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Association between *Helicobacter pylori* and Rheumatic Heart Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Author GTA update literature. Authors ALAM and SAB wrote first draft. Author SSM revised for publication. All authors read and approved the final manuscript.

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ABSTRACT

Rheumatic heart disease (RHD) is an inflammation in=of the heart valves that lead to rheumatic fever. This event can occur immediately after *a streptococcal* infection, such as a sore throat or scarlet fever. Acute rheumatic fever (ARF) is caused by autoimmune response to *streptococcal* pharyngitis group derived from genetically sensitive individuals. The immune response caused an inflammatory disease in the body that can lead to persistent valve damage. About 60% of rheumatic fever (RF) patients in endemic countries developed chronic RHD which is a complication of RF. RHD is a chronic disease characterized by complications such as arrhythmias and heart failure. This review identified the role of *H. pylori* in the development of rheumatic heart disease. ARF and RHD most often affect children and young adults. *H. pylori* infection has been proposed to be involved RHD greater than that of the normal health people. *H. pylori* can be considered as

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one of the probable risk factor for RHD through immune response mediators. It was concluded that patients with *H. pylori* should be advised to follow up in cardiology clinics to avoid any complications.

Keywords: H. Pylori; streptococcal; rheumatic heart disease.

1. INTRODUCTION

Helicobacter pylori (*H. pylori*) is a worldwide prevalent pathogenic bacterium that causes gastritis, peptic ulcers and/or gastric malignancies to varying degrees [1]. Because *H. pylori* infection is particularly common in developing countries, the infection may be affected by certain health disorders. Therefore, the status of *H. pylori* infection in the population, especially in patients with gastrointestinal diseases, should be monitored. *H. pylori* is one of the most common and widespread bacterial infections [2]. The prevalence rates vary according to public health standards, as *H. pylori* infection is more prevalent in "developing countries" compared to "developed countries". *H. pylori* have different strains that are involved in different triggers of infection [3]. Antistreptolysin O (ASO) is an antibody produced against streptolysin O; one is immunogenic, oxygen-destructive hemolytic toxins produced by streptococci. The most common antibodies produced by the immune system are ASO and anti-DNase group B [4]. High levels may demonstrate a previous or current infection. Historically, it was the first bacterial marker to diagnose and monitor rheumatic fever or scarlet fever [5].

2. MECHANISMS AND PATHO-PHYSIOLOGY

Rheumatic heart disease (RHD), is a condition in which the heart valves are irreversibly damaged by rheumatic fever. Damage to the heart valves can occur immediately after an untreated or under-treated streptococcal infection, such as a sore throat or scarlet fever. Acute rheumatic fever (ARF) is a systemic disease of the autoimmune response to streptococcal pharyngitis Group (GAS) derived from genetically sensitive individuals [6]. The immune response causes an inflammatory disease in the body that can lead to persistent valve damage. RHD has an increased risk of complications such as a defect of the heart refers to, arrhythmias such as atrial fibrillation, stroke, infectious endocarditis, and premature death [7]. RHD is the leading cause of heart disease in children and adolescents worldwide [8]. Determination of antibodies to combat the extracellular products of streptococci is of great importance in clinical practice and for the epidemiological study of streptococcal infections and their consequences [9]. The determination of antistreptolysin-O (ASO) can be of great help in the diagnosis because its values reach high values in the presence of important clinical manifestations, decreasing regardless of the subsequent course of the disease. The etiology of most autoimmune diseases is not well defined. Certain factors including genetics and environmental toxins can influence or promote autoimmunity [10]. Inappropriate immune activation that targets autoantigens causes long-lasting pathologies that result in an individual being subjected to varying degrees of autoimmune disease. Certain pathogens are thought to be associated with the pathogenesis of autoimmune diseases [11], these infectious agents cause autoimmune diseases through various mechanisms. Many bacterial infections have been linked to the development of an autoimmune like response and constitute a critical clinical problem.

The most common inflammatory indicators used to assess patients with suspected septic arthritis, osteomyelitis and rheumatic fever were C reactive protein (CRP) and Erythrocyte sedimentation rate (ESR). The production of serum CRP by the liver has already been reported as a reliable marker of oxidative stress and systemic inflammation [12]. The CRP is not only an indicator of the acute phase response that is the main process, but can also aggravate existing tissue damage. The concentration of CRP increased during inflammation in the body. It's not a specific test. Erythrocyte sedimentation rate (ESR) is a non-specific indicator of disease activity and is most commonly used by physicians to aid in the diagnosis and follow-up of many inflammatory disorders. Used ESR levels on a large scale as an indicator of the acute phase response in the immune-inflammatory diseases, including rheumatoid arthritis. However, the response patterns in the acute phase and the production of cytokines may differ in various inflammatory diseases, acute phase changes mainly reflect the presence and

severity of inflammation [13]. Re-infection generally results in a sustained or continuous increase in values, and empirical studies suggest that antibody responses are more affected by repeated exposure [14]. Previous study demonstrated that, an ASO in chronic RHD patients was significantly lower than healthy subjects. This may be due to the effects of penicillin on Streptococcus immune response [15,16].

Meanwhile, there was decreased in the serum ASO concentration in ARF patients, as a result of having anemia in these patients. It has been shown that people with anemia had carditis as the main feature, and the ARF anemia may be associated with inflammation. It may be the cause of anemia associated with the response of body's inflammatory protein to GAS infection, such as TNF-α, which may also play a role in the decrease erythropoiesis stimulating agents [17]. There is a risk that the acceptable level of ASOT in the general population can be clearly abnormal in patients. Administration of the drug, particularly penicillin, may alter the natural course of the response to streptolysin while reducing the total number of reactions and influencing the extent of the antibody response [18]. It can also be assumed that the abnormal antibody response triggers an autoimmune process [19], which gradually causes damage to the heart valves. Increased levels of CRP in people with chronic rheumatic valve disease indicate persistent inflammation in the chronic phase. A similar result has been reported by [20] who demonstrated that there was persistently elevated CRP levels in bacterial infected patients when compared to healthy control. The authors noted that the persistently elevated CRP levels highly indicative of persistent inflammation and may indicate the need for additional treatment. The author also hypothesis that chronic anemia can be a problem with RVD, especially in those with more severe inflammation. Inflammation that progresses slowly leads to asymptomatic changes in iron metabolism in RVD, these patients need to be closely monitored for future long-term problems, such as anemia [21].

Although the acute phase response patterns and cytokine production may differ in various inflammatory diseases, changes in the acute phase mainly reflect the presence and severity of inflammation. The obtained results were in agreement with [22] who reported that the ESR values were much elevated in RHD patients. In addition, the obtained result was approval with the result reported by [23] who showed that the ESR values were increased in RHD patients than healthy participants. A similar result was reported that indicated the concentration of ESR in patients with RF were dramatically increased when compared with the normal persons. ESR rate at which the blood settles among individuals, as the blood that contains less than the number of red blood cells settles more quickly, and the rate of erythrocyte sedimentation depends on the fibrinogen levels in the plasma [24,25]. However, it has been demonstrated that CRP decreases more rapidly than the ESR during treatment, making it a convenient agent to observe the response to treatment in these infectious conditions [26].

In view of the many restrictions in children, but simple and reliable tests are needed to diagnose *H*. *Pylori* infection in these children. We have chosen two types of indirect tests which are an active and passive test. Stool antigen HpSA test which detect active infection and can be used as a noninvasive screening tool specifically for *H. pylori* infection in children with RHD and IgA antibody test which detect a marker of current and previous exposure to H. pylori ,but do not indicate if the infection is in progress [27]. The positive result of serum may indicate previous exposure to *H*. *Pylori* infections.

Studies reported that *H*. *Pylori* infection is also associated with many other chronic diseases, such as heart disease, gastrointestinal disorders, hematological diseases, metabolic disorders, and others [28]. *H. pylori* colonizes the gastrointestinal tract of a huge number of individuals and most of them also remain asymptomatic. This association is thought to depend on inflammation, and it has been postulated that infection may be a substrate for the systemic inflammation seen in rheumatism. There is very strong evidence to support the effect of inflammation on pathogenesis of rheumatic disease which is accompanied by an increase in marker levels that reflect an underlying inflammatory process [29].

The *H. pylori* bacteria may be directly leading to some complications like, endothelial damage, dysfunction due to circulating endotoxins [30]. Presentation of inflammation [Fig. 1] in the immune system is a multi-step process. Frequent exposure to *H. pylori* infection leads to can disrupt the inflammatory process and the inability to fight the spread of infectious agents, which leads to a number of diseases such as heart disease and cancer. This chronic stress weakens

the body [31]. Prolonged stimulation of the immune response due to a bacterial infection stimulates the secretion of CRP, increases blood levels of leukocytes and homocysteine, promote blood clotting, induces the immune cross reactivity, proinflammatory cytokines (IL, lymphocytes) and other cytotoxic agents. It has been reported that CRP is a possible indicator of RHD. According to a recent study, the major virulence factors of *H. pylori* (cytotoxin associated gene A) is more strongly associated with the risk of heart disease, which was confirmed by the presence of anti-*H. pylori* due to serological prevalence [32].

3. HELICOBACTER PYLORI

Helicobacter pylori, formerly known as Campylobacter pylori, is a Gram-negative, is described with a spiral shape while it is able to change its shape to more helical in order to penetrate the mucous membrane of the gastrointestinal tract [33]. It is believed that its helical shape (hence the name of the genus, Helicobacter) evolved to enter the lining of the stomach and thereby establish an infection [34]. *H. pylori* has been associated with lymphoid tissue associated with the lining in the stomach, esophagus, colon, rectum, or tissues around the eye (called B-cell lymphoma of the extranodal marginal zone of the cited organ) [35].

The prevalence of *H. pylori* infection in the world varies and depends on numerous factors such as age, ethnicity, geographical and socioeconomic status. *H. Pylori* infection is the most prevalent in developing countries of Africa, South America and Asia; whereas highly developed countries are the least infected (Fig. 2).

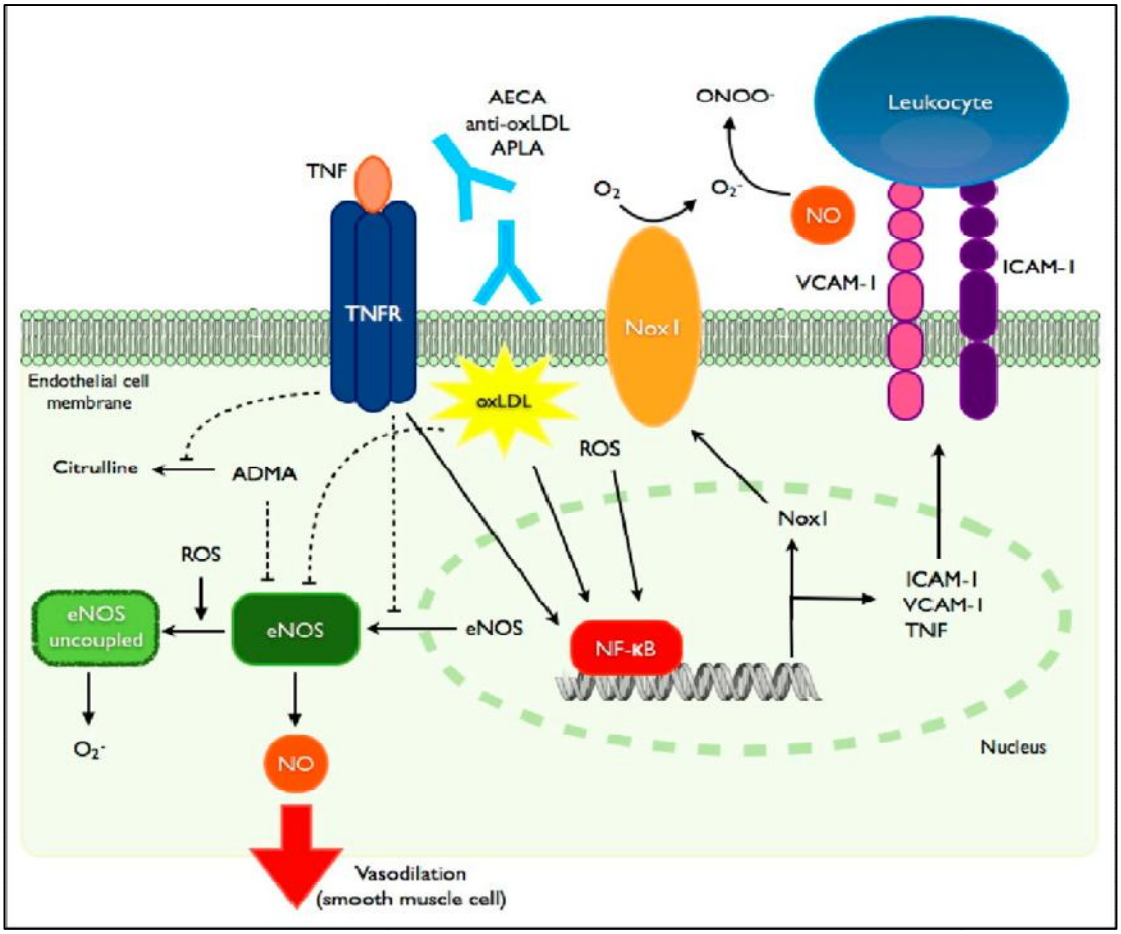

Fig. 1. Mediators in endothelial dysfunction. ICAM, VCAM (adhesion molecules; eNO (endothelial nitric oxide synthetase); ADMA (asymmetric dimethylarginine); TNF (tumor necrosis factor)

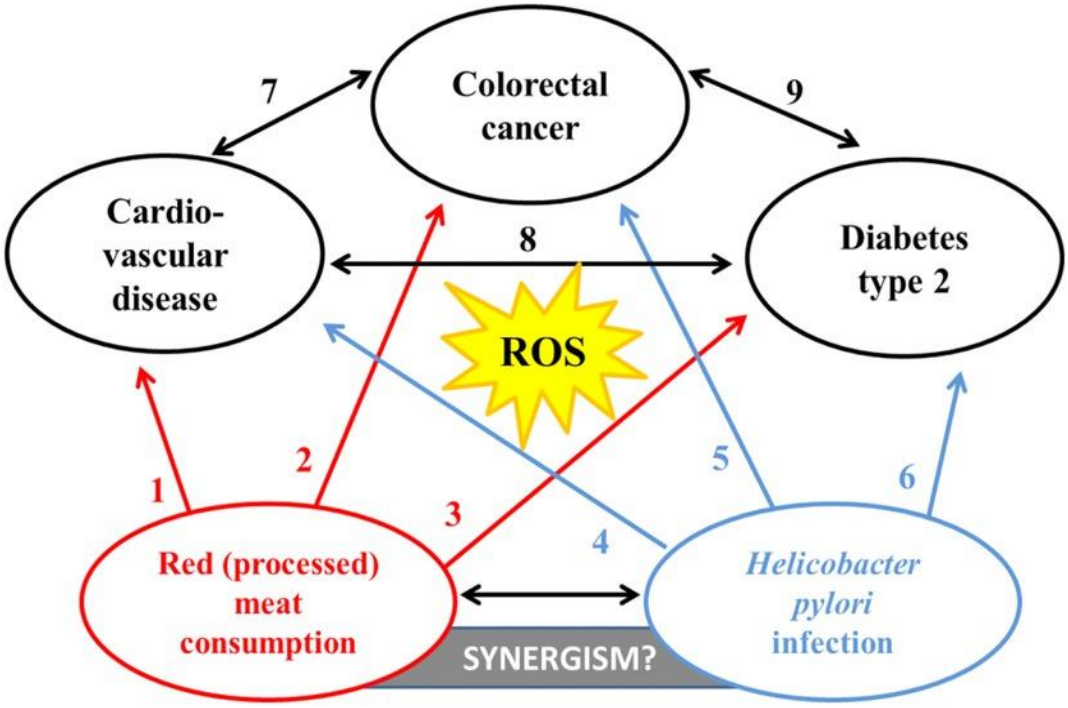

Fig. 2. Impact of *H. Pylori* and oxidative stress and diseases (Thomas Van Hecke) Incidence of heart disease with *H. Pylori*

H. *Pylori* infection concerns the development of gastrointestinal diseases and extra-gastrointestinal disorders [36]. There are several extragastric clinical manifestations associated with *H*. *Pylori* such as cardiovascular disease, lung diseases, neurological diseases and hematological disorders [37].

The mechanisms suggested in an attempt to discuss the role of *H*. *Pylori* infection in RHD. The proposed mechanisms is the pathogenesis of rheumatic disease is not depend only on an infectious agent. It likely occurs as consequence evidence and a cascade of host-specific factors. It is regulated by different genes and the method of infection. The genes polymorphisms unrelated to immunity may induce the disease through molecular mimicry. Practical investigation is needed to investigate the mechanisms by which a *H*. *Pylori* infection contributes to RHD [38,39].

4. CONCLUSION AND RE-COMMENDATION

This study demonstrated that the rate of RHD patients with *H. pylori* are (most=delete) greater than that of the normal health people participating in this research. *H. pylori* can be considered as one of the probable risk factors for RHD. To determine the potential role of *H. pylori* in the pathophysiology development of RHD we required further larger research.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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