (U/l)	Mean ± SD	27.51 ± 8.61	27.45 ± 7.30	23.95 ± 5.51	2.372•	0.099	NS
	Range	15.9 – 49.7	17 – 42	14.5 – 36			
INR	Mean ± SD	1.05 ± 0.07	1.04 ± 0.07	1.04 ± 0.06	0.395•	0.675	NS
	Range	1 – 1.2	1 – 1.2	1 – 1.2			
Total Protein (g/dl)	Mean ± SD	7.65 ± 0.65	7.40 ± 0.60	7.30 ± 0.49	2.910•	0.060	NS
	Range	6.7 – 9.2	6.3 – 8.6	6.5 – 8.3			

Table (6): Comparison between the patients' groups as regard ultrasound findings.

Ultrasound	**Group I**	**Group II**	**Test value***	**P-value**	**Sig.**
	No. = 30	**No. = 30**			
Bright liver with average Age (years) size	11 (36.7%)	26 (86.7%)	15.864	0.000	HS
Bright hepatomegaly	19 (63.3%)	4 (13.3%)			

Concerning the correlation between Fetuin-A and additional parameters in our research:

- In group I: serum Fetuin-A had a significant positive correlation with ALT, cholesterol, and TG but a statistically significant negative correlation with GGT.
- In group II**:** Fetuin-A and cholesterol had a highly significant positive correlation, while Fetuin-A and TG had a significant positive correlation.

As regards the correlation between FLI and other parameters:

- In group I, FLI and BMI showed a highly significant positive correlation.
- In group II, FLI and TG showed a significant positive correlation, and FLI and BMI showed a highly significant positive correlation.

Table .7 shows that the Fetuin-A level at a cut-off value of > 400 had a specificity of 100%, sensitivity of 100%, PPV of 100%, NPV of 100%, with diagnostic accuracy of 100%.

Table .8 shows that the Fetuin-A level at cut-off value > 1535 exhibited a sensitivity of 96.67 %, specificity of 53.33%, PPV of 67.4%, NPV of 94.1% and diagnostic accuracy of 83%.

Table (7): Diagnostic performance of Fetuin-A level in discrimination of (group I) and the control group (group III).

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV	Accuracy
>400	1.000	100.00	100.00	100.0	100.0	100.0 %

Table (8): Diagnostic performance of Fetuin-A level in the discrimination of (group I) from (group II).

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV	Accuracy
>1535	0.830	96.67	53.33	67.4	94.1	83.0 %

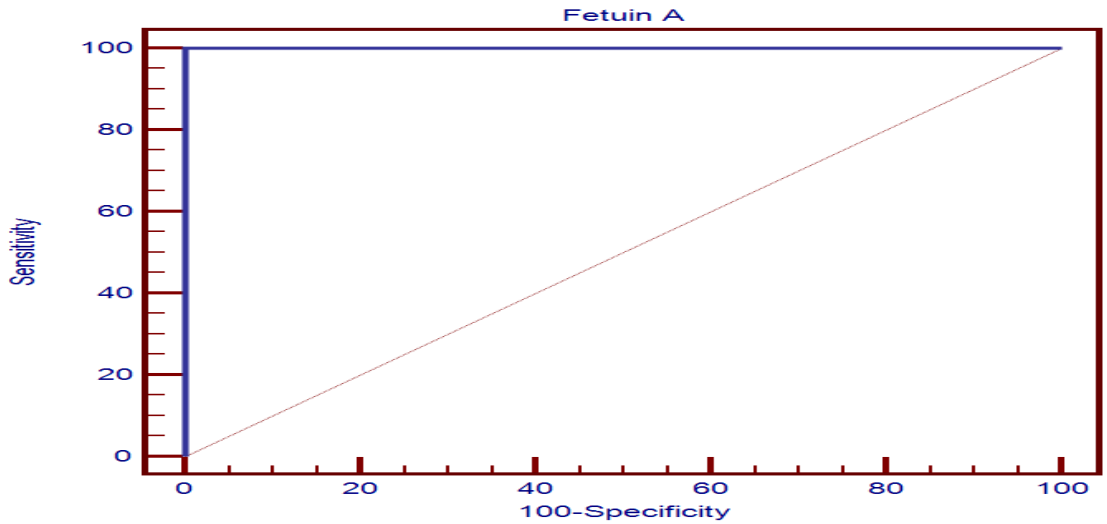

Figure (1): Receiver operating characteristic curve (ROC) between normal group (group III) and fatty liver group (group I) as regards Fetuin-A level.

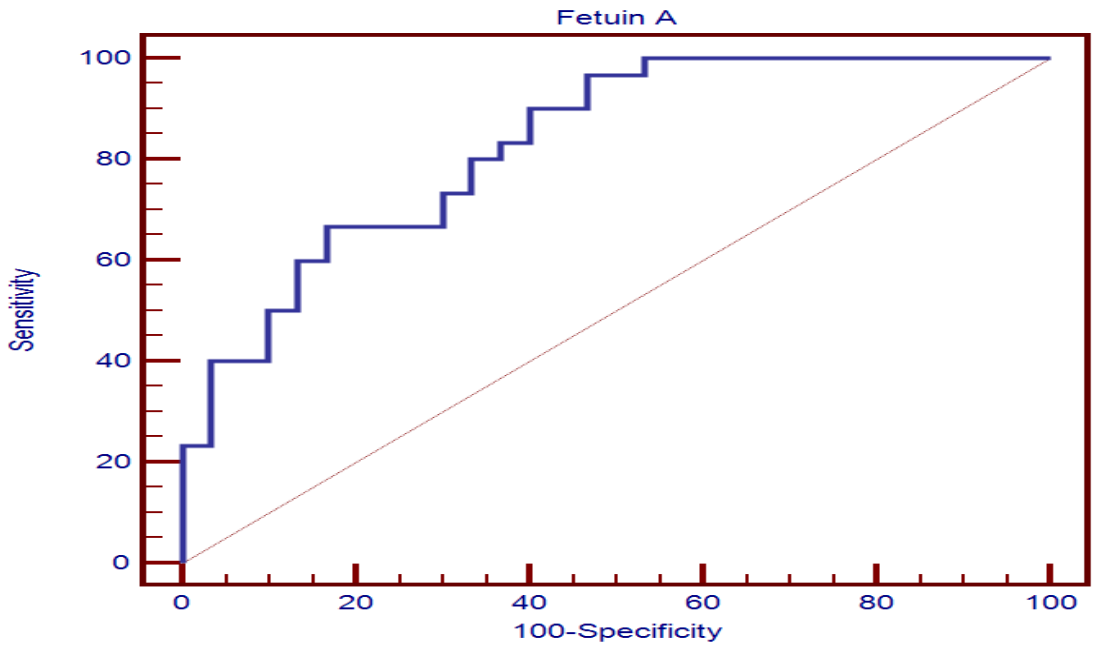

Figure (2): ROC curve between (group I) and (group II) as regards Fetuin-A level.

4. Discussion

In our study as regard to age and sex, we found that in group I, there were 4 (13.3%) men and 26 (86.7%) women. The mean age was 39.93 ± 10.16. In group II, there were 14 (46.7%) men and 16 (53.3%) women. The mean age was 43.47 ± 9.99. In group III, there were 13 (43.3%) men and 17 (56.7%) women. The mean age was 38.87 ±11.06. There have been no statistically significant differences between the groups under study.

Concerning BMI, group I had a significantly higher BMI than group II, and both groups I and II had a significantly higher BMI than group III, which was consistent with **(Sato et al., [16]; Cui et al., [17].** They discovered that NAFLD patients' BMI was higher than that of controls with similar ages and genders.

As regards the lipid profile, groups I (205.03 ± 39.79) and II (192.33 ± 33.26) had significantly higher cholesterol levels than group III (166.47 ± 30.52), but there have been no significant differences among groups I and II.

In comparison to groups II (94.80 ± 25.20) and III (89.65 ± 28.32), group I had a highly significant rise in TG (122.48 ± 38.26), while groups II and III did not differ significantly from one another.

Also, there has been a highly significant rise in LDL in groups II (121.80 ± 24.15) and I (115.93 ± 19.06) in comparison with group III (98.87 ± 10.22), but there have been no significant differences in group I than in group II.

Our findings were compatible to those of **Marzouk et al. [18]**, who found that patients with chronic HCV exhibited lower plasma levels of LDL, cholesterol, and triglycerides than those who had never been infected. This may be explained by changes in lipid metabolism caused by HCV infection, which make serum triglycerides and cholesterol lower than non-infected individuals **(Diaz et al.) [19].** This was in line with the conclusions of **Cui et al. [17],** who demonstrated a highly significant rise in cholesterol levels and triglycerides in NAFLD patients.

Sato et al. [16] reported a highly significant increase in serum triglycerides but no significant differences in serum cholesterol levels in the fatty liver group in comparison to the control group.

Our study revealed no statistically significant differences in the APRI and FIB-4 scores between the studied groups.

In the current research, we reported a highly significant rise in FLI in groups I and II (51.06 ± 16.93 and 45.93 ± 18.40, respectively) in comparison with group III (25.43 ± 10.82), while there have been no significant differences among groups I and II.

In research by **Huang et al. [20],** FLI has been shown to be a simple and reliable indicator of NAFLD and to have striking concordance with routine abdominal ultrasonography diagnosis of NAFLD.

As regards the correlation between FLI and laboratory parameters in the fatty liver group (group I), FLI and BMI exhibited a highly significant positive correlation. There has been a highly significant positive correlation between FLI and BMI in the HCV group (group II), and a significant positive correlation between FLI and TG.

As regards Fetuin A, group II (2439 (1883–2705)) showed a highly significant increase compared to groups I (1494 (915–2016)) and III (197.5 (96–301), and group I exhibited a highly significant rise compared to group III.

This was consistent with research by **Sato et al. [16]** who discovered a greater level of serum Fetuin A in patients with NAFLD than controls without a significant difference. Also, **Lebensztejn et al. [21]** discovered that children with NAFLD had greater serum fetuin A levels than those without.

However, other studies produced different results. **Cui et al. [17]** reported that NAFLD patients exhibited lower serum fetuin A levels compared to the control

group. While they observed that levels of serum Fetuin-A rise in correlation with the intensity of NAFLD, this indicates that Fetuin-A may be a predictor of NASH development.

Sheriba et al. [22] and Nafee et al. [23] found that chronic hepatitis C patients exhibited significantly greater levels of Fetuin-A than healthy controls.

As regards the correlation between serum Fetuin-A and lab parameters in the fatty liver group (group I) of our research, there has been a significant positive relationship among serum Fetuin-A and ALT, cholesterol, and TG, but there has been a negative association between serum Fetuin-A and GGT.

Serum Fetuin-A levels were discovered to be significantly correlated with increased FLI, ALT, and AST levels that were early indications of NAFLD by **Huang et al. [24].**

Also, **Filardi et al. [1]** discovered a positive correlation between Fetuin-A and BMI, waist circumference, TG, and uric acid, while there has been a negative correlation between Fetuin-A and age.

In contrast to our results, **Haukeland et al. [25]** discovered no significant correlations between Fetuin-A and serum ALT, triglycerides, cholesterol, HDL, or LDL in the NAFLD group.

In our correlation study between Fetuin-A and lab parameters in the HCV group (group II), there has been a highly significant positive correlation between Fetuin-A and cholesterol and a significant positive correlation between Fetuin-A and TG.

According to **Sheriba et al. [22],** fetuin A was shown to have a highly significant positive correlation with BMI, as well as a significant positive correlation with FBG, fasting insulin, and HOMA-IR.

5. Conclusion

Fetuin A could be used as a simple, non-invasive test in detecting HCV related steatosis and has a good diagnostic value with high sensitivity and specificity in differentiation between steatosis in NAFLD and HCV related steatosis. Fetuin A in combination with FLI may complement each other and enhance the accuracy of steatosis detection.

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