The Influence of IL-1B Gene Polymorphisms on H. pylori Infection and Triple Treatment Response Among Jordanian Population

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Background: Helicobacter pylori (H. pylori) is considered the main cause of gastritis, peptic ulcer and gastric carcinoma in the human populations. H. pylori infection influences the secretion level of several proinflammatory cytokines including IL-1β, which encoded by the IL-1B gene.

Objective: The current study aimed to investigate whether IL-1B gene polymorphisms are associated with H. pylori infection among the Jordanian population and responses to triple therapy.

Subjects and Methods: The gastroscopic examination was performed on 412 subjects for H. pylori infection diagnosis, 257 subjects were found to be infected by H. Pylori (positive cases), whereas 155 subjects were uninfected (negative controls). The IL-1B gene T-31C and C3954T polymorphisms were genotyped by PCR-RFLP.

Results: It was found that the T-31C polymorphism has a significant association with H. pylori infection (P<0.05), and the TT genotype frequency was significantly higher in infected subjects (50.2%) compared to controls (38.7%). On the other hand, no significant association was detected between C3954T SNPs and H. pylori infection among the Jordanian population. In addition, none of the examined polymorphisms were found to influence the responses to triple therapy.

Conclusion: The IL-1B gene T-31C SNP might be associated with an enhanced risk of H. pylori infection among the Jordanian population.

Keywords: IL1B gene, IL-1β, single nucleotide polymorphism, Helicobacter pylori, interleukins

Introduction

One of the main risk factors in human gastrointestinal diseases is Helicobacter pylori (H. pylori), which is gram-negative microaerophiles human pathogen bacteria. Different gastrointestinal diseases such as chronic gastritis, peptic ulcer, and gastric carcinoma have been linked to H. pylori infection.1,2 A strong association was found between H. pylori and the host immune system during progress of gastrointestinal diseases,3 where H. pylori induces the production of many proinflammatory cytokines, such as interleukin 1 beta (IL-1β), interleukin 10 (IL-10) and tumor necrosis factor-alpha.4

It has been found that certain polymorphisms have an impact on the secretion levels of these cytokines, such as IL-1β, which is encoded by IL-1B gene on the long arm of chromosome 2 at band q13.5 IL-1β is produced by activated...
macrophages as a proprotein that is proteolytically processed to its active form by caspase 1. IL-1β plays an important role as a mediator of inflammatory response and has been shown to be involved in cell proliferation, differentiation, and apoptosis. It was also shown to be a vital pro-inflammatory cytokine in the pathogenesis of H. pylori associated gastrointestinal diseases. Two key single nucleotide polymorphisms (SNPs) were detected in the IL-1B gene (IL-1B T-31C and IL-1B C3954T), where they were shown to reduce the IL-1B gene expression levels. Consequently, reduced IL-1β levels decrease gastric acid secretion, which provides a proper environment for H. pylori to provoke an infection in the human stomach. The correlation between IL-1B promoter polymorphisms and H. pylori infection has been studied previously in populations such as Turkish, Brazilian, and Italian. For example, in meta-analysis studies, a strong synergistic interaction between IL-1β polymorphisms and H. pylori infection in the development of gastric cancer was detected. In addition, an association between IL-1β polymorphisms and H. pylori infection was reported in Asian, European, and Latin American populations. Polymorphisms in IL-1B have also been shown to influence the responses to H. pylori triple therapy in different populations including American, Japanese, and Korean. However, no association between IL-1B and response to triple therapy was detected among the Chinese population. Thus, the association between IL-1B and H. pylori infection/response to triple treatment could be population-specific and affected by the genetic background of the individual. Therefore, in the current study, the impact of IL-1β on H. pylori infection and its eradication by triple therapy were examined in the Jordanian population.

Subjects and Methods

Subjects

The study participants were adult patients who underwent a gastroscopic examination at King Abdullah University Hospital (KAUH) for suspected H. pylori infection. Inclusion criteria were patients diagnosed with non-ulcer dyspepsia in the gastroscopy examination with normal finding/mild gastritis. Exclusion criteria were individuals who had gastric surgery or were under medications of anticoagulants, antibiotics, and proton pump inhibitors. This study procedure was conducted in accordance with the Declaration of Helsinki. The IRB of Jordan University of Science and Technology approved the study (approval ID number: 16/6/14/3141). Written informed consent was obtained from all participants according to the IRB regulations. Of the invited subjects, 412 agreed to participate from which 257 subjects were found to be H. pylori positive (cases). The rest 155 patients were found to be H. pylori negative and were considered as control group. Demographics of the participants and medical information were obtained using a structured form and medical files.

Diagnosis of H. pylori Infection

To diagnose H. pylori infection, biopsy samples from the gastric antrum were obtained from all participants by an expert physician. Biopsy samples were directly sent to the pathological examination to diagnose H. pylori infection. In brief, samples were stained using Harris’ hematoxylin-eosin and Giemsa staining as previously described. Stained sections were evaluated for the presence of H. pylori infection by two experts under the oil immersion objective (1,000×). Positive diagnosis of H. pylori was reported for cases that showed typical H. pylori morphology (comma/S-shaped bacilli of 2 to 4 μm long and 0.5 to 1 μm thick) attached to the surface of the cells or free in the mucous layer, and forming small colonies for the least. Otherwise, the diagnosis was considered negative. To validate the result, a positive control tissue and a negative control tissue were included with every run.

Therapeutic Regimens

Patients who participated in the study were revisited after taking their standard H. pylori eradication therapy as per hospital procedures. The used triple eradication therapy consisted of clarithromycin 500 mg twice daily, amoxicillin 1g twice daily, and PPIs twice daily, for 14 days. Responsiveness to therapy was defined as improvement in clinical symptoms and reduction in IgG serum levels 3 months after treatment, which are considered as alternative less invasive methods for detection of responsiveness of treatment compared to endoscopy.

Isolation of Genomic DNA

DNA was isolated from whole blood (collected in EDTA tubes) using a Promega kit (Madison, USA) according to the manufacturer’s instructions. The quality and quantity of isolated DNA were evaluated using a Bio-Rad
SmartSpect_3000 instrument (Hertfordshire, UK). Samples were stored at -20°C until used for the genotyping of IL-1B SNPs.

Genotyping of IL-1B Polymorphisms

The IL-1B T-31C and C3954T polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP) as previously described.\textsuperscript{41-43} The PCR reaction was done using Eppendorf thermocycler (Hamburg, Germany). Amplification was performed in 0.2 µL PCR tubes containing 50 ng of DNA, 1 μ of each primer and ready to use PCR master mix obtained from Promega (Madison, USA). Table 1 shows primer used, PCR conditions and restriction conditions. Digestion of the PCR products of the IL-1B T-31C and C3954T polymorphisms was mediated by the AluI and Taq I restriction enzymes (New England Biolabs, Beverly, CA, USA) respectively. The restriction reaction contained 10 µg of the PCR, 10 units of the restriction enzyme and appropriate amounts of deionized H₂O and the smart cut buffer (supplied with the kit). The reaction mixture was incubated in the water bath at 37°C for 16 hours. The reaction was then heat inactivated by incubation at 80°C for 20 minutes. Electrophoresis conditions were 1% TBE buffer, 2% agarose, 80 volts for 45 minutes.

Statistical Analysis

Analysis of the association between IL-1B polymorphisms and \textit{H. pylori} infection/response to triple treatment was achieved using SNPstat statistical software. G. Power version 3.0.10 was used for power analysis (Franz Faul, Universität Kiel, Kiel, Germany). Distribution of examined SNPs according to Hardy–Weinberg equilibrium was also examined using SNPstat. A \(P\) value of less than 0.05 was used to infer statistical significance.

| Parameter                  | Control Group | Cases Group |
|----------------------------|---------------|-------------|
| Mean age ± SD              | 42.6 ± 14.7   | 40.8 ± 15.2 |
| Gender (%)                 |               |             |
| Male                       | 41.3%         | 49%         |
| Female                     | 48.7%         | 51%         |
| Mean BMI ± SD              | 28.0 ± 4.51   | 28.49 ± 5.22|
| Hypertension (%)           | 16.1%         | 22.2%       |
| Diabetes mellitus          | 9.0%          | 13.6%       |
| Thyroid dysfunction        | 5.1%          | 3.5%        |
| Kidney/liver diseases      | 1.9%          | 3.1%        |

Abbreviations: SD, standard deviation; BMI, body mass index.

Results

Table 2 shows the demographics of the study subjects. The mean age of the control group was 43 years and for the cases was 41 years. Male participants represented 51.3% of the control group and 49% of the cases group. No differences in medical history and other demographics were detected between the two groups (Table 2).

The association between SNPs of the IL1B gene (C3954T and T-31C) and \textit{H. pylori} infection is shown in Table 3. A significant association between T-31C and \textit{H. pylori} infection was detected \((P<0.05)\). The frequency of the TT genotype was significantly higher in cases (50.2%) compared to controls (38.7%). Thus, homozygotes TT state was associated with higher \textit{H. pylori} infection risk compared to other genotypes. In addition, the T allele was enriched in cases (66%) compared to controls (60%). With respect to C3954T SNP, no significant association was detected with \textit{H. pylori} infection \((P>0.05\), Table 3).

Haplotype analysis of C3954T and T-31C SNPs is shown in Table 4. Among all examined haplotypes, the

**Table 1** PCR and Restriction Conditions of IL-1B Gene Polymorphisms

| Polymorphism | Primers: 5’-3’ | PCR Conditions | Restriction Conditions | Fragment Sizes |
|--------------|----------------|----------------|------------------------|----------------|
| T-31C        | F: AGA AGC TTC CAC CAA TAC TC R: ACC ACC TAG TTG TAA GGA | 35 cycles: 94°C for 30s, 61°C for 45s, 72°C for 45s | Alu I, 37°C, 16 h | C allele: 239 Tallele: 152, 87 |
| C+3954T      | F: GTT GTC ATC AGA CTT TGA CC R: TTC AGT TCA TAT GGA CCA GA | 35 cycles: 94°C for 45s, 55°C for 45s, 72°C for 45s | TaqI, 37°C, 16 h | T allele: 249 C allele:135, 114 |
Table 3 Association Between IL-1B SNPs and H. pylori Infection

| IL-1β SNP | Cases | Controls | Odds Ratio (95% CI) | P value |
|-----------|-------|----------|---------------------|---------|
| C3954T CC | 117 (46) | 55 (35) | 1.00 | — |
| CT        | 123 (48) | 90 (58) | 1.12 (0.76–1.62) | 0.37 |
| TT        | 17 (7) | 10 (6) | 1.38 (0.54–3.60) | 0.50 |
| Allele C  | 357 (69) | 200 (65) | — | — |
| Allele T  | 157 (31) | 110 (35) | — | — |

Table 4 Analysis of IL-1B Haplotypes of the Examined Polymorphisms

| Haplotype | Cases | Controls | Odds Ratio (95% CI) | P value |
|-----------|-------|----------|---------------------|---------|
| CC        | 57 (28) | 24 (13) | 1.38 (0.54–3.60) | 0.50 |
| CT        | 14 (7) | 10 (5) | 1.00 | — |
| TT        | 14 (7) | 10 (5) | 1.00 | — |
| Allele C  | 80 (43) | 45 (25) | — | — |
| Allele T  | 40 (22) | 25 (14) | — | — |

Abbreviation: CI, confidence interval.

The TC haplotype was present in 2.58% of cases compared to 8.62% of controls (P < 0.005). Thus, TC haplotype seems to lower the risk of H. pylori infection. No significant association between the rest of the haplotype and H. pylori infection was observed (P > 0.05) (Table 4).

Among the 257 patients, 41 patients showed resistance to triple therapy (resistance rate of 16%). The IL-1B C3954T and T-31C SNPs were tested for their association with triple therapy response (Table 5). The results showed no association between examined SNPs and response to triple therapy (P > 0.05). In addition, none of the haplotypes were associated with response to triple therapy (data not shown). Thus, IL-1B SNPs might not be associated with response to triple therapy treatment of H. pylori infection among Jordanians.

Discussion

The aim of the study is to assess whether there is an association between IL-1B gene polymorphisms and H. pylori infection in the Jordanian population. Current data revealed a significant association between IL-1B - T-31C genetic polymorphism and H. pylori infection. The TT genotype was higher in H. pylori positive subjects compared to the control ones.

The study findings are consistent with previous studies that reported a role for IL-1B-C31T SNP in the development of H. pylori-related diseases, particularly gastrroduodenal diseases. Similarly, IL-1B T-31C has a significant association with H. pylori infection among Uzbek population. In a case–control study among the Chinese population that was conducted on 392 patients, an association between IL-1B T-31C and gastric cancer was reported, which further augmented by H. pylori. In the Brazilian population, a strong association was found between IL-1B T-31C and gastric cancer was reported, which further augmented by H. pylori.

Table 5 IL-1B SNPs Association with Triple Therapy Response

| IL-1β SNP | Resistance to Triple Therapy | Responsive to Triple Therapy | Odds Ratio (95% CI) | P-value |
|-----------|-----------------------------|-----------------------------|---------------------|---------|
| CC        | 19 (46) | 98 (46) | 1.00 | — |
| CT        | 19 (46) | 104 (46) | 1.06 (0.53–2.12) | 0.97 |
| TT        | 3 (7) | 14 (6) | 0.90 (0.24–3.46) | 0.33 |

Abbreviation: CI, confidence interval.

The mechanism by which IL-1B T-31C polymorphism might modulate H. pylori infection needs to be investigated. This might involve changes in IL-1B protein level in the gastric epithelium and the subsequent modulation of gastric acid secretion.

The clinical significance of IL-1B T-31C polymorphism in the modulation of infection risk has been examined in several studies. For example, the TT genotype at IL-1B-31 has been showed to increase the risk of chronic HBV infection.

Our haplotype analysis of T-31C and C3954T SNPs showed that the frequency of TC haplotype was lower in cases than in controls, which indicate that TC haplotype might reduce the risk of H. pylori infection among Jordanian population. More studies are required to confirm the present findings.

Among all patients, only a small number (16%) showed resistance to H. pylori triple therapy, and current results did not show any association between response to...
triple therapy, and IL-1B SNPs/haplotypes. The role of IL-1B polymorphisms in H. pylori eradication has been studied in different populations and came up with controversial findings. For example, in Japanese population, IL-1B polymorphisms were found to influence triple therapy of H. pylori infection. However, no effect for IL-1B polymorphisms was detected on the eradication of H. pylori in the Chinese population. Thus, H. pylori eradication might be influenced by different factors, such as lifestyle behavior, bacterial resistance to antibiotics, treatment adherence, and bacterial virulence factors. This might explain the reason for the inconsistency observed in the different studies.

In conclusion, current results indicated that the IL-1B T-31C polymorphism was significantly correlated to H. pylori infection among Jordanian, while no association was detected between H. pylori infection and IL-1B C3954T polymorphism. Examining other cytokine polymorphisms such as IL-8 SNPs that previously has been reported to associate with H. pylori infection is strongly recommended in future studies.

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Disclosure
The authors report no conflicts of interest in this work.

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