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ASSOCIATION BETWEEN INFECTION OF HELICOBACTER PYLORI AND IRON DEFICIENCY ANEMIA OF UNKNOWN ORIGIN: A SYSTEMATIC REVIEW

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ABSTRACT

Infection with Helicobacter pylori, a Gram-negative bacterium, is common worldwide, affecting approximately 50% of the world's population. Complications arising from H. pylori infections can have serious health consequences. In addition to gastritis, peptic ulcer disease and gastric cancer, conditions widely described in the literature, scientists are also examining the connection between H. pylori infection and the development of iron deficiency anemia (IDA). Iron is an element necessary for the proper functioning of red blood cells and for proper human development, starting in utero. Iron deficiency is the most common micronutrient deficiency in the world. The unknown etiology of iron deficiency and, consequently, anemia, is a serious problem for clinicians, but also provides an opportunity for scientific research. The aim of this paper is to review the literature investigating links between H. pylori infection and IDA development. The literature review was carried out using Google Scholar and PubMed, and took into account the mechanism of H. pylori infection in IDA development, and the impact of this microorganism on iron metabolism and hematological parameters. The research on iron management and hematological parameters to date has produced varying results. In some cases, the worsening of laboratory results characteristic of IDA was associated with the presence of H. pylori infection. However, there are plenty of studies showing no association between IDA and ongoing infection. Thus, due to insufficient research on the potential mechanistic links between infection and anemia, the influence of H. pylori infection on IDA development cannot be clearly defined.

KEYWORDS: Helicobacter pylori, iron metabolism disorders, hematologic tests, erythrocyte indices

BACKGROUND

Helicobacter pylori is a Gram-negative type of bacteria first described and classified by Marshall and Warren in 1984 [1]. The occurrence of this bacterium is common worldwide and H. pylori infection affects approximately 50% of the world population [2]. Infection with H. pylori can result in serious health consequences, with the most common being chronic gastritis, stomach and duodenal ulcer disease, and atrophic gastritis. These complications can serve as a basis for the development of stomach cancers. Indeed, the association between cancer development and H. pylori infection has been researched for many years and is widely described in the literature [3,4].

The prevalence of H. pylori infections among children and adults is higher in developing countries [2], and research suggests that infection with this bacterium is associated with a lower income and a poor education [2,5]. The spread of H. pylori in the world is also related to the degree of urbanization–with increased levels of urbanization in rural areas the number of people infected with the microorganism

decreases [5]. In addition, a diet poor in vegetables and fruits, but rich in fried products, is associated with a higher percentage of infection among people. Furthermore, maintaining personal hygiene protects against infection [2,5]. Due to a greater risk of contact with the pathogen, H. pylori infection is more prevalent among adults as compared to children; however, there are no significant differences in number of infected between men and women [6].

According to research conducted from 1993–2005, and reviewed by the WHO in 2008, iron deficiency (ID) affects about 2 billion people worldwide and is recognized as the most prevalent micronutrient deficiency [7]. The most common cause of reduced iron levels (and anemia, which is a consequence of prolonged and increasing deficiency) is insufficient dietary intake of iron [7]. In addition to direct ID resulting from food intake, iron deficiency anemia (IDA) can also be caused by the reduced absorption of this element from the gastrointestinal tract. This mechanism is observed in celiac disease, inflammatory bowel diseases, atrophic gastritis, and after gastrectomy [8]. IDA is also a common problem in children and pregnant women due to an increase in the body's need for iron at these stages [9,10]. However, most anemia patients are in the group of non-pregnant women [7]. Anemia also develops as a result of blood loss, including from gastrointestinal bleeding during peptic ulcer disease, which may be a consequence of H. pylori infection. A rare cause of IDA is a genetic mutation of the genes (e.g., DMT1 and TMPRSS3) involved in iron metabolism [11].

A lack of iron reserves and erythropoiesis disorders in anemia can threaten the life of a patient at any age. Thus, it is important to understand the basis of anemia, and to develop rapid and effective treatments for this disorder. Numerous studies have examined the impact of H. pylori infection on iron metabolism, and have investigated the association between this microorganism and the occurrence of IDA of unknown etiology. Here, we review this literature with a focus on studies examining potential mechanisms linking H. pylori infection with IDA, and those exploring the effect of the bacteria on iron metabolism and hematological parameters.

MATERIAL AND METHODS

A systematic literature search was conducted using Google Scholar and the PubMed database. The literature search focused on identifying studies that examined the mechanisms linking H. pylori infection with IDA with unknown etiology, and the effect of this microorganism on iron metabolism and hematological parameters. For this search, keywords such as "Helicobacter pylori", "iron deficiency" and "anemia" were used. In total, 29 studies written in English were included for review. Papers that did not contain any pertinent data were excluded. The search process used for the literature review is outlined in Figure 1.

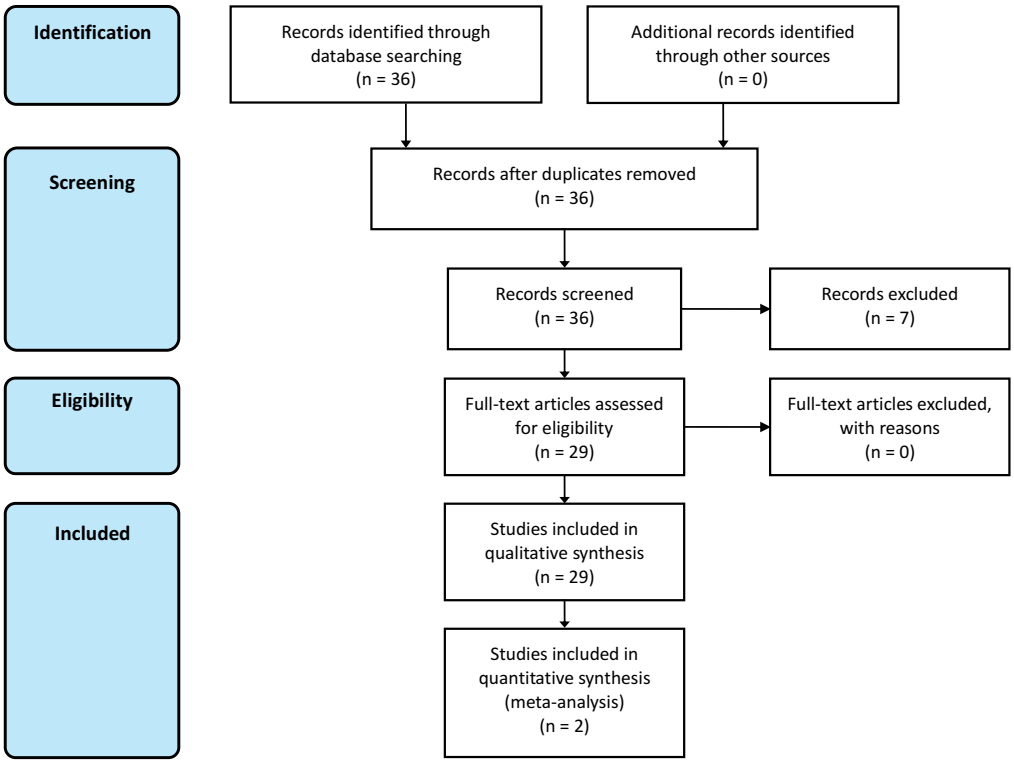

Figure 1. PRISMA 2009 Flow Diagram [12] (for more information, visit www.prisma-statement.org)

RESULTS

Potential mechanisms linking H. pylori infection to IDA with unknown etiology

There is no universal mechanism that can associate H. pylori infection with the changes in iron metabolism leading to IDA. However, the first reports investigating the effect of this bacterium on micronutrient absorption appeared in the late 1990s. Worst et al. described the possible participation of iron repressible outer membrane proteins (IROMPs) of bacteria that capture and bind iron from the host [13]. In addition, Dhaenens et al. focused on the Lactoferrin-binding protein (Lbp), which allows H. pylori to obtain iron from human lactoferrin [14].

More recently, studies on the impact of H. pylori infection on human iron metabolism have focused on the genetics of the bacteria. For example, Shan et al. compared the iron binding abilities of the neutrophil-activating protein (NapA) from different H. pylori strains. Others had previously shown that people infected with H. pylori strains with threonine at amino acid residue 70 of the NapA protein (Thr70-NapA) are more likely to have IDA [15]. Shan et al. examined the iron-binding ability, stability, structural changes, and DNA-binding ability of the Ser70-NapA and Thr70-NapA proteins, and confirmed that Thr70-NapA strains are characterized by a greater ability to bind iron ions. In addition, it was reported that changes in iron concentration may regulate DNA-binding and cause destabilization of Thr70-NapA protein structure. Changes in DNA-binding ability may be related to protecting bacterial DNA from the oxidative stress caused by iron excess [16].

Kato et al., in their work, focused on identifying H. pylori genes whose expression is associated with the occurrence of IDA. In their study, H. pylori strains were isolated from 4 children (aged 13–16 years) suffering from IDA and compared with bacteria obtained from 4 children with normal iron metabolism. Using cDNA microarrays and real-time RT-PCR, 29 differentially expressed genes were identified. Among the detected genes, 11 were characterized by higher or lower expression under conditions of rich or lean iron concentrations. Special attention was paid to two particular genes: sabA and vacA. The sabA gene works by facilitating the binding of the bacteria to human stomach epithelium, while vacA increases the vacuolization activity of bacteria. According to the conclusions drawn by Kato et al., high expression of the sabA gene increases the body's need for iron, and the vacA gene may promote this effect [17].

Another potential correlation between H. pylori infection and IDA was described by Chen et al. Here, the relationships between single nucleotide polymorphisms (SNPs) in several genes and the risk of iron deficiency in individuals with H. pylori infection was examined. In this study, 644 school children, aged 10–18 years, were first examined for the presence of H. pylori antibodies. 69 children were identified as having a prior or current infection with H. pylori, while 575 children without the presence of antibodies formed the control group. Iron levels were measured and SNPs in several genes, including IL1B, CXCL8, IL10 and ABO, were examined. An increased frequency of the IL1B T allele (rs1143627) was found to be associated with an increased risk of ID in children infected with H. pylori. However, the role of IL1B in the development of ID following H. pylori infection remains unknown [18]. A similar study was carried out by Serrano et al., who examined 105 children with H. pylori infection symptoms. 33 of the participants were H. pylori positive and, of these, 9 were diagnosed with ID; hence, H. pylori infection was positively correlated with ID. However, in this case, no significant differences were found in allele frequency of the IL1B gene polymorphisms between infected and uninfected children. Nonetheless, it was reported that children infected with H. pylori and exhibiting ID showed a higher expression of gastric IL1B mRNA as compared to infected children without ID. A positive correlation was also observed between IL1B mRNA expression in the gastric mucosa and fasting gastric pH. The significant increase of pH in children with H. pylori infection and ID, compared to children with normal iron metabolism and without infection, allowed the authors to suggest the involvement of IL1B in the development of ID [19].

Iron metabolism and hematological parameters in H. pylori infection

Iron, ferritin and total iron-binding capacity (TIBC) are some of the key parameters used in IDA diagnostics. This disorder is typically diagnosed in patients with iron levels below 50 g/dl, ferritin below 20 ng/dl, and TIBC values exceeding 350 g/dl [20]. Research has shown that H. pylori infection may lead to alterations in the levels of these parameters [21,22]. Darvishi et al. conducted a case-control study examining the prevalence of H. pylori infection in 64 children with diagnosed IDA and 70 healthy controls. The levels of iron and ferritin were found to be lower, and TIBC was higher, in the group of patients with IDA. In addition, in 81.3% of anemic cases and 14.3% of healthy controls there was a positive H. pylori antibody level [23]. Moreover, a meta-analysis conducted by Muhsen and Cohen in 2008 revealed an association between both symptomatic and asymptomatic

H. pylori infection and reduced iron stores, especially among children and adult females [24].

Hematological parameters such as hemoglobin (Hb), hematocrit (Hct) and red blood cell count (RBC) also play an important role in IDA diagnostics. Hb concentration in anemia is typically lower than 14 g/dl in men and 12 g/dl in women [25]. IDA is also characterized by reduced values of red cell indices including mean corpuscular volume (MCV), mean corpuscular Hb (MCH), and mean corpuscular Hb concentration. H. pylori infection has been associated with decreased Hb, Hct and RBC levels in some studies [23,26]. Mwafy and Afana, in a study on 300 adults, reported that patients infected with H. pylori had lower levels of various hematological parameters, including Hb, Hct and RBC, as compared to controls [21]. Another study examining Hb and Hct, MCV and MCH levels in children from Brazil, Chile and the United Kingdom, also reported a decrease in all of the above parameters in H. pylori-positive individuals [22]. However, some studies do not find significant changes in the above-mentioned parameters among patients with H. pylori infection [20,27,28]. Shih et al. showed no correlation between chronic H. pylori infection and IDA, despite lower levels of serum iron, ferritin and Hb, and a higher level of TIBC (changes did not have any statistical significance) [25]. Likewise, in study of female adolescents from Sweden, researchers did not note significant alterations in above-mentioned parameters in an H. pylori-positive group [29].

DISCUSSION

The etiology of IDA and its effects on human health are commonly discussed in the medical literature. While the causes of IDA can be unclear, one of the proposed factors leading to the development of this disorder is H. pylori infection. The current literature review has identified a number of papers proposing different mechanisms for the impacts of H. pylori on iron metabolism. Early work in this area suggested the participation of several H. pylori proteins, including IROMPs and Lbp, which can enable the bacteria to obtain iron from the host [13,14]. More recent work focused on the H. pylori iron-binding protein NapA and showed that differences in the amino acid structure of this protein can alter its iron-binding properties [15,16]. Other studies have drawn to attention to the H. pylori sabA and vacA genes and indicated that elevated expression of these genes increases the need for iron in the host [17]. Additional work has focused on impact of SNPs of several genes, like IL1B, on iron metabolism. However, research in this area has produced differing results regarding the influence of IL1B gene polymorphisms on ID development [18,19]. Although much research has been conducted on the potential mechanisms connecting H. pylori infection and ID development, none of the mechanisms described above has been sufficiently tested and confirmed.

H. pylori infection can also affect iron metabolism and hematological parameters. Several studies have noted changes in iron, ferritin and TIBC levels that are indicative of IDA development in infected individuals [21-24]. In addition, changes in Hb, Hct, RBC and red blood cell indices have been observed in individuals infected with H. pylori [21-23,26]. These results suggest that eradication of H. pylori may have an influence on the recovery of patients with iron-refractory or iron-dependent anemia. Indeed, it has been reported that the eradication of H. pylori by using a triple regimen of omeprazole, amoxicillin and clarithromycin can return serum ferritin to normal levels after 6 to 12 months, especially among men and postmenopausal women. Moreover, this treatment leads to a long-term resolution of IDA, without a relapse, or a need for further iron supplementation [30]. Similarly, in a group of adults suffering from IDA and H. pylori infection, iron and hematological parameters improved after 3 months of combined triple therapy with iron supplementation [20]. Thus, eradication of H. pylori combined with iron supplementation can likely bring more satisfactory effects as compared to iron supplementation alone.

While these results are promising, some studies have not observed a relationship between infection with H. pylori and the development of IDA [20,25,27-29]. It is worth noting that the results from various studies may differ due to the use of varied laboratory parameters or groups of patients (e.g., children or adults, males or females). In addition, factors such as the type of country (developed or developing), level of risk of IDA occurrence (low or high risk), socioeconomic conditions, type of diet, and blood loss (i.e., gastrointestinal bleeding, menstruation) may have contributed to the varying results. The tendency for an association between H. pylori infection and IDA development was mainly observed in developing countries with low socioeconomic status and inadequate diet, especially among children. Furthermore, most of the studies reported here were performed on subjects from one country, which is also a limitation. Therefore, more research should be done on groups of patients from different countries.

CONCLUSIONS

In this systematic review, the association between H. pylori infection and IDA with an unclear etiology was examined. Studies investigating possible mech-

anisms for the contribution of H. pylori to IDA development, and the impact of this infection on iron metabolism and hematological parameters were reviewed. In sum, it is not yet possible to clearly determine if H. pylori infection has any effect on IDA development. While this microorganism can affect iron metabolism and hematological parameters, there is no one universal mechanism to explain the relationship between H. pylori infection and IDA. Nonetheless, scientists have proposed various mechanisms that have been outlined above. Clearly, further research will be necessary to examine the potential links between H. pylori infection and IDA development. The identification of a mechanistic connection will likely reduce the number of IDA cases, especially among those patients with an unclear etiology.

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