

The Relation between *Helicobacter Pylori* Infection and Hepatocellular Carcinoma in Egyptian Patients

Waleed Mohamed Serag

Department of Chemistry, Faculty of Science, Suez University, Suez, Egypt

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E-mail: waleedserag3@yahoo.com

Abstract: This work to show the relation between *Helicobacter Pylori* infection and Hepatocellular Carcinoma in Egyptian patients. This study was completed at National liver institute in Egypt. Patients in this study were recognized cases of chronic Hepatitis C virus liver disease with and without hepatocellular carcinoma. Serum samples of patients of hepatocellular carcinoma with hepatitis C Virus (HCV) of 40 male and 30 female adults had been collected, *Helicobacter pylori* (*H. pylori*) was detected by enzyme linked immunosorbent assay with comparison with ten males and ten females patients as control groups with chronic Hepatitis C Virus (HCV) without HCC. All patients were free from hepatitis B virus (HBV) infection, without cigarette smoking and without alcohol drinking. Positive *H. pylori* was found more in male and female patients with hepatocellular carcinoma combined by chronic HCV than those with HCV without hepatocellular carcinoma and there was significant difference between both groups. There is a significant association between infection with *H. pylori*, elevated titers of *H. pylori* antibodies and the increased risk of hepatocellular carcinoma in males and females Egyptian patients.

Keywords: Chronic Hepatitis C Virus, Hepatocellular Carcinoma, *H. pylori* Infection

Introduction

Hepatocellular Carcinoma (HCC) is a major cancer in developing countries. Etiologically it is a multifactorial disease that has been linked to both viral and chemical carcinogens. Established causal risk factors include hepatitis B (HBV) infection, dietary aflatoxin exposure, chronic alcohol consumption and cirrhosis of the liver (Farazi and DePinho, 2006). Hepatitis C Virus (HCV) also appears to have contributed to the increasing incidence of HCC in North America and Europe over the past two decades and will probably become the dominant viral cause of this cancer in these low-risk regions. In France, around 90% of HCC occur on cirrhotic livers, with heavy drinking the principal causal factor (Munaka *et al.*, 2003). Hepatocellular Carcinoma (HCC) comprises nearly 6% of all incident cancer cases worldwide, with the overwhelming majority occurring in the developing world. One of the least curable malignancies, HCC is the third most frequent cause of cancer mortality among men worldwide (Parkin *et al.*, 2005). Liver cancers are strongly linked to hepatitis B Virus (HBV) and hepatitis C virus (HCV). Egypt has the highest

prevalence of HCV worldwide and has rising rates of Hepatocellular Carcinoma (HCC). Egypt's unique nature of liver disease presents questions regarding the distribution of HBV and HCV in the etiology of HCC (Lehman and Wilson, 2009).

Helicobacter pylori are a gastric pathogen that colonizes approximately 50% of the world's population. Infection with *H. pylori* causes chronic inflammation and significantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. Infection with *H. pylori* is the strongest known risk factor for gastric cancer, which is the second leading cause of cancer-related deaths worldwide (Wroblewski *et al.*, 2010). Approximately half of the world's population is infected with *H. pylori* and the majority of colonized individuals develop coexisting chronic inflammation. In most persons, *H. pylori* colonization does not cause any symptoms (Peek and Blaser, 2002). However, long-term carriage of *H. pylori* significantly increases the risk of developing site-specific diseases. Among infected individuals, approximately 10% develop peptic ulcer disease, 1 to 3% develops gastric adenocarcinoma and < 0.1% develops Mucosa-Associated Lymphoid Tissue

(MALT) lymphoma (Peek and Crabtree, 2006). At early stages, gastric MALT lymphoma can be cured completely by eradication of *H. pylori* and therefore is considered the first clonal lesion which can be eliminated by treatment with antibiotics (Stolte *et al.*, 2002). In 1994, *H. pylori* was recognized as a type I carcinogen and now it is considered the most common etiologic agent of infection-related cancers, which represent 5.5% of the global cancer burden (Parkin *et al.*, 2011).

Subjects and Methods

This study is a descriptive cross-sectional one was done in The National liver institute in Egypt from attendants of outpatient clinic and from inpatients in the period between June 2014 till December 2014. 90 patients were enrolled in the study with response rate were 65%.

The samples of this study were possessed from National liver institute in Egypt. The patients in this study were completely diagnosed with HCC with chronic HCV liver disease with or without HCC. Data such as age and gender were detected. Blood samples for the measurement of *H. pylori* was detected by measuring Ig G antibody in serum samples by an Enzyme Linked Immunosorbent Assay (ELISA) Serum specimens were tested for the presence of Ig G antibodies against *H. pylori* using a quantitative ELISA (HEL-pTEST II; AMRAD, Kew, Australia). Reference standards were used to produce a standard curve to quantitate *H. pylori* antibody levels in patient samples. The present study was carried out to determine the presence or absence of *H. pylori* in Egyptian HCC patients. *H. pylori* was screened in 90 patients that were classify into two groups: Group 1: HCC with chronic HCV patients (n = 70), 40 males (Mean: 3.5 ng mL⁻¹, S.D: ± 1.57) and 30 females (Mean: 3.3 ng mL⁻¹, S.D:

± 1.28) Group 2: Patients with chronic HCV without HCC (control group) (n = 20), 10 males (Mean: 0.65 ng mL⁻¹, S.D: ± 0.06) and 10 females (Mean: 0.63 ng mL⁻¹, S.D: ± 0.05) with age between 50 to 70 year. Both of them with age between 50 to 70 year. All samples had confidence level with 95%. All patients were diagnosis HCC by computerized tomography, Ultrasound, liver scan and biomarker (alpha fetoprotein ≥ 800) by physicians. The method used for alpha fetoprotein measurement by the electrochemiluminescence immunoassay “ECLIA” Cobas e 602 immunoassay analyzers. Cobas, Roche. Inclusion criteria were all patients without HBV infection, without cigarette smoking and without alcohol drinking.

Ethical Consideration

Informed consent was taken from all participants. Each participant has the right to accept or refuse participation after explaining the objectives. Confidentiality of collected data was guaranteed to participants. The research have been approved by institutional review board of national liver institute, Cairo.

Results

H. pylori antibodies titer was positively detected in HCC with chronic HCV (group I) versus Chronic HCV without HCC group (group II), 40 males of group I (Mean: 3.5 ng mL⁻¹, S.D: ± 1.57) against ten males of group II (Mean: 0.65 ng mL⁻¹, S.D: ± 0.06) and 30 females of group I (Mean: 3.3 ng mL⁻¹, S.D: ± 1.28) against ten females of group II (Mean: 0.63 ng mL⁻¹, S.D: ± 0.05) with fixation of other risk factors as HBS Ag, alcohol drinking and cigarette smoking and the difference in between is statistically highly significant (Table 1, 2 and Fig. 1).

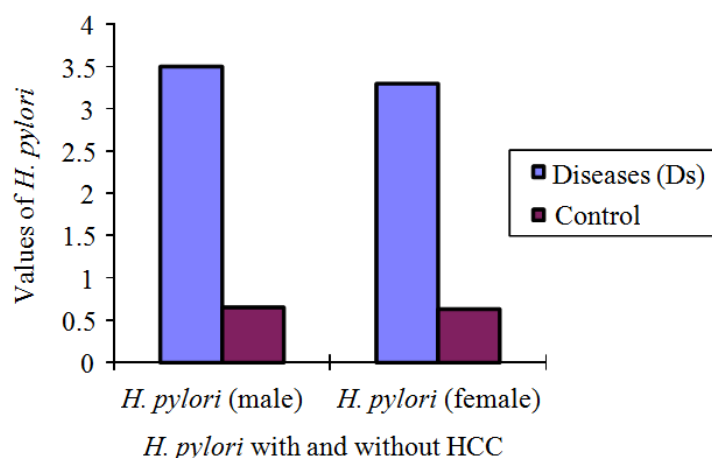


Fig. 1. *H. pylori* in male and female HCC

Table 1. Comparison of *H. pylori* antibodies titer among male of the study group

Variable	Measure	Male of Group (I) (N = 40)	Male of Group (II) (N = 10)	P
Male	Mean±SD of <i>H. pylori</i> antibodies titer (ng/dL)	3.5±1.57	0.65±0.06	#S

#Independent t-test = 11.44 s = significant

Table 2. Comparison of *H. pylori* antibodies titer among female of the study group

Variable	Measure	Male of group (I) (N = 30)	Male of group (II) (N = 10)	P
Female	Mean±SD of <i>H. pylori</i> antibodies titer (ng/dL)	3.3±1.28	0.63±0.05	#S

#Independent t-test = 11.3 s = significant

Discussion

Over a decade, there was nearly a twofold increase of the proportion of HCC among CLD patients in Egypt with a significant decline of HBV and slight increase of HCV as risk factors (El-Zayadi *et al.*, 2005). In this study, there is no relationship between HCV and *H. Pylori* but as the ongoing research deals with patients with liver cancer and where most of the patients with liver cancer in Egypt be a result of a virus infection such as hepatic B & C and mostly with virus C. So there is an overlap between virus C and liver cancer. So it had to be compared the results of patients with liver cancer group with virus C patients group.

H. pylori infection is a classical model with which to study cancer development as a consequence of chronic inflammation. The estimated total of infection-attributed malignancies per year is 1.9 million cases or 17.8% of the global cancer burden. Among the principal carcinogenic agents, *H. pylori* are a leading factor, being responsible for 5.5% of all cancers. *H. pylori* was classified as a type I carcinogen by the International Agency for Research on Cancer in 1994. A striking finding is that bacterial infection of the liver in healthy male mice is capable of inducing a strong inflammatory change in the parenchyma (for example, hepatitis) leading to HCC (11). In this study, it was found that high levels of serum *H. pylori* antibodies titer was associated with HCV infected group with HCC among both male and female patients more than the antibodies titer among HCV infected group without HCC and the difference in between were statistically significant. This association between *H. pylori* infection and HCC persisted even after controlling for the effect of HBs Ag carrier status, anti-HCV positivity, alcohol drinking, cigarette smoking, past liver disease history. In accordance with this study, a study by (Xuan *et al.*, 2008) conclude that a positive association between *H. pylori* infection and the risk of HCC, with an indication of possible publication bias and possible confounders due to study designs that showed results of less pronounced association, this was the first published meta-analysis investigating the association between *H. pylori* and hepatocellular carcinoma risk. *H.*

pylori are associated with an increased risk of death from liver cancer among rural Chinese residents (Wang *et al.*, 2013). A greater incidence of *H. pylori* infection in the liver is identified in patients with liver cancer than in healthy subjects and CLD patients, suggesting a potential correlation between *H. pylori* infections to liver cancer (Chen *et al.*, 2010). HCV patients coinfecting with *H. pylori* recorded higher NIC score and pronounced fibrosis stages than HCV patients. Glycogen and total proteins decreased in hepatocytes and cirrhotic nodules in HCV patients. Such decrease was marked in liver of HCV patients coinfecting with *H. pylori* (Sakr *et al.*, 2013). The mechanisms underlying his association between *H. pylori* and HCC infection are still largely unclear. Another finding indicates that *Helicobacter pylori* infection in cirrhosis has the same epidemiological pattern as in the general population. Suggestions that the etiology or the severity of the liver disease could be related to *Helicobacter pylori* infection were not confirmed (Calvet *et al.*, 1997). *H. pylori* is a gastric pathogen that does not promote hepatocellular cancer and suggest that the HCV transgene is associated with amelioration of specific liver and gastric lesions observed during concurrent *H. pylori* infection in mice (García *et al.*, 2013). The present study suggest that a large happening of *H. pylori* infection in the liver is specified in patients with hepatocellular carcinoma than in chronic liver diseases patients, propose a prospective correlation between *H. pylori* infection and liver cancer so *H. pylori* infection associate with the development of hepatocellular carcinoma. On the other hand a study by (Wu and Chen, 2006) reveals *Helicobacter pylori* can be detected in liver tissue resected from patients with hepatocellular carcinoma. Conflicting reports regarding the relationship between *H. pylori* and hepatocellular carcinoma mean it is uncertain whether *H. pylori* acts as a troublemaker, co-risk factor or innocent bystander to the development of hepatocellular carcinoma. Clinical studies in patients without known causes of hepatocellular carcinoma are important to discover whether *H. pylori* are involved in the carcinogenesis of hepatocellular carcinoma. High quality prospective studies in patients

with hepatocellular carcinoma, hepatitis C virus infection and no cirrhosis are needed to determine whether *H. pylori* is a co-risk factor for hepatocellular carcinoma.

Despite its limitations, the present analysis has some implications: As relatively few studies are available in this field and current evidence remains limited, the necessity to conduct large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results, should be emphasized; for example, tissue from unaffected liver metastatic carcinoma could be used as a suitable control.

Cancer and its treatment can weaken the body's immune system by affecting the blood cells that protect it against disease and germs. As a result, the body cannot fight infection, foreign substances and disease as well as a healthy person's body can. During the treatment for cancer, there will be times when the body will not be able to protect itself very well. While the immune system is recovering, you may be told to try to avoid being exposed to possible infection-causing germs (Grant *et al.*, 2010).

Conclusion

There is a significant association between infection with *H. pylori*, elevated titers of *H. pylori* antibodies and increased risk of hepatocellular carcinoma in males and females Egyptian patients.

Conflict of Interest:

The author declares that they have no conflict of interest.

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