بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / هناء محمد علي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: ....

Study for the significance of Osteopontin vs Alpha Feto Protein as a diagnostic marker for Hepatocellular carcinoma in cirrhotic patients with HCV

Thesis
Submitted For Partial Fulfillment of Master Degree
In cirrhotic patients with HCV

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Ain-Shams University
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2021

قُلْ إِنَّ صَلاَتِي وَنُسُكِي وَمَحْيَايَ وَمَمَاتِي لِلَّهِ رَبِّ الْعَالَمِينَ * لاَ شَرِيكَ لَهُ وَبِذَلِكَ أُمِرْتُ وَأَنَاْ أَوَّلُ الْمُسْلِمِينَ

سورة الأنعام

أية (١٦٢ ، ١٦٣)

Acknowledgements

Praise to "*Allah*", the Most Gracious and the Most Merciful Who Guides Us to the Right Way.

I would like to express my indebtedness and deepest gratitude to **Prof. Dr. Mohamed Abdelmoghny Mostafa,** Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, *Ain-Shams* University for his valuable advice, guidance and constructive criticism, also for the invaluable assistance and efforts he devoted in the supervision of this study.

I'll never forget, how co-operative was **Prof. Dr. Hany Haroun Kaisar**, Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, *Ain-Shams* University, also he was encouraging all the time. It is honorable to be supervised by him.

I would like also, to express my great thanks to **Prof. Dr. Ramy Samir Ghait**, Lecturer of Internal Medicine and Gastroenterology, and Faculty of Medicine – *Ain-Shams* University. His valuable advises and continuous support facilitated completing this work.

I would like to thank all the staff members of the Internal Medicine and Gastroenterology department.
Finally, I would like to express my appreciation and gratitude to all my family, especially my caring and loving parents who enlighten my life.

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2021

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
APASL	Asian Pacific Association for the Study of the Liver
CEUS	contrast-enhanced ultrasound
CLD	chronic liver disease
CT	computed tomography
DAA	direct acting antiviral
DCP	des-gamma-carboxy prothrombin
EASL	European Association for the Study of the Liver
EGFR	epithelial growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EPCAM	epithelial cell adhesion molecule
FDA	Food and Drug Administration
FGF	fibroblast growth factor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGF	hepatocyte growth factor
IFN-γ	interferon-γ
IGF1R	growth factor receptor 1
IL-12	interleukin-12
IL–3	interleukin-3
MELD	Model for End-Stage Liver Disease
miRNA	microRNA
MMP-3,7	matrix metalloprotease 3 and 7
MRI	magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NCCN	National Comprehensive Cancer Network
OPN	Osteopontin
OPTN	Organ Procurement and Transplantation Network
PTM	Post-translational modifications
TGF β	tumour growth factor β
UNOS	United Network for Organ Sharing
US	Ultrasound

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ABSTRACT

Background; Outcome of hepatocellular carcinoma (HCC) depends mainly on its early diagnosis. The performance of traditional biomarkers is not satisfactory. Alpha-fetoprotein (AFP) is the most widely used serum biomarker for hepatocellular carcinoma (HCC), despite its limitations. Several studies have reported that osteopontin (OPN) is a promising marker for the diagnosis of hepatocellular carcinoma (HCC); however, some studies emerged with conflicting results, **Aim and objectives;** to evaluate the clinical significance of the plasma osteopontin (OPN) versus alpha-fetoprotein (AFP) in the diagnosis of HCC in cirrhotic patients, **Subjects and methods;** This study was Case-Control study, was conducted at internal Medicine and Gastroenterology outpatient clinics and ward in Ain Shams University Hospitals on Patients divided into 3 groups: (Group 1): 50 patients with previously diagnosed HCC on top of chronic HCV induced cirrhosis, (Group II): 15 chronic HCV patients with cirrhosis, (Group III):15 healthy controls during a period of Six months, **Result;** There was high statistically significant difference between the studied groups as regard OPN and AFP, **Conclusion;** plasma OPN level was elevated in the HCV-related HCC patients by comparison to the chronic HCV patients with cirrhosis and healthy controls. OPN is a promising tumor marker that could be added to the current standard tests for the diagnosis of HCC in patients with liver cirrhosis, due to Chronic HCV infection, in order to detect the disease at an early stage and, hence, improve the prognosis and survival rates of these patients, **Keywords; Hepatocellular carcinoma; α-fetoprotein; Osteopontin.**

Introduction

Hepatocellular carcinoma (HCC) is one of the most aggressive cancers worldwide as well as the third cause of cancer-related mortality **(Bertino G et al., 2012)**

Because most patients are not diagnosed until the disease progresses to advanced liver cancer and the prognosis of HCC is generally poor, the 5-year survival rate is <10%–15% (**Stefaniuk P et al., 2010).** Early detection of liver cancer can give an opportunity for surgical resection and transplantation, which can benefit a number of patients. Therefore, it is particularly important to diagnose HCC early and accurately (**Dhanasekaran et al., 2012)**

Generally, the diagnostic methods for HCC include blood chemistry tests like alpha-fetoprotein (AFP) and imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (**Aghoram R et al., 2012)**

However, although ultrasound is an indirect diagnosis method, which is convenient and noninvasive, its accuracy depends largely on the skill of the operator, and the ability to distinguish HCC from nonneoplastic nodules is limited.CT and MRI can produce higher resolution images than ultrasonography, but they are more expensive and CT is related to radiation exposure **(Abd El Gawad et al., 2014)**

Furthermore, for small and well-differentiated lesions, the sensitivity of CT and MRI was lower. Presently, AFP is widely used in the diagnosis of HCC. However, the diagnostic performance is not ideal

because its sensitivity only ranges from 40% to 65% (**Morris KL et al., 2014)**

Therefore, it is particularly important to identify a new biomarker with superior diagnostic accuracy.

Osteopontin (OPN) is a multifunctional phosphorylated glycoprotein, which could be expressed in a variety of cell types including T lymphocytes, macrophages, dendritic cells, and osteoclasts (**Bandopadhyay M et al., 2014)**

Recent studies have reported that OPN overexpression has been detected in lung cancer, breast cancer, and HCC. Two major studies have identified that OPN as a promising biomarker for the diagnosis of HCC had greater performance than AFP in distinguishing HCC cases from liver cirrhosis patients.Furthermore, Shang et al found that the level of serum OPN was already increased a year prior to HCC diagnosis, indicating that OPN is a promising diagnostic marker for HCC (**Shang S et al., 2012)**

Aim of the Work

The aim of this study is to evaluate the clinical significance of the plasma osteopontin (OPN) versus alpha-fetoprotein (AFP) in the diagnosis of HCC in cirrhotic patients.

Chapter (1)

Hepatitis C Virus Infection in Egypt: Current Situation and Future Perspective

HCV, and its long-term resultant consequences, is a major endemic medical health problem in Egypt. Having taken a representative sample of the country, from both urban and rural areas, an Egyptian demographic health survey conducted in 2008 concluded that 14.7% of the population have been infected, making this the highest prevalence in any population in the world. In the Nile Delta and Upper Egypt, infection rates can be much higher at around 26% and 28%, respectively. With incidence rates between 2 and 6 per 1000 every year, this leads to an estimated 170,000 new cases every year to add to the 11.5 million patients suffering from the disease **(Elghitany, 2019).**

I. What is HCV?

HCV is a hepatotropic RNA virus of the genus Hepacivirus in the Flaviviridae family. The virus exists as an enveloped, positive-stranded RNA virus which is ~50 nm in size (**Figure** 1). The HCV RNA strand is made up of ~9600 nucleotide bases and is covered by an icosahedral nucleocapsid which is further surrounded by a lipid bilayer and glycoproteins. HCV is grouped into 6 major genotypes that exhibit at least 30% variation in nucleotide sequence from one another. This genetic variation within the population is a powerful selection mechanism for resistance to both medicinal drugs and evasion of the immune system. The most common HCV RNA genotype in Egypt is genotype 4, representing >85% of all HCV cases in Egypt **(Badawi et al., 2018).**

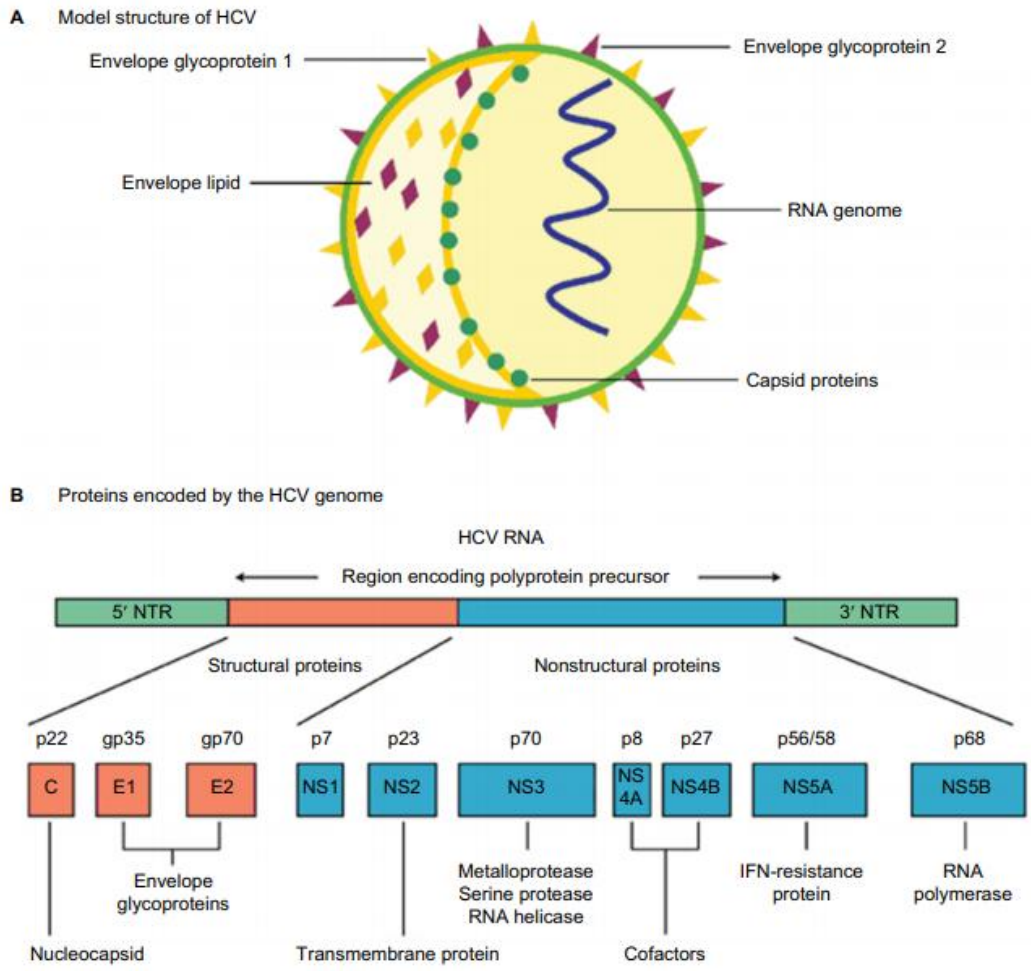

Figure 1: HCV: model structure and genome organization. **Notes**: (A) Model structure of HCV (B) Proteins encoded by the HCV genome. Expert review in Molecular Medicine © 2003 Cambridge University Press. **Abbreviations**: HCV, hepatitis C viral; IFN, interferon; NTR, nontranslated RNA (**Badawi et al., 2018).**

II. History of the infection

With HCV seroprevalence at up to 40% in some areas of Egypt, based on blood-bank surveys, it is obvious that HCV is a huge public health issue within the country.A particular focus is placed on the Nile delta region which holds the greatest rates of infection and was, historically, the main focus for schistosomiasis.The primary two schistosome species in Egypt are Schistosoma mansoni and Schistosoma haematobium. Until the HCV epidemic became apparent, schistosomiasis was the most important public health problem in Egypt with S. mansoni

being the primary cause of liver disease within Egypt historically **(Elghitany, 2019).**

In 1918, JB Christopherson made the discovery that injections with the antimony salt, tartar emetic, could induce a cure. Egypt, at the time, had the greatest schistosomiasis burden in the world, and mass treatment of the parasite was introduced via primary health care services **(Elgharably et al., 2017).**

From the 1950s to the 1980s, community-wide mass antischistosomal therapy was introduced by the Egyptian Ministry of Health with the advice and support of the WHO. At the time, tartar emetic injections were the standard treatment. They were injected intravenously, unlike some other nowarchaicantischistosomal drugs that were injected intramuscularly. Over 2 million injections were given annually to an average of 250,000 patients, meaning over the 18 years of treatment, 36 million injections were administered. Each patient was supposed to have a series of injections with the average number of injections per patient being nine in the 1960s, which then dropped to six after 1975 **(Kileng, 2019).**

III. How HCV affects the liver

Hepatitis C viral infection is largely asymptomatic with little visible symptoms in its acute infection stage. It is only when a patient has been harboring the disease for anywhere between 20–40 years and therefore has a chronic HCV infection when noticeable symptoms or signs will occur. HCV is a significant “precursor” for fibrosis, cirrhosis, and ultimately, hepatocellular carcinoma, but it is important to understand this is only in long-term, chronic cases. In Egypt, up to 85% of HCV infections persist for life, leading to chronic hepatitis. The major cause of