Possible role of H.pylori infection in NAFLD and Its Progression to NASH in a sector of Egyptian population

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List of Abbreviations

ACC1 ..... Acetyle-CoA carboxylase1

BabA ..... Blood group antigen binding adhesin A

BMD ..... Bone mass density

CagA ..... Cytotoxin-associated gene A

CCL4 ..... Carbon tetrachloride 4

ChREBP ... Carbohydrate response element-binding protein

CK-18 ..... Cytokeratin-18 fragments

DNL ..... De novo lipogenesis

DupA ..... Duodenal ulcer promoting gene

GGT ..... Gamma glutamyl transpeptidase

GH ..... Growth hormone

HSL ..... Hormone-sensitive lipase

IGF1 ..... Insulin-like growth factor 1

JAK ..... Janus kinase

MAPK ..... Mitogen-activated protein kinase

MCP-1 ..... Macrophage chemotactic protein 1

NAFL ..... Non- alcoholic fatty liver

NAFLD ..... Non-alcoholic fatty liver disease

NASH ..... Non-alcoholic steatohepatitis

OipA ..... Outer inflammatory protein A

PAMPs ..... Pathogen-associated microbial patterns

PDFF ..... Proton density fat fraction

PNPLA3 .... Patatin like phospholipase domain containing 3

PPARg ..... Peroxisome proliferator-activated receptor gamma

SabA ..... Sialic acid-binding adhesion A

SREBP1C . Sterol response element-binding protein1C

STAT ..... Signal transducer and activator of transcription

TGFβ1 ..... Tissue growth factor

TLRs ..... Toll-like receptors

TM6SF2 .... The transmembrane 6 superfamily member 2

TNF ..... Tumour nectrotic factor

VacA ..... Vacuolating cytotoxin A

WAT ..... White adipose tissues

Abstract

Background: Helicobacter pylori (H.pylori) is a chronic persistent infection and its main symptoms are gastric symptoms(chronic gastritis,Peptic ulcer,gastric lymphoma and gastric cancer) but recently H. pylori infection implicated in extragastrointestinal diseases including(obesity, type 2 diabetes mellitus, cardiovascular disease, and liver disease). There has been a special focus on H. pylori infection as a risk factor for the development of nonalcoholic fatty liver disease (NAFLD). NAFLD is currently considered to be the most common liver disorder and the mechanisms of pathogenesis of underlying NAFLD remain unclear at present and therapeutic options are limited. The growing awareness of the role of H. pylori in NAFLD is thus important to aid the development of novel intervention and prevention strategies, because the eradication of H. pylori is easy and much less expensive than long-term treatment of the other risk factors. H. pylori infection is involved in the pathogenesis of insulin resistance (IR) which is closely linked with NAFLD. This review explaining the possible relationship between H. pylori and NAFLD by its role in IR. **Methods:** This cross sectional, case control study was conducted on 80 patients presented with fatty or bright liver by abdominal ultrasound in Cairo hospitals (ahmed maher and dar elsalam general hospital) during the period from January 2017 to March 2018. Inclusion criteria: Patients diagnosed as fatty liver by abdominal ultrasound, Exclusion criteria: Hepatitis Viral infection (HCV Abs, HBsAg), History of drug induced hepatitis, history of alcoholism, Diabetes mellitus and history of receiving the eradication therapy of H.pylori .The patients divided into three groups (Active,eradicated and control) according to H.pylori Abs and H.pylori Ag in the stool. Measurments: HOMA-IR score,NAFLD fibrosis score and FIB4 score performed to each group **Results:** age of the studied subjects ranging between 22 and 70 years old with a mean age of 41.1±9.4years, gender of the studied subjects showed that equal incidence in both male and female. subjects with serum H.pylori Abs positive were 60 (75%) and 45 of them 56.2% were positive for H.pylori Ag in the stool (active infection) and the remainder 15 patients 18.8% were negative for Ag in the stool (eradicated infection)**,**20 subjects 25% were negative for H.pylori Abs (Control). subjects with **active** infection presented with IR were 22 (48.9%) compared with 23 in number 51.1% were normal IR and subjects with eradicated infection presented with IR were 6 (40%)compared with 9(60%) with normal IR and subjects who were controls (uninfected) presented with IR were 12(60%) compared with 8 (40%) with normal IR .in FIB-4 score and NAFLD-**score** all subjects in the study were presented with No fibrosis except that there were only 2 subjects 2.5% in the grey zone according to FIB-4 score. **Conclusion:** fatty liver was significantly more frequent in previously infected subjects (cases), insignificant correlation between H.pylori and insulin resistance.

Key word: ACCI, Baba, DNL, GGT, GH, NAFL

INTRODUCTION

H. Pylori is a spiral-shaped gram negative bacteria and it is the most common infection of the stomach and can colonize in the stomach since childhood and persist throughout the life causing disease symptoms mainly in adults. The most common known diseases are usually confined to the stomach in the form of:

- Chronic gastritis.
- Peptic ulcer disease
- Gastric Mucosa-associated lymphoid tissue lymphoma.
- Gastric cancer **(Amieva et al., 2008).**

Recent studies become interested more about extra-gastric effects of H. pylori such as cardiovascular, liver and biliary diseases. So, screening of this infection is recommended to apply the treatment early in life and to avoid gastric and extra gastric-effects **(Polyzos et al., 2009).** The accumulating evidence has implicated H. pylori infection in development of non-alcoholic fatty liver disease and its progression to non-alcoholic steatohepatitis. So, it is important to develop a novel interventions and prevention strategies to eradicate H. pylori infection specially that's easy and less expensive and may aid in preventing the progression of the non-alcoholic fatty liver and non-alcoholic steatohepatitis to cirrhosis **(Dunn et al., 1997).**

Non-Alcoholic Fatty Liver is a complex disease trait with pathogenesis and progression determined by genetic and environmental factors. And it is a benign state in which triglycerides accumulated in the liver and triglycerides not lipotoxic and usually associated with type 2 diabetes, obesity and insulin resistance **(Tiniako et al., 2010).**

Non-alcoholic steatohepatitis is a progression of non-alcoholic fatty liver disease in which, there is lipotoxic injury to hepatocytes by non triglyceride metabolites of free fatty acides (Hepatocyte Ballooning and lobular inflammation) **(Wallace et al., 2004):**

Insulin resistance (IR) plays a major role in developing of non-alcoholic fatty liver disease and its progression to non-alcoholic steatohepatitis **(Bonora et al., 2000)**.

Insulin resistance associated with hyperinsulinemia favors accumulation of free fatty acides in the liver because of inhibition of hepatic mitochondrial beta-oxidation of free fatty acides (**fong et al., 2000).**

AIM OF THE STUDY

To study the possible role of the Helicobacter pylori (H.Pylori) as one of the contributing factors for development of non-alcoholic fatty liver disease (NAFLD), and its progression to non-alcoholic steatohepatitis (NASH), through its possible role in development of insulin resistance (IR) accompanied with hyperinsulinemia in a sector of Egyptian population.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Definition

NAFLD is defined as a complex disease trait with pathogenesis and progression that determined by combination of genetic and enviromental factors associated with accumulation of hepatic fat evidenced by imaging or histological study with no coexisting cause of chronic liver disease or secondary cause of hepatic steatosis including significant alcoholic use, medications or an inherited or acquired metablic state **(Speliotes et al., 2011)** and is divided into two subtypes:-

NAFL (non-alcoholic fatty liver) which is characterized by benign intrahepatic accumulation of trigycerides with steatosis including inflammation in at least 5% of the hepatocytes and NAFL usually does not progress to liver damage or NASH but by various mechanisms and possible insults to the liver, it may also progress into a non-alcoholic steatohepatitis (NASH) **(Chalasani,et al 2018).**

NASH (non-alcoholic steatohepatitis) which is defined as features that include steatosis, lobular and portal inflammation and liver cell injury in the form of hepatocytes ballooning **(Chalasani et al., 2012)** according to histological