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The Association Between ABO Blood Group Distribution and *Helicobacter Pylori* Infection: A Cross-Sectional Study

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1. Abstract

1.1. Purpose: *H. pylori* infection has always been associated with the external factors of hygiene, but there is a lack of credible information about its association with ABO blood group. We attempted to establish the role and involvement of internal factors including age, blood group and electrolytes in manifestation of this disease.

1.2. Method: We recruited 100 patients of *H. pylori* infection from an outpatient clinic in Saudi Arabia. Patients with any comorbid disease were not incuded. Blood samples were analyzed for presence of H. pylori antibody, blood group and Rhesus type (ABO/Rh) and plasma electrolytes levels. Plasma concentration of Na^+, K^+ and Mg^{2+} were measured. *SPSS 21* was used for statistical analysis, values with $p<0.05$ were considered to be significant statistically.

1.3. Results: Our results indicated that *H. pylori* infection was most prevalent in the patients, particularly 31-40 years old, with O+ve and A+ve blood group, followed by B+ve and AB+ve. Patients with Rh- were found to be least affected. Na^+ conc was not altered in 43% patients, however it was below normal in 32% and above normal in 25% patients. There was a significant increase in K+ and Mg2+ ions in almost the patients, with Mg2+ significantly higher in males.

1.4. Conclusion: The study proves that blood group, age and electrolytes contribute in manifestation of *H. pylori* infection. Patients of both the genders with blood group system A+ve and O+ve are more susceptible, followed by those with B+ve and AB+ve group. This study will be clinically significant in taking ABO blood group into account before initiating the drug therapy for treatment of *H. pylori* infection, especially if the drug has a tendency to cause electrolyte imbalance. Also blood transfusion of a specific blood group with a history of *H. pylori* infection should be cautiously considered.

2. Introduction

Peptic ulcer is one of the most prevalent bacterial infections caused by *Helicobacter pylori (H. pylori)* [□ 1]. The pathogen majorly invades human gastric mucosa and causes chronic gastric inflammation. Chronic infection results in erosion of gastric mucosal lining with bleeding ulcers. If untreated, the condition may lead to lymphoma or gastric carcinoma [□ 2]. About 5.5% of all types of cancer comprise of *H. pylori* induced gastric carcinoma. Also it constitutes 25% of cancers with an etiology of infection [3]. The major targets of this pathogen are cholesterol, bicarbonates and some amino acids regulated by chemotaxic system, however, it is repelled by the low pH [4]. Being a gram negative bacterium, *H. pylori* comprises of glycosylated cholesterol and an outer lipopolysaccharide layer. These layers enable the bacterium to resist environmental stress [5] and the inflammatory response of host [6], thus help bacteria to survive and prolong infection. The O-specific chains in lipopolysaccharide layers

contain blood group antigens [7]. It is reported that ABO gene does not code directly for ABO antigen, rather for glycosyltransferases on chromosome 9q34, the enzymes which transfer nucleotide sugars to the H antigen to form antigens of blood groups A and B. N-galactosamine is the nucleotide sugar for group A, and that for group B is D- galactose [8]. Starting from ABO gene, the A and B antigens have a characteristic feature of autosomal codominance [9]. The Homozygous inheritance of 2 null ABO alleles makes O an autosomal recessive phenotype. People possessing this phenotype exhibit H-antigen expression. H-antigen is required for the synthesis of the antigens A and B [10]. ABH antigens are expressed not only in red blood cells (RBCs), but also in kidney, heart, intestinal mucosa, endothelium and several other organs and tissues [11].

Typing of RBCs along with plasma and serum is necessary for ABO blood group system [12]. In this study we explored the corelation between prevalance of *Helicobacter pylori* infection with the patients' blood group.

3. Patients and Method

3.1. Experimental Design

One hundred patients, both males and females, aged 7 to 66 years, from outpatient clinic of Center of King Abdulaziz University were recruited for the study. Inclusion criteria was the absence of any disease other than *Helicobacter pylori* infection. Ethics Committee, Faculty of Medicine, King Abdulaziz University evaluated the study and approved (Reference code: 666-19). Age and gender of each patient was recorded for demographic evaluation. Blood samples were collected in EDTA coated test tubes to detect H. pylori antibody, ABO/Rh antigen typing and plasma electrolye levels. Quickvue test was used to diagnose *H. pylori* infection in the patients who presented with clinical signs and symptoms of GI disease.

3.2. Reagents and Instruments Used

Lorn Blood Grouping Reagent, Lorn Laboratory Ltd, UK, was used to determine ABO-Rh type, serum electrolyte concentrations were measured by enzymatic methods using Automated-Chemical Analyzer, Dimension-R Clinical Chemistry System, USA, Murine Monoclonal antibody to Human IgG (test-line), Rabbit Polyclonal antibody (control-line) and test- cassettes; positive control (diluted human plasma containing *H. pylori* specific IgG and 0.01% thimerosal) and negative control (diluted human plasma containing only 0.01% thimerosal) were all from Eli Lilly. SPSS software (version9.05, SPSS Inc., Chicago, IL), Chi square, Variance and Fisher's exact test were applied for statistical analysis. Values with $p<0.05$ were considered to be significant statistically.

3.3. Serum Electrolytes Test

Serum levels of Na^+, K^+ and Mg^{2+} ion concentrations were measured *in vitro* using Dimension Vista System, Re; K800A.

4. Results

4.1. H. pylori Infection Associated with Age and Gender

Statistically, there was no significant difference in the number of male and female patients. Most of the patients were from 31-40 years of age. Only 3 patients were above 60, and 8 under 20 years (Table1).

Table 1: Demographic Data of Patients with H. Pylori Infection (N=100)

Variables	N
Gender	
Male	46
Female	54
Age Group	
<20	8
21-30	23
31-40	37
41-50	17
51-60	12
>60	03

4.2. Association of H. pylori with Blood Group and Rh Factor

Patients were classified according to their blood group. It was observed that 33% of the patients, with no significant difference in the sex, possessed O+ blood group. A+ was found in 38% patients, where number of females (n=23) was almost 40% higher than those of males (n=15). Similarly, number of females from B+ group (n=10) was twice those of males (n=5). However, AB+ group showed number of males (n=5) to be higher by 25% than females (n=3) (Figure 1). It was observed that out of all the recruited patients, only 6% had RH-, irrespective of any of the ABO blood group (Figure 2). Among those, 3 males but no female were from O- category, one female but no male from B-, one male and female patient each from AB- category, while none of them belonged to A- category (Figure 1).

4.3. Alterations in Sodium ion concentration

Electrolytes play an important role in human physiological functions. We measured Sodium (Na^+) ion concentration in *H. pylori* patients with varied ABO blood group. It was observed that the sodium level was normal (135- 145 mEq/liter) in 43% of the patients. Among those, 17 had O+ blood group, 15 had A+, 7 B+ and 4 AB+. 32% patients exhibited below normal range of Na^+concentration, with 13 patients comprising of A+, 7 each with O+ and B+, and 3 had AB+ blood group type. Among the 25% patients who exceeded the normal range of Na^+concentration, 10 possessed A+, 9 O+, 1 B+ and 4 AB+ (Figure 3.1). There was no significant difference in sodium concentration among both the genders with *H. pylori* infection (Table 2).

Table 2: Distribution of electrolyte concentration with respect to gender of H. pylori patients

		Mean ± SD			
Gender	N	Na	K	Cl	Mg
		135-145 mEg/L	3.6-5.2 mmol/L	97-107 mEg/L	0.85-1.10 mmol/L
Male	46	139.78 ± 18.29	9.37 ± 1.24	91.48 ± 14.19	2.68 ± 0.80*
Female	54	135.06 ± 15.72	9.51 ± 1.25	85.81 ± 08.44	2.36 ± 0.84
P-value		0.17 (NS)	0.57 (NS)	0.01 (S)	0.05 (S)

One –way Anova with Post-hoc analysis (n=100); *p<0.05; N: significant; NS: non- significant

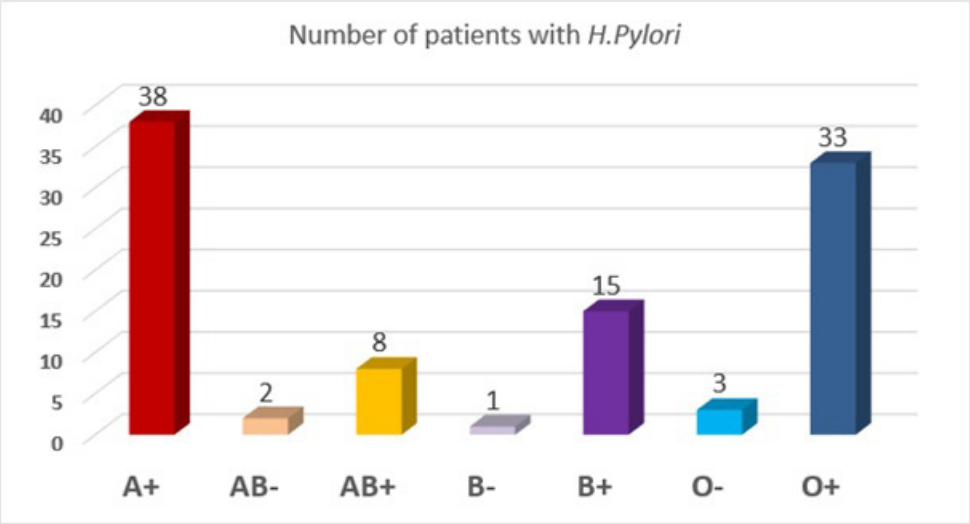

Figure 1: Comparison of Blood group of the patients with H. pylori infection

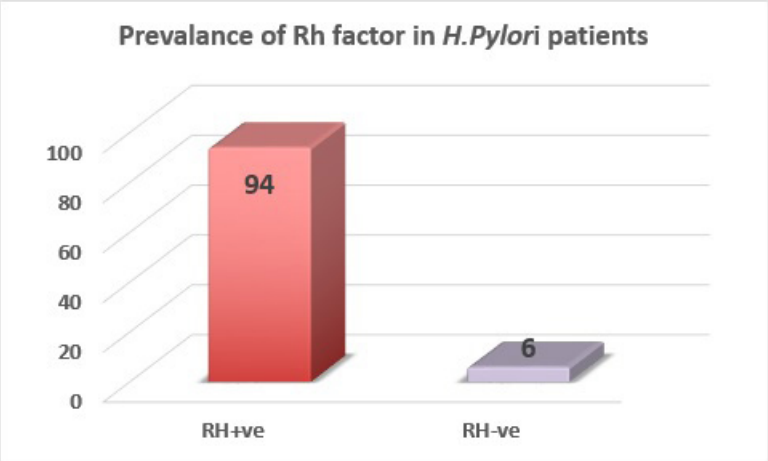

Figure 2: Distribution of Rh factor with respect to H. pylori disease

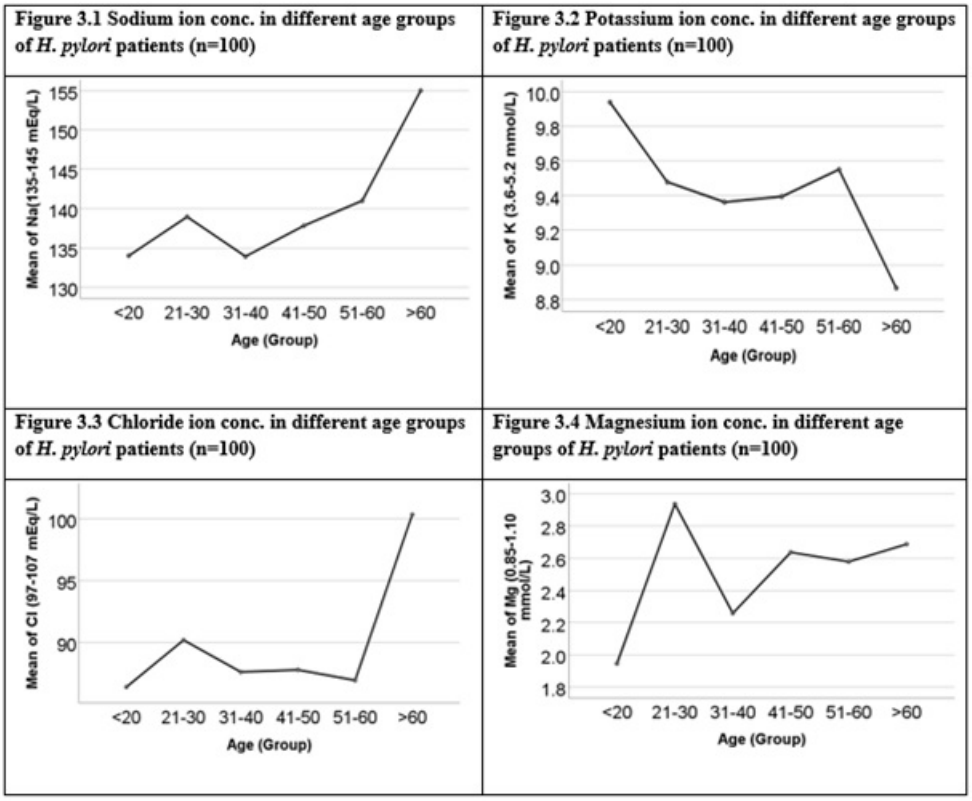

Figure 3: Serum concentration of electrolytes in different age groups of patients with H. pylori infection (n=100). One –way Anova with Post-hoc analysis

4.4. Alterations in Potassium Ions Concentration in Different Blood Groups

Serum potassium levels were measured in H. pylori patients. We observed that only 2% of the patients, 1 each with O+ and B- blood group exibited normal conc. of K^+ ion (3.5-5.5 mEq/L). However, 98% patients, irrespective of sex, with diferent ABO-Rh type, exhibited significantly higher concentration of K^+ ion ($p<0.001$) than the normal level (Figure 3.2) (Table 2).

4.5. Alterations in Magnesium Ion Concentration

The normal Mg^{2+} ion concentration in a healthy person is 1.7-2.2 mg/dl. In the present study, the serum magnesium ion concentration was found to be significantly elevated in the patients of all the age groups, with maximum being in the age of 21-30 years, irrespective of their blood group and Rh factor (Fig 3.4). When compared among different genders, Mg^{2+} levels in males (2.68±0.80 mmol/L) was significantly higher ($p<0.05$) than those of female patients (2.36 ± 0.84 mmol/L) (Table 2).

5. Discussion

To our knowledge, this study is conducted for the first time in Saudi Arabia to explore that the infection caused by *H. pylori* bacteria is associated with the blood group and Rh factor of patients. These rod-shaped, gram-negative micro-aerophilic pathogens colonize in gastrointestinal tract of human and target mucus lining of stomach [13]. Epidemiologically, about 50% of the world's population is infected by this bacteria [14]. People generally remain asymptomatic initially, but if not treated, it may cause gastritis and peptic ulcers. Chronic complications in rare cases, may even progress to gastric carcinoma [15].

We determined the ABO-Rh type of the patients, both males and females, who presented with *H. pylori* infection. It was observed that 33% of the patients, irrespective of the gender, had 'O+' blood group. Mattos et al [16] have also reported earlier that infection caused by *H. pylori* is more commomnly seen in people with blood group O. Further, we obseved that 38% of the patients were from A+ group. Here the number of females was approx 21% higher than those of males. Similar trend was seen in blood group B+, where females were 33% higher in number than males. AB+ blood group was found in only 8% of the patients under study, where male patients outnumbered females by 25%. Another interesting pattern observed was that 94% of patients, with varied ABO blood groups were Rh+ve, while only 6% exhibited RH-ve type. Among those, 50% had blood group O –ve, and were all males, 16.67% had B –ve, and were all females and 33.33% constituted blood group AB –ve, with equal number of males and females. No patient was found to possess blood group A –ve.

Blood group antigen is a polymorphic trait inherited in individuals. These antigens may be specific to certain diseases, including the bacterial infection caused by *H. pylori* [17]. *H. pylori* recognize histo-blood group antigens as a receptor, and attach to them making the susceptible to infection [18;19]. Blood group antigens are known to facilitate membrane microdynamics for intra-cellular uptake, signal trans-

duction and/or adhesion [20, 21]. Several researchers have reported that blood group antigen can modify the innate immune response to infection [22, 23]. Likewise, in the present study, we observed a variation in *H. pylori* infection in the patients with different antigens.

It is established that H. pylori can stimulate the antibody response against blood-group antigens [24]. Here the blood group of patients seems to be an important factor associated with infection.

Rheus (Rh) type for ABO blood group system indicates the absence or presence of an antigen on cellular membranes of RBCs [25]. Positive or negative expression of Rh factor determines the risk and severity of infection in certain blood group related diseases, caused particularly by *H. pylori* and *V. cholera* [18, 26]. The results of this study demonstrate that antigen was present (Rh+) in 94% of the patients, with no significant difference in number of males and females. This clearly illustrates that people with ABO-Rh+ of either sex are highly susceptible to *H.pylori* disease as compared to those possessing Rh negative (Rh-). However, further studies are required to develop a proper mechanistic approach which can decipher the molecular mechanism responsible for discrimination in infection by *H. pylori* and explain why Rh+ are more prone to infection but not Rh-.

Age plays a crucial role in the incidence and severity of an infection [27, 28]. Adaptive immune system of neonates is not much developed, which makes them an easy target to infections [29]. However, in our study, minimum number of patients were observed in the age category of 0 - 19 years. Also, none of the patients in this category exhibited A-, B- and AB- blood group. Female to male ratio was 5:1, which gives an insight of higher risk of infection in young females who have not crossed their teens. Patients from 20- 30 years of age exhibited similar number of cases with A+ and O+, followed by B+ and AB+, with no significant difference in the sex ratio. Maximum number of patients from both the genders fall under the 31-40 years of age. Here again similar pattern was observed with maximum patients having A+, followed by O+ve, B+ve and AB+ve respectively. A fall in the trend was seen in the patients belonging to the group of 41-50 and 51-60 years of age. In both these groups, the female patients were more compared to male. Despite decrease in number of patients, there was no change in the uniformity of the pattern, from A+ve, to O+ve , B+ve and AB+ve. Interestingly, none of the patients from any age group had A-ve type and only one had B-ve blood group. This variation in infection with respect to age has totally changed the dynamics of *H. pylori*, where it is most resisted by elderly people, who generally become immunocompromised at this age. Low infection rates in neonates seems to be justified as they recieve the maternal antibodies from mother via suckling, which protects them against infection. But why the incidence of infection is low in elderly, is still an unanswered question. On the contrary, there are several reports which evidence that elderly are more susceptible to *H. pylori* as compared to younger generation [30, 31]. Graham et al reported in their study that 60-70% of elderly population is at risk to H. pylori infection, while on other hand, less than 20% of young population (aged 25-30 years) is susceptible [32]. However, these studies do not address the specific pathogenesis and the underlying mechanism behind the difference in prevalence of disease with respect to age.

Sodium plays an important role in ionoregulation in human body [33]. Kidneys regulate and maintain the normal fluid balance via various mechanisms. One of the mechanisms in electrolyte homeostasis involves Sodium Hydrogen Exchanger Regulatory Factor-1 (NHERF1) [34]. It is reported that GIT diseases, e.g., dysentery and cholera may alter the expression of NHERF1 [35, 36], resulting in dysregulation of renal sodium transport. We tried to explore in our study, if there exists any relation between sodium (Na^+) concentration of *H. pylori* infected patients of different ages and their blood group. The normal serum Na^+ levels are between 135 -145 mEq/liter [37]. We observed that plasma Na^+ levels were above normal in 25% patients, which is concurrent to the reports by Ioannidou [38]. However, 32% patients exhibited plasma sodium level below the normal range, majority of them belonging to A+ blood group, followed by equal number of patients with A+ and B+ type. Bacterial, viral and prasitic infections may result in marked loss of sodium [39]. It is reported that hyponatremia commonly occurs in 30-67% of people suffering from tropical diseases. It may be the result of decreased activity of Na^+K^+ATPase, thereby inhibiting sodium influx into the cells [40], with an increased levels of ADH [41, 42]. Alteration in electrolyte permeability through cellular membranes may be an important factor governing the blood group system in patients with H. pylori infection The change in electrolyte membrane permeability may be the most important factor responsible for governing the blood group in patients with *H. pylori* infection, as also observed *C. jejuni* infection [43].

5.1. Potassium (K^+), One of The Most Abundant Intracellular Ions

Potassium (K^+), the most abundant intracellular cation is important for normal host metabolism in mammalian as well as bacterial cells, and its concentration varies with immune responses [44, 45]. Reports suggest that K^+ regulates osmoprotection in bacteria [46, 47]. We measured the serum poatssium levels of *H. pylori* patients. The results denotaed that only 2% of the patients showed normal K^+ concentration (3.5-5.5 mEq/L), 1% each with O+ve and B-ve blood group. However 98% patients of all blood group types exhibited hyperkalemia, with majority having A+ (38%), followed by O+ (32%), B+ (15%), AB+ (8%), O- (3%) and AB- (2%). Elevated concentrations indicate increase in K^+ uptake. It is well established that increase in environmental potassium levels lead to increased expression of virulence factors and stimulate the pathogens for host invasion [48]. K+ uptake by H. pylori [49] might be a process during signal cascade, enabling the bacterial coordination in metabolic state of projection. Similar pathway is seen in case of B. subtilis biofilm [50].

Magnesium (Mg^{2+}) is found in several natural food components. Its an intracellular cation, which works as a co-factor for more than 900 enzymes. It is highly involved in cellular metabolic processes and functions, like DNA transcription, maintaining structural integrity of DNA, cell proliferation, differentiation and apoptosis along with bone metabolism [51, 52]. Factors affecting Mg^{2+} concentration may interfere with cellular functions. Malnutrition, malabsorption and renal diseases may result in ion deficiency causing Hypomagnesia (Mg^{2+}<1.5 mEq/L). On the other hand, hypermagneia (Mg^{2+}>2.5mEq/L) may occur due to factors like milk alkali syndrome, depression, Addison's disease and infections. Serum Mg^{2+} concentration of *H. pylori* patients was measured in this study. The results depicted 100% of patients with elevated concentration, where 94% patients had Rh+ ABO blood. Only 6% patients showed absence of blood group antigen (Rh-). Our results are in accordance to other studies which exhibit that magnesium concentration increases in patients with H. pylori infection, [55, 56], but to our knowledge, we have explored it for the first time that the increase in Mg^{2+} level is most prevalent in the patients with blood group ABO Rh+ve type. It has been observed that kidney function is altered in *H. pylori* infection [57]. A factor that may possibly facilitate the increase in ionic concentration is that in presence of blood group antigen, *H. pylori* metabolites may alter renal functions and decrease the excretion of magnesium ions.

6. Conclusion

Our study proves that the blood group, age and electrolytes contribute in manifestation of *H. pylori* infection. Our results indicate that the patients with blood group O+ and A+, irrespective of sex, are at higher risk of *H. pylori* infection. Hence more safety measures are required for the universal blood group O+ donor in high endemic areas. Similar precautions are needed to taken for B+ blood group. Interestingly ABO with Rh- is the least effected population with minimum risk. We also concluded that there occurs a major increase in plasma levels of K^+ and Mg^{2+} ions in *H. pylori* infection. The change in electrolytes is most prevalent in patients with blood group A, followed by O, B and AB, all with Rh+ve type. This study will be clinically significant in taking ABO blood group into account before initiating the drug therapy for treatment of *H. pylori* infection, especially if the drug has a tendency to cause electrolyte imbalance. Also blood transfusion of a specific blood group with a history of *H. pylori* infection should be cautiously considered.

The only limitation associated with this study is the patient or population sample size, further the ethnicity could have also been taken into account along with family history.

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