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THE EFFECT OF HELICOBACTER PYLORI ON METABOLIC SYNDROME

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ABSTRACT

H. pylorus is the main cause of various gastric diseases such as peptic ulcer, duodenal ulcer, and gastric cancer. Cardiovascular diseases like congestive heart disease, metabolic disorders like DM, lipid metabolism disorders like atherosclerosis are also caused by H. pylori. H. pylori infection causes secretion imbalance of pro-inflammatory cytokines and CRPs, angiotensinogen, leptin hormone, and free fatty acids, however, the exact association of metabolic syndrome and Helicobacter pylori infection is not clear. The main mechanism of a metabolic syndrome caused by H. pylori is that the bacterium causes a disturbance in the host's immunological response which leads to the production of proteins such as CagA, VacA, BabA, and SabA. This mechanism is seen in the association of H. pylori infection and gastrointestinal diseases, diabetes mellitus, lipid profile changes as well as cardiovascular diseases. The inflammation and production of inflammatory cytokines along with different hormonal imbalances is caused by the bacterium. Since there are no specific treatment guidelines for the management of metabolic syndrome associated with HP infection, total eradication of the infection is the goal to be achieved done by the standard triple therapy. H. pylori eradication must be done as early as possible for the management of gastro- and extra gastrointestinal diseases caused by the bacterium.

INTRODUCTION

Helicobacter Pylori, a spiral shaped bacterium that can inhabit various areas of the stomach, particularly Antrum. Formerly, it was named as Campylobacter Pylori is then it was renamed as Helicobacter Pylori,[1] is considered as an infectious disease disregarding the patients individual symptoms and disease state.[4] H Pylori is transmitted from person to person through direct contact with saliva, vomit or fecal matter.[3] It is well adapted in acidic environment and it can also change their and reduce their acidity thus allowing them to survive.[3] Clinical symptoms range from asymptomatic to Gastrointestinal malignancy.[3]

H Pylori infection underlies gastric diseases such as Peptic Ulcer Disease, Gastric Cancer, Duodenal Ulcer,[2] and not only gastro related diseases it also causes cardiovascular like Congestive Heart Disease, Metabolic disorders like Diabetes Mellitus, lipid metabolism disorders like changes in lipid profile causes diseases like Atherosclerosis. Association between Helicobacter Pylori and metabolic disorders are discussed in below topics.

How does h. Pylori cause metabolic syndrome

Metabolic syndrome is a heterogeneous disease which is caused by factors such as genetic, infectious or environmental factors. The relationship between metabolic syndrome and Helicobacter pylori infection is unclear, whereas it is known that the secretion balance of pro-inflammatory cytokines and C – reactive proteins, angiotensinogen, leptin hormone and free fatty acids are impaired by H. pylori infection. This in turn causes accumulation of reactive oxygen radicals. Cytokine imbalance and impaired stimulation of macrophages can cause subclinical chronic inflammation.[6]

H. pylori-infected mucosa causes an over expression of interleukin – 8 (IL -8) production. This is caused due to the stimulation of oxidization of LDL by monocytes which causes an increased engagement of smooth muscle cells and T lymphocytes which promote plaque formation.[4]

In many studies conducted, H. pylori-infected diabetic patients were detected to have lower FBG level than in non-infected patients, which may have been caused due to a decrease in both basal and meal-stimulates glucose. H. pylori increase antral gastrin release which in turn causes inhibition of glucose absorption in the small

intestine while increasing the release of insulin that is glucose-stimulated in females, but not in men.[4]

Relationship Between Helicobacter Pylori And Gastrointestinal Diseases

Most common disease caused by Helicobacter Pylori is Peptic Ulcer. The Incidence Rate of Peptic Ulcer was fluctuating in the past. There was a rapid increase in its prevalence in 20th century. In over the past four decades their incidence and prevalence rate was notably declined.[7] Overall, Helicobacter pylori infected persons had higher prevalence of metabolic syndrome than uninfected ones.[8] There are extensive evidence that Helicobacter Pylori is behind the Pathogenesis of Peptic Ulcer.[9]

Unlike most bacterial pathogenesis, Helicobacter Pylori colonises host for its life until treatment is given. Mostly infected persons do not develop overt disease, which leads to a hypothesis that some strains are harmless and even beneficial. Association between Helicobacter Pylori and Gastric diseases mainly involves Urea and Ammonia. The virulence factors involved in this mechanism is CagA (Cytotoxin associated gene A), VacA (Vacuolating toxin A), BabA and SabA (sialic acid-binding adhesins).

Mechanism behind this association is

1. Lacking of glucosylated cholesterol reduces CagA mediated activities and interactions with T cells.
2. Non-toxic lipopolysaccharide (LPS) in Helicobacter Pylori limits the host's inflammatory response.

Helicobacter Pylori beyond the stomach, affects mouth, nose, ears and skin. Whether Helicobacter Pylori is responsible for the diseases or colonises only after other agents initiate disease remains to be determined.[10]

Helicobacter Pylori and Type 2 Diabetes Mellitus

Diabetes mellitus is one of the underlying diseases in Helicobacter Pylori infection. Since GI problems were observed in diabetes patients, and it was necessary to treat the infection. The reason in development of Helicobacter pylori infection which induce, inflammation and production of inflammatory cytokines,[11] it plays an important role in distortion of glucose and lipids absorption that altered lipid metabolism and energy harvesting and insulin resistance were linked to impaired blood glucose.[12] And also that causes different hormonal imbalance by this bacterium, which were associated with diabetes mellitus. Diabetes Mellitus patients had a symptoms of digestive problems in >75% of patients. Evidence showed that, with the chronic and insulin-resistant inflammation may increase the risk for T2DM. In gastritis, helicobacter pylori which potentially affects the gut-related hormones and inflammatory cytokines.

Reasons to discuss about the relationship on diabetes with H. pylori

1. There had an impairment in the function of the cellular and humoral immunity, which increases the sensitivity to helicobacter pylori infection.
2. Diabetes causes reduction in GI movements and secretion of gastric acid, which will increase colonization and bacterial infection.
3. There will be changes in glucose metabolism which alter chemical production in gastric mucosa that resulted in colonization of more bacteria.

There had a link which shows a controversy between H. pylori infection and diabetes mellitus, some of the study showed a higher prevalence of infection in diabetes mellitus. In comparison with healthy individuals people with H. pylori infection would suffer more in diabetes patients.[11] Other study indicates that in patients with type 2 diabetes the Helicobacter pylori treatment could improve the mean glycosylated haemoglobin.[12]

Changes In Lipid Profile

Changes in lipid profile including cholesterol, triglyceride and lipoproteins HDL – C and LDL – C may be caused by the presence of H. pylori in digestive system ulcers, according to many studies,[13,5] Inflammatory cytokines like interleukin – 1, interleukin – 6 or TNF – α mediated by a chronic inflammatory condition like H. pylori infection alters the lipid profile.[14,3] In various studies, the results were significantly low in HDL – C levels in patients with cardiovascular diseases and gastritis (Pilotto and Malfertheiner (2002), Yudkin (1997)),[13] In a study conducted by Tae Jun Kim et. al., they found that Helicobacter pylori infection was a significant and independent risk factor for hyperlipidemia (high LDL – C and HDL – C levels). Atherogenic lipid profile, i.e., increased total cholesterol, LDL – C and decrease in HDL – C, promotes atherosclerosis in carotid, coronary and peripheral vessels.[5] Association of H. pylori infection and metabolism of lipid in previous studies show reliable evidence but also contradictory results exist. Studies also show that low socioeconomic status is a common risk factor for both dyslipidemia and H. pylori infection.[14,5] Even though studies show a significant association between H. pylori and dyslipidemia there was no evidential association with other cardiovascular risk factors like obesity and glucose tolerance. Total eradication of the infection is required for H. pylori and cardiovascular disease patients to reduce complications and prevalence of such conditions.[14,5]

Cardiovascular Disease Due To Helicobacter Pylori Infection

Worsening of H. pylori infection leads to the development of gastrointestinal diseases as well as extra-gastrointestinal disorders. Among other extra-gastrointestinal, coronary heart disease (CHD) is the most prevalent type of heart disease and distinguished by atherosclerosis in the epicardial coronary arteries.[15]

The mechanism of how H. pylori cause CHD is that H. pylori disturb host immunological responses by the production of the proteins cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) which causes the release of pro-inflammatory cytokines.[15]

Eventually, the increase in the production of various pro-inflammatory and inflammatory metabolites affects blood vessel motility and leads to endothelial dysfunction, which results in the blocking of arteries, thereby increases the risk of heart attack. It has been reported that C-reactive protein is a potential indicator of disease associated with the heart and may play a crucial role in vessel mortality.[16]

Management

The main role in the cause of heart disease is the irregular functioning of the immune system, both at the cellular and systemic level.[16]

There are no any specific treatment guidelines for the management of Metabolic syndrome (MetS) which is associated with H. pylori infection. However, H. pylori eradication helps to decrease these formerly described conditions by following a standard double, triple or quadrapole therapy for the cure of H. pylori infection.[17]

The most advisable treatment for H. pylori eradication is the standard triple therapy which comprises of a proton pump inhibitor or Ranitidine, Bismuth citrate, combined with Clarithromycin and Amoxicillin or Metronidazole.[17]

DISCUSSION

Metabolic syndrome is a group of metabolic risk factors which are associated with an increased risk of atherosclerotic cardiovascular disease, Type 2 DM and their complications. These factors include atherogenic dyslipidemia, elevated blood pressure and elevated fasting glucose levels or pre-diabetes which leads to a pro-thrombotic and pro-inflammatory state.[18] Most of the studies published about the relationship between helicobacter pylori and type 2 diabetes mellitus. In many aspects there are controversies in studies, some of them reported that, there is a significant effect of helicobacter pylori infection on hba1c and insulin resistance, and other studies showed that there were no relationship between helicobacter pylori infection and glucose control.[19] Because of cellular and humoral immune deficiency, diabetes mellitus patients were prone to chronic infections. Due to delayed gastric emptying, bacterial overgrowth occurs, and this poses a risk for H. Pylori infections. Compared to the control group, prevalence of helicobacter pylori were significantly higher in the diabetes mellitus group.[20] Some of the studies showed that microvascular damage caused by helicobacter pylori infection which triggers the premature development of atherosclerosis in patients. Due to the endotoxins produced by this bacteria play a role in the maturation of monocytes which leads to the production of inflammatory cytokines, then it triggers platelet aggregation and pro-coagulant activity, there by IL-6 increases the production of hepatic gluconeogenesis and triglycerides, TNF-$\alpha$and there will be modification in the lipid levels by inhibiting the lipoprotein lipase activity and activating hepatic lipogenesis. The reason for inflammation which formed by triggering the helicobacter pylori via by increasing in the production of various superoxidases and activation of macrophages, T-lymphocytes, and lipoprotein-a, peroxidation of membrane lipids, oxidation of LDL cholesterol, antioxidant loss.[20] Mechanism of helicobacter pylori which increases the risk of diabetes in presence of gram-negative bacteria, which leads to an increased production of lipopolysaccharide in the gut microbiota, and also activates innate inflammatory processes. In this study the markers of inflammation implicated in insulin resistance and development of diabetes correlates with elevated levels of CRP, IL-6, and tumor necrosis factor-a. From this finding for H. pylori, BMI, diastolic blood pressure, and vascular disease was positively associated with diabetes mellitus. Whereas, HDL were inversely associated with diabetes.[21] In this study, showed a report in healthy children, that CPN, HP, or CMV seropositivity in childhood have no association with pro atherogenic alterations in serum lipid, lipoprotein, or apolipoprotein values. In adults, several studies showed that there is an association between CPN, HP, and CMV IgG antibody titers, and clearly atherogenic lipid profiles. The Lp(a) values are elevated in connection with CMV seropositivity. This study explains that, in men, there is a significant association with an increased triglyceride and decreased HDL cholesterol concentrations in serological markers of chronic CPN infection. These changes also present during the acute phase of a CPN infection.[22] A well known risk factor for cardiovascular disease was associated with an increased serum levels of fibrinogen and lipids, eradication of helicobacter pylori may also improve persistent low grade gastric inflammation. Result demonstrated that, after an adjustment on covariant factor, including BMI, smoking and drinking habits. In our subjects the serum level of HDLC were higher in eradication of helicobacter pylori, and the serum levels of total cholesterol LDLC and triglycerides were lower in comparison to subjects with continuous H. pylori infection. And total cholesterol LDLC and triglycerides were higher in level with continuous H. Pylori infection was frequently observed.[23] In this study documentation was done that a rise in HSCRP production by the liver is due to rise in inflammatory cytokine-interleukin-6. Gaurav Shashikant said that a significant increase in HSCRP levels in H. Pylori infection was associated with higher risk of cardiovascular events. H. Pylori carrying the cytotoxin strain, in terms of raising serum lipid levels, associated gene a (cag a) was a pathogen as compared to strains lacking it.[24] In elderly Koreans, H. Pylori infection, which was independently, associated with elevated LDL cholesterol levels. These findings suggested that H. Pylori infection might cause lipid alteration and, partially

contribute to the atherosclerotic process where LDL cholesterol levels increased with increasing H. Pylori severity. This study explains that an indicator for the assessment of cardiovascular risk is h. Pylori infection and it is a predisposing factor for the atherosclerotic process. Here eradication of H. Pylori may play a role in preventing atherosclerosis by decreasing LDL cholesterol levels, particularly in elderly Koreans.[25] Patients with both DM and H. Pylori infection the risk of gastric cancer were increased. Researchers found an increased prevalence, that hyperglycemia is one of the possible cofactors which increases the carcinogen by increasing reactive oxygen -related damage to DNA of H. pylori infection, which results in genetic changes to the gastric epithelial cells of h. Pylori-infection, which is a pre-cancer lesion which develops into colorectal carcinoma. It was also found to increase the risk of colorectal adenoma.[26] In patients with NASH, H. Pylori infection plays a main role in IR and the clamp technique hyperinsulinemic-euglycemic were considered as the gold standard for the assessing IR, in clinical practice and epidemiologic studies HOMAIR is the most common method for assessing IR. The original hypothesis said that H. Pylori induced chronic gastritis which resulted in IR. Chronic inflammation and alternations in counter-regulatory hormones were deemed responsible for IR pathogenesis. In this study the H. Pylori infection status have not revealed any reciprocal changes during h. Pylori eradication treatment. Due to low bacterial load and the adaptation of the bacteria to a specific environment, as reported in murine liver was unable to detect the H pylori by polyclonal antibody stain in one of the study.[27] This study explains the diagnostic value, will increase in H. Pylori infection since it mainly colonizes the mucosal surfaces. Between the NAFLD and the control group a significant difference were found for IgA seroprevalence and serum Helicobacter Pylori - IgA titer. This proves that, irrespective of the presence of IgG titres, the presence of significant IgA antibody titers is an important evidence of H. Pylori infection. In NASH patients as compared to NAFLD patient's serum H. Pylori IgG and serum H. Pylori IgA were not statistically higher. This study showed that both current and past H. Pylori infection have not caused any progression of the fatty liver disease. Our study results showed contrast with some of the studies and have shown that H. Pylori infection is associated with an unfavourable metabolic profile in NAFLD patient.[28] In non-alcoholic fatty liver patients, this study was designed to answer the uncertainties regarding the effectiveness of HP treatment. From the result, in liver injury, the alt indicator was important and the eradication of HP have a significant effect on the improvement of patient's fatty liver. Factors involved in eradication method of helicobacter pylori are duration of dietary intervention, nature of exercise, intensity and volume of aerobic exercise, and individual differences. In the variables of triglyceride, total cholesterol, LDL, and HDL in both groups, a significant decrease were seen. In all lipid indicators exercise could lead to a significant change. A significant improvement was found in the blood glucose index in both groups, and the difference between the two groups was not considerable.[29]

CONCLUSION

It is familiar that H. Pylori causes gastrointestinal diseases but its role in extra gastrointestinal diseases are not widely known, whereas the influence of the bacteria in other diseases should also be taken into consideration as we have seen earlier that it slows the rate of eradication as well as aggravate other complications related to each condition. Hence it's very important that H. Pylori eradication should be done as early as possible which is the only management to both gastrointestinal as well as extra gastrointestinal diseases caused by H. Pylori.

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