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Correlation between visfatin serum levels and chronic hepatitis C infection in Egyptian patients

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Abstract: Background: Chronic hepatitis C infection (CHC) is common all over the world and remains a significant disease burden for many patients. Apart from its hepatotropic characteristic, replication of HCV in diseased extra hepatic organs may have direct cytopathic effects, this leading to a wide range of extra hepatic manifestations. Cytokines activation, which interacts with innate and/or adaptive immune responses, is a major hidden player of the scenario. Visfatin is one of the members of the adipokines family that regulates immunity and inflammation. Visfatin has been cloned as pre-B cell colony-enhancing factor (PBEF). It has the ability to activate leucocytes and induce cytokines and adhesion molecules production. **Objective:** It was the assessment of visfatin in chronic hepatitis C patients and find out the relation between them. **Subjects and Methods:** This study included 30 patients with CHC and 18 healthy individuals as a control group. We assessed serum visfatin levels in both with other routine laboratory investigations. **Results:** There was a highly statistical significant difference between all patients and control groups as regard serum visfatin level (mean of serum visfatin in patients and control groups were 39.23± 11.35and 9.67± 2.14 respectively, p= < 0.001) visfatin was negatively correlated with the necro inflammatory state of the disease. **Conclusion:** Chronic hepatitis C patients showed marked elevation of circulating visfatin levels and it negatively correlated with the necro inflammatory state. This identifies subjects with worse inflammatory state and therefore it may be used as a marker for the rate of development of chronic hepatitis C complications.

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1. Introduction

Viral hepatitis is the leading public health problem that facing Egypt nowadays, the prevalence of HCV antibodies was 6.3% in 2015 in Egypt [(1)].

Adipose tissue has emerged as an important endocrine organ that produce a wide spectrum of secreted factors called adipocytokines. The adipocytokine family has been extended by the addition of the new member, visfatin [(2)].

Visfatin was firstlydiscovered by **Samal et al**. [(3)] in their search for molecules secreted from human peripheral blood lymphocytes and termed it pre-B cell colony-enhancing factor 1. It has been identified as a new adipocytokine with immunomodulating and proinflammatory properties that may activate peripheral blood leucocytes and induce cytokine and adhesion molecule production [(4)]. Furthermore, visfatin can promote neo angiogenesis [(5)]. On the opposing, it has insulin-like activity [(6)] and protective role in myocardial infarction [(7)]

Visfatin has been described as a factor solving the 'dialogue' between inflammation and obesity [(8)]. Visfatin is released by a diversity of cells, and elevated in the systemic circulation of patients suffering from both acute and chronic inflammatory diseases [(9)]. During any inflammatory liver disease such as viral hepatitis [(10)] and nonalcoholic steatohepatitis (NASH) [(11)], number of lymphocytes increases in the liver.

The studies performed before have revealed that, the direct effect of the hepatotropic virus on hepatocytes and the immune system play a crucial role in the pathogenesis of the hepatic injury.

The exact role of adipokines in the pathogenesis of viral hepatitis is still undefined. Some studies have revealed that some adipokines has a major role as regulators of the hepatic fibrogenic process [(12)]. Till now, only few adipokines, such as adiponectin [(13)] and leptin [(14)], have been closely studied in chronic hepatitis C (CHC), but there is a little data about

visfatin in CHC and its rolein the inflammatory activity.

So, we assumed that visfatin may interfere with the immune responsein CHC. Therefore, we assessed visfatin serum level in CHC patients.

2. Subjects

This study was conducted in collaboration between the Clinical Pathology and Tropical Medicine department at Al-Hussein University Hospital, Faculty of Medicine, at Al-Azhar University. **This study was accepted by the Ethics Board of Al-AzharUniversity.**

All patients were collected from the outpatient clinic and Tropical Medicine department at Al-Hussein University Hospital over a period from 10th December 2018 to 4th February 2019, with appropriate consent to participate in this study after clarification to the patients how much it is helpful in the diagnosis and treatment. Also after explaining to them that, it is just a blood sample collection. Those subjects were divided into 2 groups: (patients group) and (control group).

Patients group (B) including 30 patients suffering from chronic hepatitis C disease.

Controls group (A) including 18 apparently healthy persons not suffering from chronic hepatitis C either clinically or laboratory.

Inclusion criteria

Patients suffering from chronic hepatitis C disease collected from the outpatient clinic and Tropical Medicine department at Al-Hussein University Hospital.

Diagnosis was based on:

History of chronic hepatitis C with persistently elevated alanine amino- transferase (ALT) level for at least 6 months.

The diagnosis of CHC was confirmed by serum HCV-RNA assay and viral load by HCV PCR.

Exclusion criteria:

Patients with history of: Hepatitis B virus, Patients receiving hepatotoxic drugs or alcohol intake and patients with known malignant disease, systemic inflammatory disease or autoimmune disease.

Samples and methods

All subjects were subjected to full history (personal, family, medical, occupational…etc.) and clinical examination. Ten ml venous blood were withdrawn from all participants of the study and divided into five portions: the first portion (two ml) was put in EDTA tube for HCV PCR. The second portion (two ml) was put in heparin tubes for routine biochemical tests. The third portion (2ml) was put in EDTA tubes for CBC & ESR. The routine biochemical tests were done using Cobas c311 & Intejra analyzer (RocheDiagnostics). The fourth portion (two ml) was put in citrate tubes for PT analysis. The fifth portion (two ml) was put in plain tube and left to clot at room temperature for 2 hours then centrifuged and the serum was separated and stored at (-20 °c) until assessed for visfatin using enzyme linked immunosorbent assay (ELISA), commercial kits Catalogue No.E0025Hu; Shanghai Korain Biotech Co., Ltd.

Statistical analysis

All results were analyzed using Statistical package for social science (SPSS V.15, IBM Corp. U.S.A).

Descriptive statistics was used for quantitative data analysis: They were; Mean ±SD while Qualitative data were expressed as frequency and percentage.

Pearson correlation coefficient was used to check for correlation between two quantitative parametric data.

For all analysis, a two-tailed test was used and p <0.05 was considered statistically significant.

3. Results

As regard to serum visfatin level, there was a highly statistical significant difference (p-value < 0.001) between studied groups regarding to serum visfatin level, table (1).

Results show a highly statistical significant (p-value < 0.001) negative correlation between visfatin and (age, AST, INR, FIB-4 score, APRI score, ESR) in patients group while there was a high statistically significant (p-value < 0.05) positive correlation between visfatin and (ALT, Alb., PLTs) in patients group, table (2).

Table (1): Comparison between studied groups as regard visfatin

Variables		Patients (N = 30)	Control (N = 18)	**P-value**
Visfatin (ng/ml)	**Mean**	**39.23**	**9.67**	**< 0.001 HS**
	±SD	**11.35**	**2.14**	

Table (2): Correlation study between visfatin and other studied parameters in patients group.

Groups / Parameters	Patients group (r)	p-value
Visfatin vs. age	-0.63	**< 0.001**
Visfatin vs. ALT	0.75	**< 0.001**
Visfatin vs. AST	-0.73	**< 0.001**
Visfatin vs. Albumin	0.93	**< 0.001**
Visfatin vs. INR	-0.89	**< 0.001**
Visfatin vs. Fib-4	-0.92	**< 0.001**
Visfatin vs. APRI	-0.92	**< 0.001**
Visfatin vs. PLTs	0.86	**< 0.001**
Visfatin vs. ESR	-0.90	**< 0.001**
Visfatin vs. PCR	-0.46	**0.01**

4. Discussion

In this study, levels of serum visfatin were significantly higher in CHC as compared to controls. This suggests that visfatin may play a major role in the regulation of the inflammatory process in CHC. Interestingly, levels of serum visfatin were negatively correlated to grade of the inflammation. Minimal or mild inflammation was associated with significantly higher levels. Although visfatin was significantly elevated in CHC patients, its serum levels fell in cases of moderate or severe inflammation, but were still twice higher than control group. These notes may point to the protective role of visfatin against inflammation and hepatocyte injury in CHC disease.

Moreover, visfatin exerts a positive effect on IL-6 synthesis in dendritic cells and peripheral blood mononuclear cells (PBMCs) [(4)]. IL-6 stimulates hepatocytes to produce a wide variety of acute-phase proteins [(15)] but, it plays a significant role in liver regeneration and protection against liver injury during inflammation [(16)]. These observations may also support the protective role of visfatin against inflammatory liver injury.

Aspartate aminotransferase to platelet ratio index (APRI) is one of the commonest non-invasive markers for liver fibrosis calculated in CHC patients. There was a very strong positive correlation between APRI score and the stage of fibrosis. Additionally positive, but weaker correlation was detected between APRI and inflammatory activity. As stated above, visfatin was positively associated with inflammatory activity but not fibrosis stage. However, a negative correlation was found between APRI and serum visfatin levels. It may be due to the positive correlation between APRI and inflammatory activity on one side and the negative correlation between visfatin and inflammatory activity on the other or positive association between visfatin and platelet count.

This case control study aimed at evaluating circulating plasma visfatin levels in adult patients with chronic hepatitis C in comparison with healthy subjects. The patients were suffering from CHC for 6 more than 6 months at least with (mean 52.53±7.44 years). Their viral load varies from 0.001 – 21.17 million IU/ml (mean 2.08 ± 4.05, min. 0.001, and max. 21.17).

Serum concentration of visfatin was (mean ± SD: 39.23 ± 11.35 ng/mL vs. 9.67 ± 2.14 ng/mL, $p < 0.001$) in patients and control groups respectively and its level was negatively correlated with the necro inflammatory process. It was significantly higher in CHC patients without cirrhosis compared to those with cirrhosis. Also, it was negatively correlated with the degree of fibrosis. Those with mild degree of fibrosis had higher visfatin level than those with moderate or severe form of fibrosis. Also, those patients without any form of fibrosis had higher visfatin level than other patients.

This result was in agreement with that of **Kukla et al., 2010**[(17)]. They reported that the serum concentration of visfatin was (mean ± SD: 55.6 ± 23.1 ng/mL vs. 23.7 ± 3.8 ng/mL, $p < 0.00$) in patients and control groups respectively and visfatin was negatively associated with the grade of necro inflammatory activity ($r = 0.36$; $P = 0.007$). The lowest levels were found in patients with the most advanced inflammation: (grade 3/4: 46.8 ± 17.1, grade 2: 52.6 ± 18.4 and grade 1: 75.2 ± 27.6 ng/mL; $P = 0.017$).

Also, **De Boer et al 2008**[(18)] found that patients with early clinical stages of cirrhosis had significantly higher visfatin levels (grade 1: 23.9 ± 3.2 ng/ml), compared with grade 2 or grade 3 patients (14.0 ± 2.0, 12.3 ± 2.6 ng/ml, respectively).

On the other hand, both ***Huang et al. 2010*** [(19)] and ***Kukla et al. 2009*** [(20)] showed that serum visfatin was positively correlated with the severity of chronic

hepatitis C, the degree of fibrosis and cirrhosis as demonstrated in liver pathology of portal inflammation. They suggested that visfatin may induce and activate proinflammatory cytokines and systemic inflammatory response in patients with chronic hepatitis C.

The differences between the results of this study and other investigations could be attributed to the differences in number of cases in various studies, association of other epidemiological factors affecting visfatin and differences on the cut-off value of visfatin normal value.

5. Conclusion

Our study showed that serum levels of visfatin are increased in patients with CHC. These findings confirm that visfatin may play a specific role in the pathogenesis of the inflammatory process in CHC. Visfatin may have a pro-inflammatory and/or protective factor against hepatocyte injury in inflammatory process. So, the measurement of visfatin concentration may serve as a supplementary tool in determining more advanced grades of necro-inflammatory activity but it seems unlikely that its measurement might replace histopathology assessment. Visfatin does not seem to be associated with liver fibrosis in CHC. However, further investigations with a greater number of cases are necessary to better define the exact role of visfatin in the pathogenesis of CHC.

Recommendation

Further studies on visfatin level in the serum of CHC patients with and without cirrhosis. Further studies are required on large number of patients. To investigate serum visfatin level before and after medical treatment of viral hepatitis as its level might be considered as an indicator for degree of fibrosis even cirrhosis.

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