Original Article

Incidence of *Helicobacter pylori* in Type I Diabetes Mellitus Patients and Association with Certain HLA Alleles

Samir S. Aljawahiry, Naer A. M. Alkaabawi, Alaa A. Jawad[1]

College of Veterinary Medicine, Al-Muthanna University, Samawah, Al-Muthanna, Iraq, [1]College of Veterinary Medicine, University of Al-Qadisiyah, Al Diwaniyah, Al-Qadisiyah, Iraq

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Abstract

Background: *Helicobacter pylori* infection was mainly the factor that causes both gastric tumors and lymphomas. **Objectives:** This study aimed to detect *H. pylori* infection and investigate any relationship between the infection of *H. pylori* and the disease of diabetes, to find out if there is an association with certain human leukocyte antigen (HLA), and to study the frequency of *H. pylori* infection among type l diabetic and nondiabetic patients. **Materials and Methods:** Several 140 patients diagnosed with type 1 diabetes mellitus (T1DM), as well as 60 healthy individuals (nondiabetic) were enrolled in this study. The oligonucleotide technique of sequence-specific was performed for genotyping of HLAs using a polymerase chain reaction machine. A specific screening (*H. pylori* antibodies combo rapid test) is used to diagnose *H. pylori* infection by detection of specific antibodies in the samples. **Results:** This study revealed that people who are diagnosed T1DM are more predisposed to be infected by *H. pylori* (61%) compared with healthier people, and the pathogen infects significantly females compared with males. Results also revealed a great frequency of DQB1*0101 allele within diabetics (30%) in comparison with healthy (control) group, whereas HLA-A*3301,*1122 B*0826,*3948, DRB1*0701,*1101, and HLA-DQB1-*0604,*630,*730 alleles were recorded noteworthy low frequency according to the results after statistical analysis of P value ($P < 0.05$) in patients compared with healthy control groups. **Conclusion:** Diabetic women of the same age are more susceptible to the infection compared with males. The great frequencies of HLA-DQB1*0101 alleles could be a risk factor for T1DM patients.

Keywords: Auto-Lipa, HLA, *H. pylori*, PCR-SSO, T1DM

Introduction

A Gram-negative, micro-aerophilic bacterium, *Helicobacter pylori* infection was documented as a global public metabolic health problem that causes damage to epithelial tissue of gastric mucous layer epithelial lining, it was considered the main reason for chronic gastritis.[1] Around half of the world's population was reported to be positive for *H. pylori*, which was surprisingly found in developing countries more than the developed countries.[2] Especially, in Asian Americans, Hispanics, low socioeconomic populations, as well as older adults. Those individuals, who were infected with this bacterium, are highly exposed to being diagnosed with gastric cancer with responsibility for approximately 90% of all peptic ulcer cases (A). The infection of *H. pylori* was defined as one of the greatest problems for diabetics with gastric symptoms. Although, diabetes mellitus and *H. pylori* infection are different diseases, it was experimented that the higher rates of *H. pylori* infection lead to poor glycemic control in type 2 diabetics.[3] Therefore, it was stated as a main infection of the gastric antrum for diabetes patients causing dyspepsia to delayed gastric emptying and immobility, as well as its major role of increasing the blood glucose concentration in diabetic dyspepsia.[4,5] *H. pylori* infection or the silent infection could be induced by hyperglycemia with reactivation to produce symptoms

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Address for correspondence: Dr. Naer A. M. Alkaabawi, Department of Parasitology, College of Veterinary Medicine, Al-Muthanna University, Samawah, Al-Muthanna, Iraq.
E-mail: naaralkaabi@mu.edu.iq

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of dyspepsia in diabetics. It was also reported that gastric cancer and lymphomas might commonly occur due to the infection of *H. pylori*.[6]

Based on the diagnostic criteria, the commonness of *H. pylori* was reported in 61% of diabetics in comparison with 49% of nondiabetics.[7] *H. pylori* was found to be capable of improving the body's resistance to insulin via the eradication of infected organs.[8] As well as, the noticeable contribution of *H. pylori* in the incidence of cardiovascular disease via raising the levels of C-reactive protein and interleukin 6 as inflammatory cytokines.[9] The relationship between diabetes mellitus and infection of *H. pylori* was studied significantly. However, much research showed no significant relationship between the occurrence of *H. pylori* infection and patients with diabetes mellitus.[10]

Different mechanisms made diabetics more susceptible to infection than others. First of all, diabetes induces cellular weakness and stimulates humeral immunity against *H. pylori* infection.[11] Second, gastrointestinal motility can be decreased by diabetes with the promotion of pathogen foundation due to acidic secretion and the proportion of infection in the gastrointestinal tract.[12] Third, *H. pylori* colonization could be stimulated through chemical changes of altering glucose metabolism in the gastric mucosa.[13] Finally, this pathogen was frequently reported in diabetics, who are regularly visiting hospitals or health centers than healthy people.[14]

Since there were very few researches studied the association between diabetes mellitus and the infection of *H pylori*, this study focused on this relationship, especially with type 1 diabetes mellitus (T1DM) and studying the role of human leukocyte antigen (HLA) alleles.

Materials and Methods

Patients and study design

Total samples of 140 were collected from Iraqi patients diagnosed with T1DM at Al-Yarmouk and Al-Kadhumyia Teaching Hospitals in Baghdad, Iraq, from January 2020 to February 2021. Samples involved 84 females and 56 males; the age range was (8–54) years. All selected patients were absolute dependents on insulin according to their medical case history for diagnosis of diabetes mellitus (DM) as described by the American Diabetes Association.[15] A total of 60 healthy volunteers were involved in this project including 37 females and 23 males between 6 and 52 years old. All of them had a negative DM family history.

First, blood samples were taken from individuals under aseptic conditions using two ethylenediaminetetraacetic acid tubes (1.5 mg/mL), stored at −20°C for *H. pylori* detection and genotyping for A and B of HLA class I and DR and DQ of class II. One blood drop of each sample from the patients and controls was added to sample wells in a specific device for the detection of a specific anti-*H. pylori* antigen (IgG) using a kit produced by Epitope Diagnostic Inc. (San Diego, United States) Positive readings appeared after 1 min.

Deoxyribonucleic acid (DNA) extraction and genotyping of DNA were carried out. Ready Kit (QIAGEN, Hilden, Germany) was used for DNA extraction following the manufacturer's instructions. All extracted DNAs were stored at −20°C until needed. Genotyping of HLA alleles was performed via primed polymerase chain reaction sequence-specific oligonucleotide (PCR) for sequence-specific oligonucleotide (SSO; PCR-SSO) to amplify the HLA-DRBI and HLA-DQ alleles by utilizing an appropriate kit (Lipa, HLA DRB, Innogenetics, Ghent, Belgium; Murex Biotech Limited, Hartford, UK). A reverse dot blot hybridization of Automatic Line probe assay (Auto-Lipa) was applied for molecular typing of HLA alleles provided by the same company. According to the typing table provided with the kit, positive probes on each strip were detected. The HLA-typing laboratory was used for HLA genotyping at Al-Karama Teaching Hospital in Baghdad, Iraq.

Statistical analysis

The results were statistically analyzed based on percentage frequencies, and the significance of differences was measured by Fisher's exact probability (P) of 0.05. In addition, allele variations between patients and controls were determined by odds ratio and etiological fraction.

Ethical approval

The study was approved by Baghdad Health Directorate, Baghdad, Iraq. Patients were informed about enrollment in the study and verbal consent was obtained from all patients. According to document number 693, a local ethics commission reviewed and gave its approval to the study protocol, subject information, and permission form on January 2, 2020.

Results

In this study, the T1DM patients were in different ages between 8 and 54 years. There was a female predominance number among patients' samples about (60%), this was similar to the ratio of control samples. The male-to-female ratio was 1:1.2. The main age of onset for DM disease was (16–35) years with around (54%) of overall samples [Table 1].

The immunological examination of *H. Pylori* infection exposed that the majority of T1DM patients (61%) were infected by *H. Pylori*, whereas female patients recorded the highest ratio of total samples (60%). Meanwhile, the control group recorded (38%) of total samples were infected, and a high record was assigned to male samples (61%) [Figure 1].

Additionally, the results show that the critical ages of diabetic patients who are infected with *H. pylori* were

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between 26 and 35 years, which recorded 53% followed by the age of 16–25 years (27%), and the females were the dominant at these ages with 63% and 65%, respectively. Meanwhile, the males take the lead in the healthy group which records 73% of the infected people with *H. pylori* at the age between 26 and 35 years. In addition, the majority of infected individuals in the healthy group were of the same age (48%) [Figure 2].

Table 1: Cases according to age and sex

Age (years)	Control		Diabetic patients	
<15	9		26	
16-25	16		36	
26-35	22		40	
36-45	7		20	
>46	6		18	
Total	60		140	
Gender	F (37)	M (23)	F (84)	M (56)

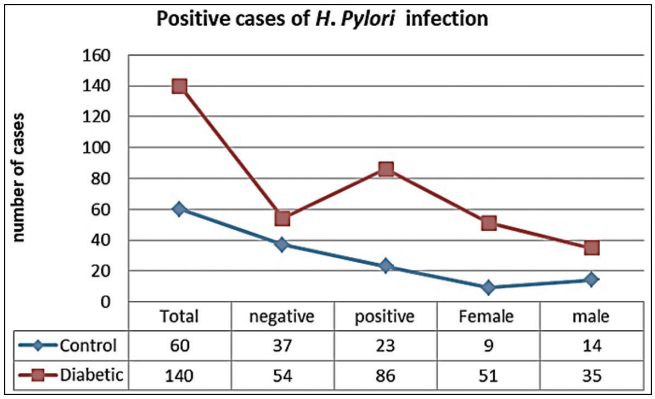

Figure 1: The number of infected samples by *H. pylori* in healthy (control) and diabetic groups. It is clear to see that the diabetes group members are more infected compared with the healthy members. Regarding the results, the infection rate was in males higher than in females in the control group, whereas it was reversed in the patient group

HLA-A and HLA-B genotyping

The results presented several HLA-alleles deviations in frequencies between patients and the control group. Because of the large number of HLA-A, HLA-B, HLA-DR, and HLA-DDQ alleles in the present study, Tables 2 and 3 included only alleles that showed significant or high variations between T1DM patients and the control group.

The results of PCR-SSO revealed a high frequency of HLA-A alleles (*3301, *3105, *1122, *0301, and *3002) in the control group compared with the patients group with a great ratio of *3301 allele (60%). Similarly, HLA-B alleles (*0826, *0412, *0206, *0708,*0801, and *3948) also recorded great frequencies in the control group [Figure 3]. The statistical analysis of HLA-A and HLA-B revealed significant differences of ($P < 0.05$) was (0–0.037) as shown in Table 2.

Genotyping HLA-DR and HLA DQ alleles

The results of PCR-SSO revealed a high frequency of HLA-DR alleles (*0701, *1101, *1107, *1109, *0459, and *0456) in the control group compared with the patients group with a great ratio of *0701 alleles (75%). Similarly, HLA-B alleles (*0604, *1359,*0730,*0630, and *0503) also recorded great frequencies in the control group, except the *0101 alleles were more frequent in patients than the control group as appeared in Figure 4. The statistical analysis of HLA-A and HLA-B showed high differences of $P < 0.05$ was 0–0.006 as shown in Table 3.

Discussion

It was reported that adult males were more likely to be infected by *H. pylori* infections as a homogenous phenomenon,[16] that is, totally agreed with our control results and what Rajesh and Reshma[17] reported in their work. The present study showed *H. pylori* infections

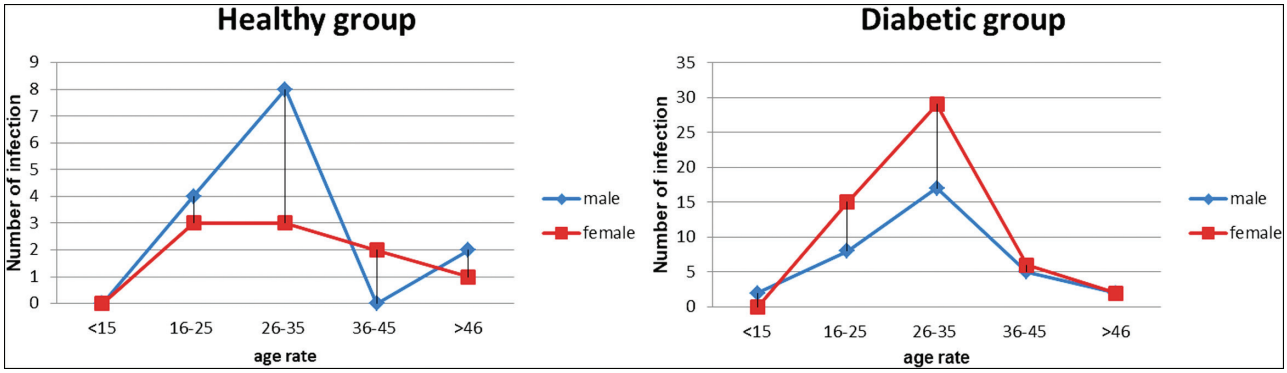

Figure 2: The peak of infection by *H. pylori* in healthy and control groups. The peak of infection was in a group of 26–35 years old in both genders. While the infection rate based on gender was variable. In the healthy group, males recorded the highest peak, whereas females were the dominant in the diabetic group at the same age period

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Table 2: Genotyping of HLA-A and HLA-B alleles of T1DM

HLA A allele	Control *N* = 23		Patients *N* = 86		χ^2	OR	EF	*P* value	HLA-B allele	Control *N* = 23		Patients *N* = 86		χ^2	OR	EF	P (Fishers Exact)
***3301**	**14**	**60%**	**4**	**5%**	**41.6**	**0.031**	**0.1**	**0**	***0826**	**8**	**35%**	**2**	**3%**	**22.9**	**0.04**	**0.06**	**0**
*3121	**0**	**0**	**4**	**5%**	**1.11**	**0**	**0.02**	**0.292**	*0103	**0**	**0**	**4**	**5%**	**1.11**	**0**	**0.02**	**0.292**
*3106	**2**	**9%**	**4**	**5%**	**0.57**	**0.51**	**0.04**	**0.450**	*0193	**6**	**26%**	**4**	**5%**	**10.01**	**0.14**	**0.06**	**0.002**
***3105**	**6**	**26%**	**4**	**5%**	**10.01**	**0.14**	**0.06**	**0.002**	*0205	**4**	**17%**	**6**	**7%**	**2.36**	**0.36**	**0.06**	**0.124**
*3027	**4**	**17%**	**6**	**7%**	**2.36**	**0.36**	**0.06**	**0.124**	*0206	**6**	**26%**	**2**	**3%**	**0.01**	**1.05**	**0.04**	**0.935**
*3020	**2**	**9%**	**4**	**5%**	**0.57**	**0.51**	**0.04**	**0.450**	*0309	**2**	**9%**	**4**	**7%**	**0.57**	**0.51**	**0.04**	**0.450**
***1122**	**4**	**17%**	**0**	**0**	**15.53**	**0**	**0.02**	**0**	***0412**	**2**	**9%**	**0**	**0**	**7.62**	**0**	**0.01**	**0.006**
*1106	**2**	**9%**	**2**	**3%**	**2.08**	**0.25**	**0.02**	**0.149**	***0708**	**4**	**17%**	**4**	**7%**	**4.33**	**0.23**	**0.05**	**0.037**
*0290	**4**	**17%**	**6**	**7%**	**3.36**	**0.36**	**0.06**	**0.124**	***0801**	**6**	**26%**	**0**	**0**	**23.74**	**0**	**0.04**	**0**
***0301**	**4**	**17%**	**2**	**3%**	**7.92**	**0.11**	**0.02**	**0.005**	*0810	**0**	**0**	**4**	**7%**	**1.11**	**0**	**0.02**	**0.292**
***3002**	**4**	**17%**	**4**	**5%**	**4.33**	**0.23**	**0.02**	**0.037**	***3948**	**8**	**35%**	**4**	**7%**	**16.82**	**0.09**	**0.07**	**0**

OR: odds ratio, EF: etiological factor, χ^2: chi-square test

Bold value form to make the recognition of alleles, which gave high frequency comparing with others, wither in healthers or patients

Table 3: Genotyping of HLA-DR and HLA-DQ alleles of T1DM

DR-allele	Control *N* = 23		Patients *N* = 86		χ^2	OR	EF	*P* (Fishers' exact)	DQ-allele	Control *N* = 23		Patients *N* = 86		χ^2	OR	EF	*P* (Fisher's exact)
***0701**	**18**	**78%**	**6**	**7%**	**53.7**	**0.02**	**0.13**	0	***0101**	**2**	**9%**	26	30%	4.41	4.55	0.15	0.036
***1101**	**14**	**60%**	**4**	**5%**	**41.6**	**0.03**	**0.1**	0	*0201	2	9%	8	9%	0.01	1.08	0.06	0.929
*0717	**2**	**9%**	**4**	**5%**	**0.57**	**0.51**	**0.04**	0.45	***0604**	**12**	**52%**	6	7%	26.89	0.07	0.1	0
*1122	**0**	**0**	**4**	**5%**	**1.11**	**0**	**0.02**	0.29	*6001	2	9%	2	3%	2.08	0.25	0.02	0.149
*1112	**2**	**9%**	**6**	**7%**	**0.08**	**0.79**	**0.05**	0.77	*1370	0	0	4	5%	1.11	0	0.02	0.292
*1107	**4**	**17%**	**2**	**3%**	**7.92**	**0.11**	**0.04**	0.005	***1359**	**6**	**26%**	4	5%	10.67	0.13	0.06	0.001
*1109	**6**	**26%**	**4**	**5%**	**10.01**	**0.14**	**0.06**	0.002	*0809	4	17%	8	9%	1.21	0.49	0.07	0.271
*0603	**4**	**17%**	**6**	**7%**	**2.36**	**0.36**	**0.06**	**0.124**	***0730**	**4**	**17%**	0	0	15.33	0	0.02	0
*0459	**2**	**9%**	**0**	**0**	**7.62**	**0**	**0.01**	**0.006**	***0630**	**6**	**26%**	2	3%	15.9	0.06	0.05	0
*0442	**0**	**0**	**6**	**7%**	**1.70**	**0**	**0.04**	**0.193**	*0503	4	17%	4	5%	4.33	0.23	0.05	0.037

OR: odds ratio, EF: etiological factor, χ^2: chi-square test

Bold value form to make the recognition of alleles, which gave high frequency comparing with others wither in heathers or patients

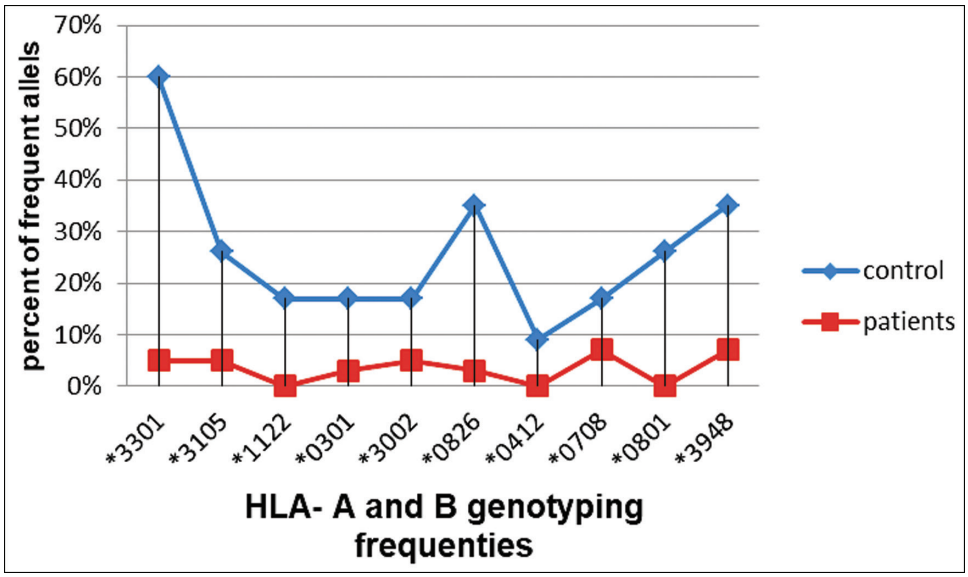

Figure 3: The peaks of some and highest frequent alleles of HLA-A and HLA-B of T1DM based on *P* value ($P < 0.05$). It is noticeable that the *3301 allele of the healthy group records a significant value within HLA-A, and *0826 and *3948 alleles of the healthy group are the highest within HLA-B in comparison with the patient's group

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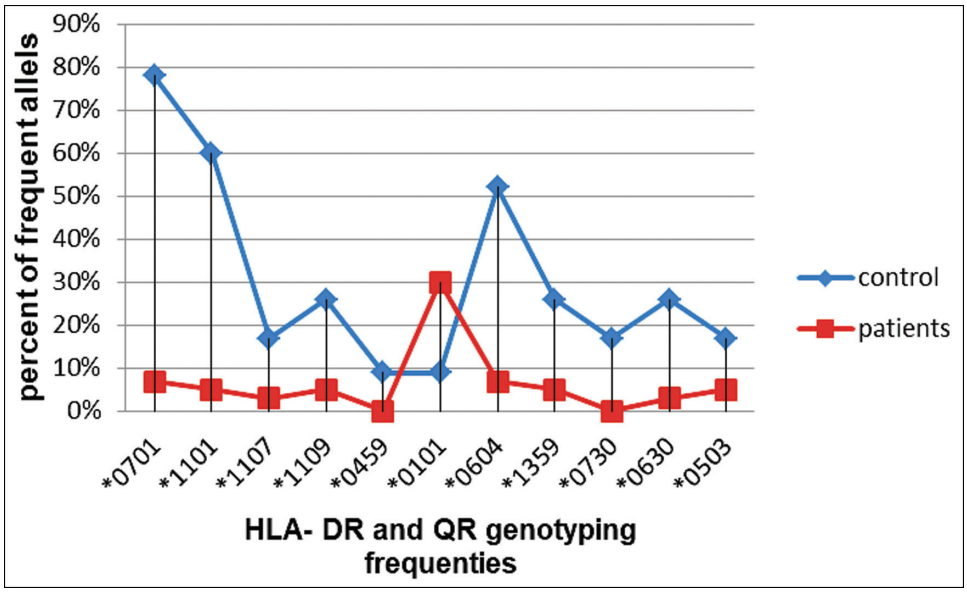

Figure 4: The peaks of some and highest frequent alleles of HLA-DR and DQ of T1DM based on *P* value ($P < 0.05$). It is obvious that *0701 and *1101 alleles of the healthy group record significant values within HLA-DR alleles, and *0604 of the healthy group is the highest within HLA-DQ in comparison with the patients group. However, *0101 of the diabetic group assigns the highest value within HLA-DQ in comparison with a healthy group

were common among females rather compared with males, especially among those who were diagnosed with diabetes. This result was compatible with Kouitcheu *et al.*[18] reported that *H. pylori* infection in diabetic females was predominant. Their finding firmly related to our statement with a probability that the glycemic status is closely related to *H. pylori* infection and gastrointestinal/gastroduodenal disorder, which is more common in females. Similarly, Agah *et al.*[19] evidenced for the first time that infected females with *H. pylori* were predominant for developing gastric cancer. However, the debate about the bond between genders and the rate of *H. pylori* infection in the level of hazard still exists.

The mean age of diabetic patients and healthy groups with *H. pylori* infection was between 26 and 35 years as those results variance with Bener *et al.*,[4] in which the 48.1 ± 7.9 years old diabetes mellitus patients were more susceptible to infection with *H. pylori* compared with 46.7 ± 5.4 years old of the nondiabetic infected subjects. However, there is no considerable difference in the ratio of *H. pylori* infection which was found in 76.7% of the diabetics in Bener *et al.*[4] compared with 61% in the present study.

Susceptibility to autoimmune DM is inherited in a polygenic fashion, until now nearly 18 IDDM genes showed involvement in the occurrence of the disease. Main histocompatibility compounds (HLA) are among the involved genes, which play a basic role.[19] In the present study, DNA genotyping techniques have been used for the identification of HLA alleles. The study was concerned with the PCR-SSO genotyping of HLA for both class I and II regions, which are located on the short arm of chromosome no. 6, and its possible association with T1DM.

The most significant allele recorded in the present study was the HLA-DQ*0101 allele, which appears in 30% of patient samples compared with just 9% frequency in healthy samples with a *P* value of 0,036, which could be considered as a predisposing allele for TIDM or as a risk factor.

The current research revealed that the HLA-A*3301 allele recorded a high frequency in the control group in 60% of cases compared with that of 41.6 in the patient's group with a *P* value of 0 revealed high variance between the two groups, and this may be explained as a prophylactic factor providing protection and resistance allele against TIDM. *3105, *1122, *0301, and *3002 were the same for these alleles but with lower incidence of variation and lower *P* value in the HLA-B *0826 alleles were higher in healthy control than with patients. With 35% frequency in the healthy compared with 3% in diabetic patients *P* valueof 0 (highly significant value). These results are at variance with other results conducted by Noble *et al.*[20] pointed out that the most significantly T1DM-associated alleles were B*5701, B*3906, A*2402, and A*0201 (as predisposing and risk factors), whereas they observed that A*1101, A*3201, A*6601, B*0702, B*4403, B*3502, C*1601, and C*0401 were significantly decreasing in patients (as protective factors).

Among the DRB1and DQB1 alleles, the present study observed that the DR*0701, DR*1101, DQ*0101, and 0604,*1359,*0730,*0630,*0503 alleles were frequent in the control group, and considered as protective factors.

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However, the frequency of DR*1101, 1107, 1109,*0459, and DR*0701 alleles was statistically significant as protective alleles as their frequency in the control group is higher. This result was in line with similar findings in Iraq[21] and in other ethnic groups.[22,23] These alleles are reported to be the risk genes among T1DM Iraqi patients, similar to those from Asian populations.[24] This was unlike findings in Japanese and Caucasian populations,[25,26] in whom DRB1*0401-DQB1*0302 was the most significant susceptibility heliotype. Shawkatova *et al.*[27] referred to that the DQB1*0302 and DQB1*0201 alleles are associated strongly with the disease development in his Slovakian study; meanwhile, they also observed that the DQB1*0602 and DQB1*0301 alleles as a defense marker. On the other hand, Saruhan-Direskeneli *et al.*[28] noticed that the Turkish patients with T1DM showed a high frequency of DQB1*0302 and DQB1*0201 alleles, whereas DQB1*0503 and DQB1*0601 alleles appeared negatively associated with the disease. In 2010, a study of HLA-typing using PCR/SSP discovered a decent association of heterozygote DQ*0203 with T1DM technique in Saudi patients.[29] In addition, the frequencies of DRB1*0701, DRB1*1101, and DQB1*0604 in our study were significantly decreased in patients compared with healthy control, which may confer a protective role in healthy individuals. This finding was comparable with other findings reported by the inheritance of both risk and protective alleles will result in disease protection or will become a neutral gene.[30]

Conclusion

Gender and age factors play an important role in increasing the rate of *H. pylori* infection. It was confirmed in this study that young people are more susceptible to infection than other ages, especially, at the age of 26–35 years old. In addition, diabetic women of the same age are more susceptible to infection than males. The variation in types of alleles associated with diabetes mellitus in several studies all over the world could be due to ethnic factors as ethnicity plays a crucial role in HLA types in addition to the size of the population and many other factors. The great frequencies of HLA-DQB1*0101 alleles could be a risk factor for type-1diabetes mellitus patients, while HLA-A*3301,*1122 B*0826,*3948, DRB1*0701, *1101, and HLA-DQB1-*0604,*630,*730 alleles of the same group could be a protective factor due to their low frequencies.

Author contributions

Samir S. Aljawahiry did the study conception, design, and monitoring of the experiments. Naer Abdulbari Alkaabawi did all preparations for sample collection, the laboratory works involving the molecular part. Alaa A. Jawad prepared and read the molecular part of the laboratory work, interpreted the data, and revised the final version of this paper.

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Conflicts of interest

There are no conflicts of interest.

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