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## Original Article

## Significance of growth differentiation factor 15 in chronic HCV patients

Mohab H. Halim<sup>a</sup>, Nour A. Abdulla<sup>b</sup>, Abdelkarim Kamel<sup>c</sup>, Nabila Abd El Maksoud<sup>a</sup>, Halla M. Ragab<sup>a,\*</sup><sup>a</sup> Biochemistry Department, National Research Center, Dokki, Giza, Egypt<sup>b</sup> Hepatology Department, National Hepatology & Tropical Medicine Research Institute, Cairo, Egypt<sup>c</sup> Medical Biochemistry, Faculty of Medicine, Cairo University, Egypt

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## ABSTRACT

**Background and objective:** Hepatitis C virus is the most common cause of chronic liver disease in Egypt. This work aims to assess the use of the simple and noninvasive biomarker Serum Growth differentiation Factor 15 (GDF-15), along with Alpha Fetoprotein (AFP) and Ferritin for the diagnosis of advanced liver disease in chronic hepatitis C patients. **Subjects and methods:** This study was conducted on 60 patients, who were recruited from the National Liver and Tropical Diseases Institute, Cairo, Egypt, who were suffering from early & advanced liver cirrhosis and chronic active hepatitis. Twenty cases of healthy subjects served as controls. Serum (GDF-15), (AFP), Ferritin and Hepatitis markers were measured by ELISA method. Measurement of different liver enzyme activity was done by the kinetic methods. **Results:** Data analysis revealed significant increase in serum levels of GDF15 in patients with Hepatocellular carcinoma (HCC) and Liver Cirrhosis (LC) compared to the healthy subjects. These results were parallel to those of serum levels of AFP, which also demonstrated significant increase in all patients groups as compared to normal control. A moderate increase in the GDF15 level was detected in the patients with chronic hepatitis C (CHC) compared to normal healthy subjects. **Conclusion:** This study demonstrated that GDF15 and AFP detection can help in the diagnosis and prediction of complications associated with CHC including liver cirrhosis and HCC. Also GDF15 can be used as a satisfactory serum marker of HCC and LC. © 2017 Production and hosting by Elsevier B.V. on behalf of Academy of Scientific Research & Technology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Hepatitis C virus has been completely outlined by molecular biology techniques. Although the infection often remains asymptomatic for many years, it can still lead to considerable damage to the liver, as liver cirrhosis (LC) and primary liver cancer [1]. In fact, it is now considered to be the leading indication for liver transplantation [2]. Early diagnosis and treatment have been found to significantly improve outcome in these patients [3]. Liver biopsy is the gold standard test for accurate diagnosis, but this procedure has potentially life-threatening complications [4]. Finding non-invasive biomarkers for liver cirrhosis and carcinoma is urgently needed.

Many markers to detect fibrosis have been introduced [5]. Hepatocellular carcinoma has the worst prognosis worldwide [6]. Similarly, liver cirrhosis is accompanied with a very high mortality

rate. Alpha-fetoprotein is recognised as a serum marker for the detection of liver cancers, but its sensitivity and specificity are unsatisfactory for cirrhosis; it has unclear results and is not significant.

GDF15 is a member of the transforming growth factor- $\beta$  (TGF- $\beta$ ) cytokine superfamily involved in fibrosis, infection, and apoptosis pathways in the presence of tissue damage or disease [7]. It was first isolated in macrophages after cytokine stimulation [8].

GDF15 mRNA is known to be distributed particularly in the liver but also in the heart, lung, and kidneys [7]. It is expressed and secreted in response to short-wave length exposure, inflammation, oxidative stress, hypoxia, telomere erosion, and tissue injuries and oncogene activation [9].

Iron in the body found in hemoglobin, hemosiderin, myoglobin and the cytochromes [10]. Ferritin is a major iron-storage protein, and acute phase protein which may be increased in conditions of inflammation, malignancy and chronic liver disease. In this study, the ferritin levels were measured in serum to show if its levels have a significant difference with the severity of disease, and whether its levels in serum can be used to detect liver cirrhosis and hepatocellular carcinoma.

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\* Corresponding author at: Biochemistry Department, Genetic Engineering and Biotechnology Research Division, National Research Center, Dokki, Giza, Egypt and Box 12311, Dokki, Cairo, Egypt.

E-mail address: [hmrageb@yahoo.com](mailto:hmrageb@yahoo.com) (H.M. Ragab).<http://dx.doi.org/10.1016/j.jgeb.2017.08.004>

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The aim of this study was to measure Serum Growth Differentiation Factor 15 (GDF15) together with Alpha Fetoprotein to determine their efficiency as serum biomarker for diagnosis of liver cirrhosis and HCC in Egyptian patients with chronic viral hepatitis C.

## 2. Subjects and methods

This study was carried out on patients who were recruited from National Liver and Tropical Diseases Institute, Cairo, Egypt between November, 2014 to April, 2015. They are suffering from chronic liver diseases including hepatic portal hypertension, liver cirrhosis with chronic active hepatitis.

Patients were classified into three groups: Group I – Include 20 cases of pure chronic viral hepatitis C (HCV) with early liver cirrhosis without peri-portal fibrosis, no history of antibilharzial treatment and negative rectal snips for bilharzial ova. Group II – Include 23 cases of mixed viral hepatitis C (HCV) and with cirrhotic changes of the liver with peri-portal fibrosis, history of antibilharzial treatment and positive rectal snips for bilharzial ova. Group III – Include 17 cases of HCC with peri-portal fibrosis and viral hepatitis C (HCV), with history of antibilharzial treatment and positive rectal snips for bilharzial ova. Control group Include 20 cases of normal healthy subjects with no known history of cancer, HBV, HCV infection, antibilharzial treatment or positive rectal snips for bilharzial ova.

### 2.1. Sample collection

Blood samples were obtained from the patients, and serum was separated at 3000 rpm and stored at  $-80^{\circ}\text{C}$ . Patients were subjected to complete medical history, full clinical examination including examination of chest and abdomen with stress on manifestation of liver cell failure.

All Patients and controls were subjected to thorough history taking, clinical examination, and laboratory investigations including complete blood count, liver and kidney functions, History of antibilharzial treatment, Rectal snips for bilharzial ova examined by transparency technique, test for hepatitis B surface antigen (HBsAg) by ELISA and test for HCV antibodies by ELISA and by quantitative polymerase chain reaction (PCR) assay.

Abdominal Ultrasonography and Duplex Doppler examination was done using a Toshiba SSA, 340A machine to measure liver and splenic size, portal vein diameter, presence of peri-portal fibrosis and liver cirrhosis. Ultrasonography was used for assessment of liver injury and its staging in all patients V) Liver biopsy was taken if feasible and the histopathological changes were assessed according to Knodell's score [11].

We excluded patients with any cause of liver disease other than chronic HCV based on the patient history, laboratory or liver biopsy findings as: HBV/HIV coinfection, serological evidence of autoimmune hepatitis, inheritable disorders as hemochromatosis, Wilson's disease or Alpha 1-antitrypsin deficiency, alcoholic liver disease and drug induced liver disease. Also, patients on anti-inflammatory drugs or those with autoimmune diseases arthritis are excluded from the study.

### 2.2. Methods

Biochemical blood tests were carried out to evaluate liver functions in the form of serum transaminases (SGOT and SGPT), alkaline phosphatase (ALP), gamma glutamate (GGT), total bilirubin, as well as albumin. Serum SGPT, SGOT, GGT and ALP levels were measured by the kinetic methods according to the recommendations of the Committee on the Enzymes of the Scandinavian Society

for Clinical Chemistry and Clinical Physiology (1974 & 1976). Serum albumin was measured by colorimetric methods.

Patients were diagnosed as having hepatitis C by detecting HCV antibodies using a third generation enzyme immunoassay, ELISA.

In CHC patients, the baseline HCV RNA load were measured using a quantitative polymerase chain reaction (PCR) assay according to the available technique (Applied Biosystem, USA), with detection limit of 30 IU/ml.

GDF15 was measured in serum using a specific ELISA kit (Cat# KT-16893, R&D Systems, Kamiya Biomedical Co., Seattle, WA), according to the manufacturer's recommended protocol.

Determination of serum Alfa fetoprotein: Serum samples were analyzed for Alfa fetoprotein using a commercially available sandwich ELISA kit (Cat# DAFP00, R&D Systems, USA & Canada).

Determination of serum Ferritin: serum samples were analyzed for Ferritin using a commercially available sandwich ELISA obtained from Sigma-Aldrich).

### 2.3. Statistical analysis

Data management and statistical analysis were performed using Statistical Package for Social Sciences [12] (SPSS) version 16. Student's *T*-test for unpaired data was used for identifying differences between the groups. A level of probability  $P < 0.05$  was accepted as statistically significant,  $P > 0.05$  as non-significant,  $P < 0.01$  as highly significant and  $P < 0.001$  as very highly significant.

## 3. Results

The patients included in this study were those who suffering from chronic liver diseases such as hepatic portal hypertension, liver cirrhosis with chronic active hepatitis and hepatocellular carcinoma. Clinical data of the patients are shown in Table 1.

Levels of AST, ALT, ALP, GGT, total bilirubin and albumin levels in the different studied groups were showed in Table 2, their levels were significantly higher in Group (I) ( $P < 0.01$ ) and very significantly higher in Groups (II) and (III) ( $P < 0.001$ ) when compared with normal controls. Serum albumin levels were significantly decreased in group I (chronic hepatitis) ( $P < 0.05$ ) and showed a very high significant decrease in groups II and III ( $P < 0.001$ ) when compared with controls and with each other. serum levels of GFD 15 were significantly higher ( $P < 0.001$ ) in Group II and III patients when compared to the normal controls while a moderate increase was shown in patients with Chronic hepatitis C (CHC) with a *P* value  $< 0.01$  when compared with normal healthy subjects, data was showed in Table 3.

Levels of AFP showed very highly increased levels in all studied groups when each was compared to normal controls ( $P < 0.001$ ). Similarly, serum levels of Ferritin showed very high significant increases ( $P < 0.001$ ) in all studied groups when compared with normal controls.

## 4. Discussion

Hepatitis C virus is the most common cause of chronic liver disease in Egypt. The prevalence of antibodies to HCV is approximately 10-fold greater than that in the United States and Europe. Anti-HCV-positive patients are more likely to have liver enzyme elevations, liver cirrhosis, portal hypertension and spleen enlargement [13]. Schistosomal liver disease in Egypt is significantly accompanied with HCV infection, with the predominance of genotype 4 [14–16].

Both liver cirrhosis and hepatocellular carcinoma have a high mortality rate. HCC is a consequence of HCV infection, rates as

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