The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89 (2), Page 6282- 6288

Assessment of Serum Fetuin A level in Patients with NAFLD and Chronic Hepatitis C

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ABSTRACT

Background: It has been suggested that an association exists between elevated Fetuin A concentration, obesity, as well as fatty liver.

Objective: Investigation of connection between NAFLD and Fetuin A in individuals with or without chronic hepatitis C virus infection in of Egyptian population.

Patients and Methods: In a cross-sectional study, we conducted our trial at Misr University for Science and Technology and the Gastroenterology and Hepatology Unit of Ain Shams University's Department of Internal Medicine. The study included 90 patients and were subdivided into three groups, group I included 30 healthy people as control group, group II included 30 patients with NAFLD (non-diabetic) and group III included 30 patients with hepatic steatosis on top of HCV infection non cirrhotic and non-diabetic.

Results: Fetuin A level and blood triglyceride were positively correlated in all patients and patient subgroups, both statistically significantly correlated (NAFLD, HCV). There was also highly statistically significant positive correlation between serum cholestrerol and fetuin A level in all patients and in patient subgroups (NAFLD, HCV) and with a cutoff point of >500, the serum level of fetuin A revealed a highly statistically significant difference between groups 1 and 2; serum fetuin A showed a highly statistically significant difference between groups 1 and 3, with a cutoff point of >1800.

Conclusion: ROC curve showed the diagnostic performance of serum Fetuin A as a marker in fatty liver.

Keywords: Fetuin A, Non-Alcoholic Fatty Liver, HCC, HCV.

INTRODUCTION

A variety of steatosis diseases, such as basic steatosis, more advanced steatosis, cirrhosis, and, in certain circumstances, hepatocellular carcinoma, are referred to as non-alcoholic fatty liver disease (NAFLD). Obesity and insulin resistance, which cause triglyceride and free fatty acid accumulation in the liver, are two factors contributing to the growing epidemic of NAFLD, which affects not just the western world but the entire world [(1)].

Hepatocellular carcinoma (HCC), the main cause of end-stage liver disease, liver-related death, and chronic HCV infection in Egypt. After 20 to 30 years of HCV infection, 10 to 20% of chronic hepatitis patients go on to develop cirrhosis, which affects 60 to 80 percent of people with HCV. In the 20 to 30 years that follow, 3 to 6 percent of individuals with liver cirrhosis and 1 to 5 percent of those with liver cancer may experience decompensation. Between 15 and 20 percent of people who experience a decompensation episode will pass away within a year [(2)].

The existence of adipokine secreting adipose tissue as an active endocrine organ is now well established. A relationship between illnesses associated with obesity and adipose tissue dysfunction can be established through altered adipokine secretion and production. They are in charge of controlling the entire body's metabolism because they affect endothelial dysfunction, atherosclerosis, inflammation, fat distribution, satiety, and appetite in addition to poor insulin sensitivity or secretion [(3)].

Fetuin A is a glycoprotein that liver cells produce and secrete in large quantities into the blood. Embryogenesis produces fetal protein A. It modulates osteogenesis, prevents ectopic calcification, and encourages bone remodeling. Human Fetuin A is a naturally occurring inhibitor of the insulin receptor's tyrosine kinase activity. In the treatment of type 2 diabetes, obesity, and other insulin-resistant disorders, fetuin A may be a novel therapeutic target as it may play a significant role in postprandial glucose clearance, insulin sensitivity, weight gain, and fat deposition [(4)].

It has been suggested that an association exists between elevated Fetuin A concentration, obesity, and fatty liver. Fetuin A promotes insulin resistance, which is the main defect causing both metabolic syndrome and fatty liver disease, which accounts for this. Adipocyte accumulation of results in an increase in fetuin secretion [(5)].

AIM OF THE STUDY

Our goal is investigation of connection between NAFLD and Fetuin A in individuals with or without chronic hepatitis C virus infection in of the Egyptian population.

PATIENTS AND METHODS

The Internal Medicine Department, Gastroenterology and Hepatology Unit, Ain Shams University Hospital, and Misr University for Science and Technology Hospital participated in the study. During the months of August 2017 and February 2018.

Ninety cases included as the following:

Group I: involved 30 healthy persons as control class.

Received: 01/07/2022
Accepted: 07/09/2022

Group II: involved 30 patients with NAFLD. Diagnosis of NAFLD based on specific ultra-sonographic features such as the presence of bright homogenous hepatomegaly, together with the exclusion of other causes of chronic liver disease as viral, autoimmune, and metabolic causes.

Group III: included 30 patients with hepatic steatosis on top of chronic HCV, diagnosed clinically, biochemically, and radiologically, non-diabetic, non-cirrhotic.

Patients with diabetes mellitus, liver cirrhosis, a history of drinking alcohol, other malignant conditions, or both were disqualified from the trial. Patients using lipid-lowering medications as well as those taking long-term steatosis-inducing drugs such corticosteroids, tamoxifen, amiodarone, and valproic acid (statins or fibrates), Patients with a BMI of 35 or above, those who are obese, and those who have additional types of liver disease, like alcoholism-related liver disease, Wilson's disease, drug-induced hepatitis, other viral hepatitis types, primary sclerosing cholangitis, primary biliary cirrhosis, alpha-1 antitrypsin deficiency, and autoimmune hepatitis are among the liver diseases that can occur.

Laboratory testing comprising complete blood count, complete blood count, full liver profile, serum creatinine, HCVAb, HBsAg, and HIVAb, lipid profile included fasting triglycerides and cholesterol levels, calculation of Fib-4, and Apri scores, Alpha-fetoprotein, were performed on all patients in addition to a complete medical evaluation, including body mass index calculation:

$$= \frac{\text{mass(kg)}}{(\text{height(m)})^2}$$

Abdominal ultrasonography with special emphasis on liver size, echotexture, splenic size, presence of ascites and HCC.

Fetuin serum utilizing a fetuin A ELISA kit and following the manufacturer's instructions, a level was determined.

Ethical considerations:

The research followed the Guidelines Laid Down in the 1975 Helsinki Statement , and it was authorised by the Medical School's Ethics Council at Ain Shams University. All patients who participated in the study did so willingly after being fully educated on the study's methodologies and signing an informed consent form.

Statistical methods

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 18 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). For qualitative variables, independent t-tests were used when there were two separate groups with parametric data to do inferential analysis. For numerical parametric data, we used Pearson correlation; for numerical nonparametric and qualitative data, we used the Spearman test. We used ROC curve and DeLong test to analyze how well different tests discriminated across various subgroups. P value < 0.05 was considered significant.

RESULTS

With the exception of BMI, which was statistically substantially higher in the patient group than the control group with a p-value of 0.001, there were no statistically significant differences in the demographic data (age and sex) between the control and patient groups, including groups II and III (table 1).

Table (1): Demographic data in both control and patients (age, sex and BMI)

		Control	**Patients**	**Test value•**	**P-value**	**Sig.**
		No. = 30	**No. = 60**			
Age	Mean ± SD Range	42.8 ± 7.85 27 – 58	45.82 ± 9.89 27 – 60	-1.465	0.149	NS
Sex	Females Males	15 (50.0%) 15 (50.0%)	31 (51.7%) 29 (48.3%)	0.022	0.882	NS
BMI	Mean ± SD Range	23.06 ± 3.6 18.4 – 29.9	26.53 ± 4.52 18.4 – 35.2	-3.655	0.001	**HS**

Table (**2**) demonstrates that, with regard to HBA1C and FBS, Groups II and III of the patient population, as well as the control group, did not differ statistically significantly from one another. Additionally, there were extremely significant differences in S. cholesterol between the control and sick groups, including groups II and III. Additionally, In terms of S. TAG, there were statistically significant differences between the control and sick groups, including groups II and III.

Table (2): Comparison of the HBA1C, FBS, S. CHO, and S. TAG values between the control group and the patient group.

		Control	Patients	Test value•	P-value	Sig.
		No. = 30	No. = 60			
HBA1C mmols/mol %	Mean ± SD	5.15 ± 0.41	5 ± 0.7	1.080	0.283	NS
FBS mg/dL	Mean ± SD	87.67 ± 8.31	89.43 ± 7.93	-0.981	0.329	NS
S.CHO mg/dL	Mean ± SD	146.67 ± 25.1	185.33 ± 43.38	-3.758	0.000	**HS**
S. TAG mg/dL	Mean ± SD	154 ± 22.68	172.17± 41.75	4.933	0.029	**S**

HBA1C: hemoglobin A1C, FBS: fasting blood sugar, S.CHO: serum Cholesterol, S. TAG: serum triacyl glyceride

Table (3) shows that neither the NAFLD nor the HCV patient groups, nor the control group had statistically different HBA1C or FBS values. Between the NAFLD group and the control, as well as between the NAFLD group and HCV, there was also a highly significant difference in S. cholesterol. Despite the fact that the HCV group and the control group differed, it was not statistically significant. Additionally, in terms of S. TAG, the NAFLD group and the control group had a statistically significant difference, but neither the NAFLD and HCV groups nor the control group and the HCV groups did.

Table (3): Comparison of laboratory data between the control group and the patient group

		Control	Patients	Test value	P-value	Sig.
		No. = 30	No. = 60			
APRI	Mean ± SD	0.19 ± 0.03	0.18 ± 0.03	0.427•	0.670	NS
FIB4	Mean ± SD	0.7 ± 0.11	0.72 ±0.10	-0.745ǂ	0.456	NS
FETUIN A mg/L	Mean ± SD	362 ± 88.85	2302.5 ± 551.4	-8.882•	0.000	**HS**

APRI: AST to Platelet Ratio Index scoring, FIB4: Fibrosis-4 Score,

Table (4) demonstrates that there was no statistically significant difference in the APRI score and FIB4 score between the control and patient groups, including groups II and III while fetuin A levels in the patient groups (groups II and III) increased significantly more than in the control groups, with a p-value of <0.001 indicating this.

Table (4): Comparison between control group and subgroups of patients (NAFLD and HCV) regarding (HBA1C, FBS, S. CHO and S. TAG)

		Control group	NAFLD group	Hepatitis C virus with fatty liver	Test value•	P-value	Sig.	Post hoc analysis		
		No. = 30	No. = 30	No. = 30				P1	P2	P3
HBA1C mmols/mol %	Mean ± SD	5.15 ± 0.41	4.93 ± 0.93	5.06 ± 0.35	0.925	0.400	NS	0.181	0.605	0.409
FBS mg/dL	Mean ± SD	87.67 ± 8.31	87.83 ± 7.42	91.03 ± 8.22	1.691	0.190	NS	0.936	0.106	0.125
S.CHO mg/dL	Mean ± SD	146.67 ± 25.1	213.67 ± 47.74	157 ± 37.08	24.574	0.000	**HS**	0.000	0.318	0.000
S. TAG mg/dL	Mean ± SD	154 ± 22.68	184.33 ± 43.79	158.33 ± 31.52	4.150	0.019	**S**	0.009	0.705	0.025

•: One Way ANOVA test, P1: Control group vs NAFLD group, P2: Control group vs Hepatitis C virus with fatty liver group, P3: NAFLD group vs Hepatitis C virus with fatty liver group

With the exception of fetuin A, which showed a highly statistically significant increase in the NAFLD group compared to the control group and in the Hepatitis C group compared to the NAFLD and control group, the previous table demonstrates that The APRI and FIB4 scores for the control group and patient subgroups did not differ in a manner that was statistically significant (table 5).

Table (5): Laboratory data comparison between the control group and patient subgroups

		Control group	NAFLD group	Hepatitis C virus with fatty liver	Test value	P-value	Sig.	Post hoc analysis		
		No. = 30	No. = 30	No. = 30				P1	P2	P3
APRI	Mean ± SD	0.19 ± 0.08	0.18 ± 0.07	0.19 ± 0.08	0.203•	0.816	NS	0.546	0.896	0.636
FIB4	Mean ± SD	0.7 ± 0.13	0.75 ± 0.14	0.7 ± 0.15	0.578ǂ	0.749	NS	0.564	0.478	0.871
FETUIN A	Mean ± SD	362 ± 89.85	1476.67 ± 358.91	3128.33 ± 771.31	117.342•	0.000	HS	0.000	0.000	0.000

Table (6) demonstrates that fetuin A and blood cholesterol and triglyceride levels in all patients and patient categories had a highly statistically significant positive link while Except for INR, which exhibited a positive association with fetuin A level in all patients, No statistically significant correlation existed between fetuin A and the other variables that were examined.

Table (6): Correlation of Fetuin A with the studied parameters in all patients group and subgroups

	FETUIN A					
	All patients		NAFLD group		Hepatitis C virus with fatty liver	
	r	P-value	R	P-value	r	P-value
Age (years)	-0.038	0.773	0.256	0.172	-0.163	0.390
BMI (kg/m^2)	0.076	0.566	0.051	0.789	-0.201	0.286
HB (g/dL)	0.009	0.944	0.346	0.061	0.027	0.886
TLC	0.075	0.571	-0.088	0.643	-0.086	0.653
PLT *1000 (mcL)	-0.197	0.131	-0.070	0.714	-0.272	0.146
AST (U/L)	0.205	0.116	0.335	0.070	0.273	0.145
ALT (U/L)	0.038	0.773	-0.051	0.789	0.200	0.288
BIL T (mg/dL)	0.002	0.987	0.076	0.691	0.006	0.975
BIL D (mg/dL)	-0.157	0.230	-0.249	0.184	-0.210	0.266
ALB (mg/dL)	0.067	0.612	-0.160	0.398	0.181	0.339
PT	0.154	0.239	0.007	0.970	0.016	0.935
INR	0.323*	0.012	0.052	0.785	-0.038	0.842
NA (mmol/l)	-0.066	0.616	-0.104	0.585	0.063	0.739
K (µg/mL)	0.073	0.581	0.101	0.595	0.008	0.967
BUN (mg/dL)	-0.151	0.329	-0.374	0.086	0.318	0.149
CREAT (mg/dl)	0.065	0.619	0.131	0.492	-0.037	0.845
HBA1C (mmols/mol %)	0.020	0.878	0.055	0.775	0.066	0.728
FBS (mg/dL)	0.222	0.088	-0.008	0.969	0.254	0.175
S.CHO (mg/dL)	0.420**	0.001	0.854**	0.000	0.912**	0.000
S. TAG (mg/dL)	0.378**	0.003	0.782**	0.000	0.393*	0.032
Alfa-feto p	-0.134	0.309	-0.044	0.817	-0.129	0.498
APRI	0.232	0.075	0.252	0.178	0.344	0.063
FIB4	0.142	0.280	0.272	0.146	0.091	0.633

In all patients and patient groupings table (7) demonstrates a very statistically significant positive association between serum cholesterol and fetuin A level while No statistically significant relationship was found between serum cholesterol and the other factors analyzed.

Table (7): Serum cholesterol levels and the investigated variables were correlated across all patient categories and subgroups.

	S. cholesterol					
	All patients		**NAFLD group**		**Hepatitis C virus with fatty liver**	
	r	**p-value**	**R**	**p-value**	**r**	**p-value**
Age (years)	-0.025	0.849	0.040	0.832	-0.160	0.400
BMI (kg/m^2)	-0.171	0.190	-0.031	0.871	-0.220	0.243
HB (g/dL)	0.209	0.110	0.332	0.073	0.099	0.604
TLC	-0.077	0.558	-0.036	0.851	-0.047	0.807
PLT *1000 (mcL)	-0.212	0.104	0.016	0.932	-0.316	0.075
AST (U/L)	0.223	0.087	0.360	0.054	0.238	0.206
ALT (U/L)	0.114	0.386	-0.148	0.435	0.182	0.336
BIL T (mg/dL)	-0.036	0.787	-0.022	0.909	-0.013	0.944
BIL D (mg/dL)	-0.179	0.081	-0.309	0.097	-0.270	0.148
ALB (mg/dL)	0.109	0.409	-0.115	0.545	0.210	0.266
PT	0.109	0.413	0.103	0.588	0.181	0.348
INR	-0.040	0.763	-0.010	0.958	0.008	0.969
NA (mmol/l)	-0.072	0.587	-0.241	0.199	0.025	0.895
K (µg/mL)	0.119	0.363	0.358	0.052	0.035	0.856
BUN (mg/dL)	0.149	0.334	-0.282	0.203	0.341	0.120
CREAT (mg/dl)	0.121	0.357	0.238	0.204	0.035	0.853
HBA1C (mmols/mol %)	-0.058	0.659	-0.112	0.556	-0.041	0.829
FBS (mg/dL)	0.034	0.799	-0.145	0.444	0.237	0.207
Alfa-feto p	0.041	0.758	-0.143	0.450	-0.011	0.952
APRI	0.105	0.421	0.247	0.188	0.270	0.252
FIB4	0.118	0.368	0.204	0.280	0.100	0.600
FETUIN A	0.420**	0.001	0.854**	0.000	0.912**	0.000

The receiver operating characteristic curve (ROC) showed that the best cutoff point to differentiate between NAFLD group and control group regarding fetuin A level was found > 500 with sensitivity of 96.67%, specificity of 100.0% and area under curve (AUC) of 97.7% (figure 1).

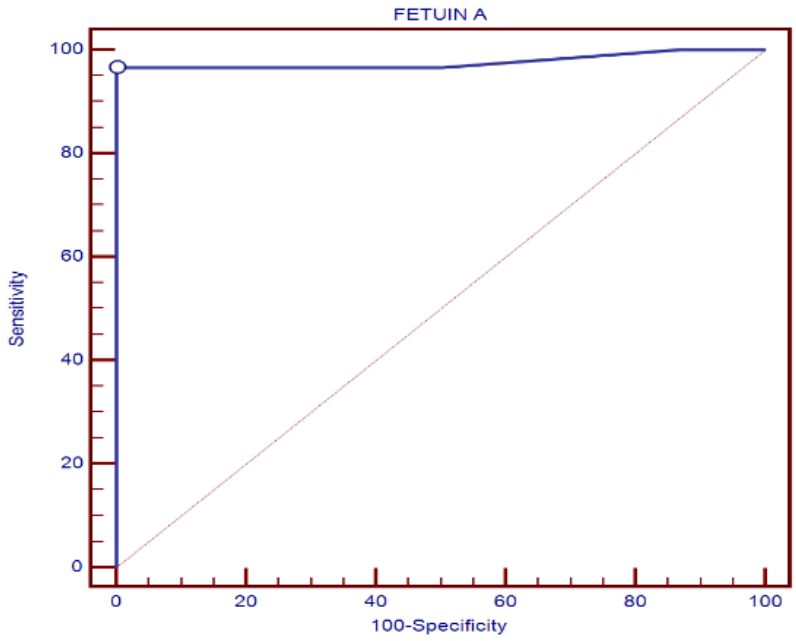

Figure (1**):** Cutoff point of serum fetuin A in diagnosing NAFLD group.

The receiver operating characteristic curve (ROC) showed that the best cutoff point to differentiate between NAFLD group and hepatitis C virus with fatty liver group regarding fetuin A level was found > 1800 with sensitivity of 93.3%, specificity of 80.0% and area under curve (AUC) of 89.9% (figure 2).

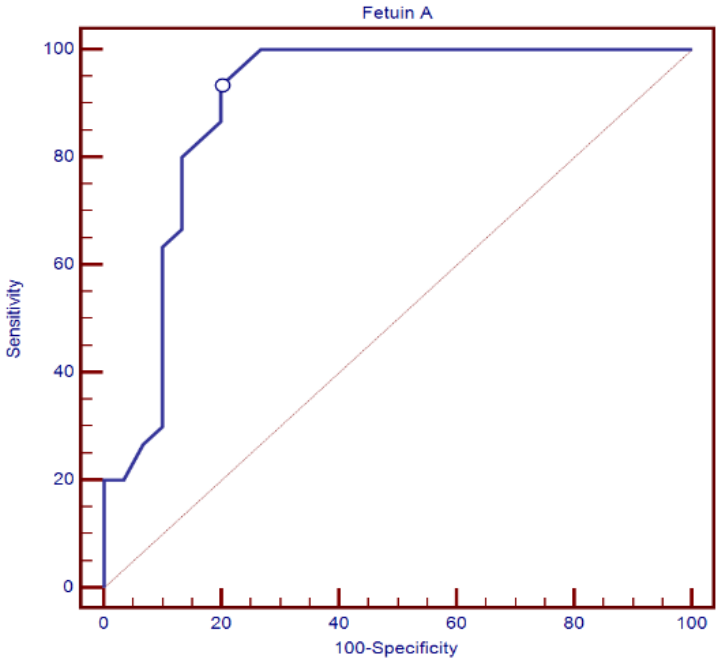

Figure (2): The best cutoff point of serum fetuin A in differentiating NAFLD group from HCV group.

DISCUSSION

A clinico-pathological syndrome called non-alcoholic fatty liver disease (NAFLD), which affects people who don't drink too much, involves lipid accumulation and associated pathological alterations [(6)].

Although liver biopsy is currently the gold standard for diagnosing NAFLD, it is not a perfect procedure because of its invasiveness and inherent sample bias. Non-invasive techniques, such as imaging investigations and serologic tests, are becoming more popular for diagnosing NAFLD [(7)].

In certain research, it was discovered that people with hepatic fat buildup had higher levels of circulating Fetuin A [(8)].

So we conducted this study to correlate between fetuin A levels and NAFLD (with or without HCV) on 90 patients divided into three groups as mentioned above, age and sex were statistically non-significant in the studied groups while Body Mass Index (BMI) was statistically significant between control group and the other two groups this was in partial agreement with **Sato *et al.*** [(9)] who studied fetuin A correlation with liver and vascular fibrosis in patients with NAFLD on 295 subjects 275 of them had NAFLD and 20 were without NAFLD who found significant difference in BMI between patients with NAFLD and people without.

Serum cholesterol and triglycerides were considerably higher in the NAFLD group compared to the control group and in the hepatic steatosis with HCV infection group, but they were also significantly higher in the NAFLD group compared to the steatosis with HCV infection group.

In a partial agreement with **Marzouk *et al.*** [(10)] who conducted a study on 765 individuals in rural Egypt to examine the metabolic and cardiovascular risk profiles and hepatitis C virus infection, He measured fasting lipid and glucose profiles and compared them to adults who had never been infected with HCV, adults who had been infected in the past, and adults who had chronic HCV infection. It was discovered that patients with chronic HCV had lower plasma levels of low density lipoproteins (LDL), cholesterol, and triglycerides than those who had never been infected. It was also discovered that patients who had previously been cured of HCV infection had higher serum levels of LDL, Therefore, it was proposed that higher triglyceride levels seen in participants who had previously been infected during the acute infection may have aided viral clearance.

This is also may be explained by changes in lipid metabolism caused by HCV infection which makes serum triglycerides and cholesterol lower than non-infected individuals [(11)].

Many researchers studied the relation between fetuin A levels and NAFLD , in our study we found that fetuin A levels were higher in NAFLD group than control group and even higher in hepatic steatosis on top of HCV infection group (as shown in table 20) it was similar to **Haukeland *et al.*** [(8)] who reported increased serum fetuin A level in patients with NAFLD more than the control group, they also reported that Without taking into account age, sex, or body mass index, NAFLD was a highly significant predictor of higher serum fetuin A levels (BMI), our results are in agreement with **Lebensztejn *et al.*** [(12)] who also found that levels of

serum fetuin A were higher in children with NAFLD than children without.

Sato *et al.* [9] reported similar results about patients with NAFLD it was found that they have higher serum fetuin A levels than controls but was statistically non-significant.

However other studies conducted different results **Cui *et al.* [6]** reported that patients with NAFLD had lower serum fetuin A levels than control group, they also reported that serum fetuin A levels increased with the severity of NAFLD which indicates that fetuin A may be a predictor of development of NASH.

Our study revealed that patients with fatty liver in chronic HCV tended to have higher serum levels of feutin A which comes with the agreement with **Nafee *et al.* [13]** in her study which was conducted in department of internal medicine and endocrinology of Ain Shams University Hospital the study included 80 subjects classified as three groups: **Group I:** Normal control group, which included 20 subjects, **Group II:** HCV +ve with type 2 diabetes subjects, which included 30 subjects, and **Group III:** HCV +ve non diabetic subjects which included 30 subjects.

The study demonstrated a highly significant difference in serum fetuin A levels between groups I, II, and III with regard to fetuin A; however, when comparing groups I and II, fetuin a levels were significantly higher in patients with HCV and Diabetes than those in the control group, as well as a highly significant difference between group I (normal) and group III (HCV without Diabetes).

The optimum serum fetuin A cutoff value for predicting fatty liver among NAFLD and HCV patients was found in the current investigation. The findings demonstrated that a serum fetuin A cutoff value of >500 ng/ml was the most accurate in predicting patients' NAFLD. This figure had a sensitivity of 98.33% and a specificity of 100%.

This work also differs from other studies in that we studied the serum level of fetuin A with hepatic steatosis in HCV infection and the effect of HCV on lipid profile as HCV infection is endemic in Egypt taking in consideration that HCV is endemic in Egypt.

CONCLUSION

There is an association between serum level of fetuin A and fatty liver in NAFLD and HCV which points to its possibility for being used as marker for prediction of NAFLD or even HCV and also predicting the future outcome for those patients.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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