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Research Article

STUDY OF FETUIN A IN PATIENTS WITH CHRONIC HCV WITH OR WITHOUT TYPE 2 DIABETES MELLITUS AND ITS RELATION TO INSULIN RESISTANCE

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ABSTRACT

Fetuin A is a hepatokine, which inhibits insulin receptor tyrosine kinase in liver. **Aim:** To assess fetuin A level in patients with chronic HCV with or without diabetes and whether it is the link between the disease and insulin resistance. A case control study was conducted on eighty subjects. Sixty patients with chronic HCV were divided into two groups thirty patients with and thirty patients without diabetes and twenty normal subjects as control group. Participants were subjected to history, examination and measurement of FBG, Fasting insulin, HOMA-IR, HbA1C, Fetuin A and alfa fetoprotein. Fetuin A was higher in patients with chronic hepatitis C with and without diabetes P<0.001, the highest level in the group with HCV with diabetes.Fetuin A correlates positively with BMI, fasting blood glucose, fasting insulin and HOMA-IR P<0.001. fetuin A may represent an important role in development of insulin resistance in patients with HCV.

INTRODUCTION

Hepatitis C virus is one of the main causes of chronic liver disease allover the world. The long-term effects of HCV infection is highly variable, from minute changes to extensive fibrosis and cirrhosis coplicated or not with hepatocellular carcinoma.(European Association for the Study of the Liver, 2015).

Type 2 diabetes is a major public health threat. The pathophysiology of type 2diabetes is complex: In addition to impaired insulin secretion, decreased insulin sensitivity plays an important role in the pathogenesis of the disease. (Stumvoll *et al*., 2005).

The asscoiation between the high prevalence of Type 2 Diabetes Mellitus and infection with HCV has been reported.(Knobler *et al*., 2005).

Fetuin A is produced exclusively by the liver in adults and its concentration decreases during the acute phase reaction, study of its changes in patients with liver diseases as acute drug-induced hepatitis, acute alcoholic hepatitis, chronic autoimmune hepatitis, fatty liver , alcoholic liver diseas will be excellent indicator of liver function.(Kalabay *et al*., 2005).

Fetuin-A is also an endogenous inhibitor of the insulin receptor tyrosine kinase. (Graham *et al*., 2006).

MATERIALS AND METHODS

Our case control study was conducted in Cairo, Egypt on 80 subjects aged 21-64 years, sixty patients were recruited from outpatient clinic and inpatients of Internal medicine and Endocrinology department of Ain Shams University Hospital, Patients were divided into two groups and the third group was the control one.

Group I: 20 normal subjects, **Group II:** 30 HCV +ve patients with type 2 diabetes, **Group III:** 30 HCV +ve non diabetic patients. This study was approved by the local ethical committee and a written consent was taken from all subjects to be included in our study. All participants were subjected to full medical history emphasizing on age, duration of illness, medications, symptoms of liver cell failure like jaundice, lower limb edema, thorough clinical examination including BMI, signs of liver cell failure. Patients with any other type of hepatitis like alcoholic, autoimmune, HBV, Patients with recent stroke or other acute inflammatory conditions and patients suffering from hepatoma as a complication of hepatitis C, Patients with renal failure and patients received interferon therapy were excluded from our study.

Type 2 diabetes was diagnosed according to ADA criteria, chronic HCV infection diagnosed by having elevated liver enzymes for more than six months, positive HCV PCR, positive HCV viremia

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Sampling and Analysis

Subjects were instructed first to fast 8 hours (overnight fasting), 5 ml was collected of venous blood by venipuncture. Serum was separated by centrifugation and the sample was used for measurement of serum FBG, Fasting insulin, HbA1C, Fetuin A andα-fetoprotein.

Laboratory Studies

Laboratory studies included FBG which was assayed by Synchron CX9 *system auto-analyzer applying enzymatic colorimetric method, Fasting insulin was assayed by Immunospec Insulin Quantitative Test Kit is based on a solid phase enzyme-linked immunosorbent assay, calculation of HOMA-IR using the following equation:HOMA I.R=fasting blood glucose level (mmol/l)*fasting serum insulin ((mU/L)/22.5**.** (Matthews *et al*., 1985) serum Fetuin A was assayed using commercially available ELISA kit with a reference range of 303- 671**(ng/ml)**, HbA1C and serum alfa fetoprotien

Statistical Analysis

After collection of data, revision and tabulation; analysis was performed using SPSS version 17. Continuous data was expressed as mean ± SD, Comparative analysis of quantitative data was done using student t-test to compare two groups and the one-way ANOVA test was used to compare parametric and quantitative variables between more than two groups. Pearson correlation coefficient (r) was used for correlation of data.

RESULTS

Descriptive data of the three studied groups are mentioned in **(table 1).** According to our study fetuin A level was significantly higher in HCV patients with and without diabetes mellitus than in control group<0.001, the highest level was in the group of HCV with diabetes **(table 2).** On comparing the three groups, there was a highly significant difference between groups regarding FBG, fasting insulin **(table 3)**, HOMA-IR **(table 4)**, HbA1c and alfa fetoprotein P<0.001.

On correlating fetuin A level with different parameters, we found a highly significant positive correlation between fetuin A and BMI **P<0.001**, significant positive correlation between fetuin A and FBG, fasting insulin and HOMA-IR **P<0.05** but there was no significant correlation with other variables **(table5).**

Table 1 Descriptive statistics of study groups **I**, **II** and **III** (n=80).

	Group I (n=20)			Group II (n=30)			Group III (n=30)		
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**Mean**	**±**	**SD**
Age(years)	30.750	±	2.268	32.033	±	7.627	33.900	±	8.318
BMI(kg/m2)	24.050	±	0.949	25.517	±	3.064	23.970	±	3.368
A1C (%)	5.120	±	0.335	8.447	±	1.024	5.180	±	0.298
FBG(mg/dl)	87.050	±	7.522	192.567	±	57.471	91.133	±	7.999
Fasting Insulin (µlU/ml)	4.480	±	1.890	57.400	±	32.959	29.167	±	22.977
HOMA-IR	0.970	±	0.428	30.245	±	23.770	6.674	±	5.505
Alfa feto (ng/ml)	4.580	±	1.063	7.045	±	3.489	10.145	±	9.676
Fetuin-A (ng/ml)	518.000	±	74.240	2259.333	±	1070.720	1800.667	±	771.662

Table 2 Comparison between group I, group II and group III as regard fetuin A

	Fetuin-A(ng/ml)					ANOVA	
	Range		**Mean**	**±**	**SD**	**F**	**P-value**
Group I (control)	380.00	- 660.00	518.000	±	74.240		
Group II (HCV+T2DM)	800.00	- 4400.00	2259.333	±	1070.720	28.482	<0.001**
Group III (HCV +ve)	900.00	- 4000.00	1800.667	±	771.662		
Tukey's test							
I&II			**I&III**			**II&III**	
<0.001**			<0.001**			0.08	

Table 3 Comparison between group I, group II and group III as regard Fasting Insulin

	Fasting Insulin(µlU/ml)					ANOVA	
	Range		**Mean**	**±**	**SD**	**F**	**P-value**
Group I (control)	1.00	- 7.00	4.480	±	1.890		
Group II (HCV+T2DM)	5.00	- 120.00	57.400	±	32.959	28.367	<0.001**
Group III (HCV +ve)	10.00	- 90.00	29.167	±	22.977		
Tukey's test							
I&II			**I&III**			**II&III**	
<0.001**			<0.001**			<0.001**	

Table 4 Comparison between group I, group II and group III as regard HOMA-IR

	HOMA-IR					ANOVA	
	Range		**Mean**	**±**	**SD**	**F**	**P-value**
Group I (control)	0.19	- 1.64	0.970	±	0.428		
Group II HCV+T2DM)	1.60	- 84.44	30.245	±	23.770	28.811	<0.001**
Group III (HCV +ve)	1.95	- 21.78	6.674	±	5.505		
Tukey's test							
I&II			**I&III**			**II&III**	
<0.001**			0.39			<0.001**	

Table 5 Correlation between fetuin-A and different parameters

Correlations		
Group II	**Fetuin A**	
	r	**P-value**
Age(years)	0.221	0.241
BMI(kg/m2)	0.624	**<0.001****
A1C(%)	0.338	0.067
FBG(mg/dl)	0.416	**0.022***
Fasting Insulin(µlU/ml)	0.498	**0.005***
HOMA-IR	0.557	**0.001***
Alfa fetoprotein (ng/ml)	0.201	0.288

DISCUSSION

Hepatitis C virus (HCV) infection is a great health problem that affects more than 170 million people worldwide. It is a main cause of cirrhosis and hepatocellular carcinoma. The virus is

considered the most common cause of liver failure and transplantation. (Gatselis *et al*., 2014) .
Hepatitis C may result in insulin resistance and there is increased risk of type 2 diabetes mellitus in persons with chronic hepatitis C. (Knobler *et al*., 2000).

Fetuin-A was found to be an inhibitor of the insulin receptor tyrosine kinase. (Dziegielewska *et al*., 1990). So, fetuin-A may be involved in the pathogenesis of insulin resistance. (Auberger *et al*., 1989).

So, we think that fetuin A may be the link between HCV infection and development of insulin resistance and type 2 diabetes mellitus.

According to our results, fetuin A was found to be significantly higher in both groups of chronic liver disease with HCV with and without diabetes than in control group. Previous studies showed the same results,a study conducted on 52 healthy individuals and 40 patients with chronic hepatitis C to observe the serum concentrations of fetuin A and other acute phase proteins (AFP) before and after treatment with IFN-a. They found that fetuin A was markedly higher in patients with chronic hepatitis C than in healthy controls. (Kalabay *et al*., 2003)

Our study demonstrated higher levels of fetuinA in patients with HCV and diabetes (group II) than in control group and that fetuin A positively correlates with markers of insulin resistance (fasting glucose, fasting insulin and HOMA-IR) ($p<0.05$).This is also in line with a cross-sectional study performed among 5,227 Chinese adults (2008 normal glucose tolerance NGT, 1621 with impaired Glucose Regulation IGR and 1598 Type 2 diabetics). This study found that Serum fetuin-A concentrations in type 2 diabetic patients were significantly higher than those with NGT or IGR. Among participants with Type 2 diabetes, the association of fetuin-A with HOMA-IR and fasting serum insulin concentrations were found. (Song *et al*., 2011)

In agreement with our data a study showed that high levels of circulating fetuin-A are associated with insulin resistance in humans, suggesting that fetuin-A may represent a mechanism involved in the pathophysiology of type 2 diabetes.(Dasgupta *et al*., 2010)

These data are in contrast to Mori *et al*. 2006, who found no difference in serum fetuin-A level in type 2 diabetic patients with IR than in non-diabetics. They explained their findings by the existence of glucose toxicity and / or protein modifications such as non-enzymatic glycation that may overcome the effect of fetuinA on IR. (Mori *et al*., 2006)

CONCLUSION

High levels of fetuin A were demonstrated in patients with HCV rather than normal individuals. Also, fetuin A showed a strong association to markers of insulin resistance. So, fetuin-A may play a role in the pathogenesis of type 2 DM in patients with HCV. This finding together with previous studies raise the possibility that fetuin-A could be a potential therapeutic target in the treatment of insulin resistance induced by HCV.

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