Relation of Osteopontin Level to Hepatic Dysfunction in Patients With Chronic Hepatitis C

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Abstract
Introduction: Hepatitis C virus (HCV) is a major cause of liver disease worldwide and a potential cause of substantial morbidity and mortality. **Aim of the work:** To study the relationship between osteopontin level changes and the affection of different liver functions in patients with chronic hepatitis C. **Subjects and Methods:** This study was carried out at the Clinical Pathology Department, Faculty of Medicine, Minia University Hospital. It was conducted on seventy eight subjects during the period from May to November 2016. **Results:** This study was carried out on 78 candidates classified into: **Discussion:** Hepatitis C has become an alarming problem worldwide. 170- 200 million people have been infected with hepatitis C virus (HCV) infection (Allam et al., 2013).
Recommendations: Longitudinal studies are needed to: 1-Investigate the predictive value of OPN level at diagnosis and disease progression, deterioration of hepatic functions & development of thrombocytopenia in HCV patients. 2-Investigate the effect of OPN downregulation on: - Delay or prevention of hepatic fibrosis. - Improvement of liver function tests. - Platelet count changes
Keywords: Adenosine triphosphate, Area under curve, Area under receiver operator characteristic curve

Introduction
Hepatitis C virus (HCV) is a major cause of liver disease worldwide and a potential cause of substantial morbidity and mortality. Egypt has the highest prevalence of HCV in the world and its complications are among the leading public health challenges (Lavanchy, 2011).

Hepatitis C virus (HCV) is a small (55–65 nm in size), enveloped single-stranded, positive sense RNA virus of the family Flaviviridae, which is 9.6 kb in length and contains a 5′-untranslated region (UTR), a single open reading frame, and a 3′-UTR (Iqbal et al., 2013).

Hepatitis C can progress to, or be complicated by other diseases. Some of these diseases, like fibrosis, cirrhosis and hepatocellular carcinoma (HCC), are very common. Extensive fibrosis is called cirrhosis (Messina et al., 2015).

Biomarkers for liver fibrosis are : (class 1) the direct markers directly correlate with or are parts of the liver matrix produced by the hepatic stellate cells during ECM turnover in the fibrosis process, (class 2) the indirect markers reflect changes in liver functions and are molecules released into the blood due to liver inflammation (Fallatah, 2014).

Osteopontin (OPN) is a pro-inflammatory cytokine and a matrix molecule that is a downstream target and effector of the Hedgehog (Hh) pathway. OPN is upregulated in the liver and serum of patients with chronic HCV, and supports increased viral replication (Choi et al., 2014).

Osteopontin levels reflect the degree of hepatic fibrosis and could be used as a biomarker to assess the stage of fibrosis in HCV patients which would help to reduce the number of liver biopsies. Furthermore, serum OPN serves as a prognostic index towards the progression of hepatic fibrosis to cirrhosis and hepatocellular carcinoma. (Matsue et al., 2015).

Osteopontin is a non-invasive parameter of portal hypertension that distinguishes patients with clinically significant portal hypertension . OPN has a potential role in inducing chronic liver disease and HCC associated with chronic HCV infection (Bruha et al., 2016).
Furthermore, it has been demonstrated that hepatocytes act as a major source of OPN, and

act in a paracrine role in activating HSCs and increasing collagen-I production (Arriazu et al., 2016).

Multiples studies have found that neutralizing OPN abrogates the development of fibrosis. These findings suggest that targeting OPN could be an effective treatment modality in hepatic fibrosis (Coombes et al., 2015 & Arffa et al., 2016).

Aim of the work

To study the relationship between osteopontin level changes and the affection of different liver functions in patients with chronic hepatitis C.

Subjects and Methods

This study was carried out at the Clinical Pathology Department, Faculty of Medicine, Minia University Hospital. It was conducted on seventy eight subjects during the period from May to November 2016.

The study included 52 chronic hepatitis C patient, they were diagnosed as HCV positive by HCV-Ab using enzyme immunoassay (EIA method) and HCV RNA was detected by RT-PCR .

These patients were divided into:

Group I : It included twenty three patients of chronic hepatitis C with preserved (compensated) liver function tests. It included eleven males and twelve females.

Group II: It included twenty nine patients of chronic hepatitis C with abnormal (decompensated) liver function tests. It included seventeen males and twelve females.

In addition to:

Group III: It included twenty six apparently healthy volunteers who served as control subjects. It included twelve males and forteen females.

Exclusion criteria:

Patients with the following disorders were excluded from the study:

1. Hepatocellular carcinoma (HCC) cases
2. Renal impairment
3. Cardiovascular disease
4. Patients are on anticoagulants

Results:

Comparison between three groups regarding routine chemistry

	Group I (n=23)	Group II (n=29)	Group III (n=26)	P value		
[(1)]**T. bilirubin**				**<0.001***		
Range (mg/dl)	(0.5-2.1)	(0.8-6.6)	(0.3-1)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	0.88±0.42	2.21±1.21	0.58±0.19	**<0.001***	0.394	**<0.001***
[(1)]**D. bilirubin**				**<0.001***		
Range (mg/dl)	(0.1-1.1)	(0.3-2.3)	(0.1-0.31)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	0.37±0.25	0.92±0.48	0.18±0.08	**<0.001***	0.115	**<0.001***
[(2)]**ALT**(U/L)				**<0.001***		
Range	(29-72)	(13-137)	(10-45)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	42.73±11.91	42.65±29.31	21.92±9.81	0.153	**<0.001***	**<0.001***
[(2)]**AST**(U/L)				**<0.001***		
Range	(14-90)	(20-266)	(14-40)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	43.91±20.84	75.27±51.23	24.96±8.41	**0.004***	**<0.001***	**<0.001***
[(1)]**ALB**(g/dl)				**<0.001***		
Range	(3.6-4.8)	(1.9-4.6)	(4.1-5.3)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	4.24±0.29	3.06±0.76	4.85±0.36	**<0.001***	**0.001***	**<0.001***
[(1)]**Total Protein**(g/d				**0.004***		
Range	(6.1-8.6)	(4.1-10.5)	(7.4-8.1)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	7.2±0.85	6.93±1.58	7.91±0.19	0.654	0.058	**0.003***
Urea (mg/dl)				0.209		
Range	(19-54)	(15-71)	(16-45)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	30.91±7.96	34.86±13.38	30.42±6.99	0.345	0.984	0.240
Creatinine(mg/dl)				0.422		
Range	(0.5-1.6)	(0.5-3.4)	(0.5-0.9)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	0.97±0.33	1.04±0.53	0.91±0.25	0.804	0.788	0.529
Glucose (mg/dl)				**0.043***		
Range	(83-371)	(79-325)	(97-121)	**I vs II**	**I vs III**	**II vs III**
Mean ± SD	150.47±82.38	137.31±63.33	108.42±7.98	0.707	**0.040***	0.175

- ***: significant difference at p value < 0.05***

Discussion

Hepatitis C has become an alarming problem worldwide. 170- 200 million people have been infected with hepatitis C virus (HCV) infection (Allam et al., 2013).

HCV infection generally leads to a chronic disease in most of the patients. These patients gradually face with hepatic inflammation and fibrosis and finally liver cirrhosis and/or hepatocellular carcinoma. HCV is also one of the main reasons of liver transplantation around the world. Recent studies have found that viral, host, and environmental factors may involve in susceptibility to HCV chronic infection or spontaneous clearance of the infection (Karkhane et al., 2016).

Chronic HCV infection is a major cause of death and morbidity due to serious liver disease complications, including cirrhosis and hepato-cellular carcinoma (HCC). Indeed, recent data suggest that the global burden of viral hepatitis has now surpassed many other common infectious diseases such as tuberculosis, AIDS, diarrheal disease, and malaria (Chang et al., 2017).

The prevalence of hepatitis C virus (HCV) infection among hemodialysis (HD) patients has been reported to range from 10% to 25%. Chronic hepatitis C (CHC) has been related with high morbidity and reduced survival in both patients with renal dysfunction and kidney transplant (KT) recipients (Cholongitas et al., 2017).

There are a major clinical challenge in the management of the increasing number of hepatitis C virus infected patients is determining the best means for evaluating liver impairment. Prognosis and treatment of chronic hepatitis C are partly dependent on the assessment of histological activity, namely cell necrosis and inflammation, and the degree of liver fibrosis. These parameters can be provided by liver biopsy; however, in addition to the risks related to an invasive procedure, liver biopsy has been associated with sampling error mostly due to suboptimal biopsy size. To avoid these pitfalls, several markers have been proposed as non-invasive alternatives for the diagnosis of liver damage i.e. biomarkers of fibrosis (Schiavon et al., 2014).

Recommendations

Longitudinal studies are needed to:

1- Investigate the predictive value of OPN level at diagnosis and disease progression, deterioration of hepatic functions & development of thrombocytopenia in HCV patients.

2- Investigate the effect of OPN down regulation on:

- Delay or prevention of hepatic fibrosis
- Improvement of liver function tests
- Platelet count changes

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