

ORIGINAL ARTICLE

γ H2AX as an Indicator for DNA Double-Strand Breaks in *Helicobacter pylori*-Associated Chronic Gastritis among Jordanian Patients: A Retrospective Study

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Abstract

Background and Aims: Serine 139 phosphorylation of H2AX (γ H2AX) is a biomarker for an early response to DNA double-strand breaks (DSB) and to monitor DNA damage and resolution. This study aimed to quantify γ H2AX expression levels associated with *H. pylori* infection in Jordanian patients with chronic gastritis.

Materials and Methods: A retrospective case-control study was designed to evaluate the rate of γ H2AX expression in the epithelium of gastric tissue in subjects chronically infected with *H. pylori*. A total of 75 gastric biopsy samples embedded in paraffin were chosen from the library, including 50 samples with chronic *H. pylori* infection and 25 negative samples for *H. pylori* and any other gastric pathologies. PCR and immunohistochemistry were used to confirm the diagnosis of *H. pylori*-infected and noninfected gastric biopsies, and the rate of γ H2AX formation was analyzed in the mucosa using immunohistochemical staining analyses.

Results: PCR and immunohistochemistry proved *H. pylori* infection in the gastric biopsies of diseased patients (n = 50) and the absence of *H. pylori* infection in negative samples (n = 25). A strong nuclear signal of γ H2AX was detected in the positive samples using immunohistochemistry compared to the undetected signal in the noninfected samples of the gastric mucosa.

Conclusion: Our findings show that *H. pylori* infection is accompanied with high levels of DSBs. This may play a role in the increased risk for tumor initiation associated with *H. pylori* carriage.

Keywords: *Helicobacter pylori*, double strand break (DSB), DNA lesions, γ H2AX, chronic inflammation, transformation

INTRODUCTION

Ionizing radiation (IR), ultraviolet light, certain chemical agents, and infectious agents are frequently associated with the alteration in the integrity of DNA, particularly DNA double-strand breaks

(DSBs) (1-3). Infectious agents that might potentiate cellular transformation and oncogenesis are associated with the induction of DSB; hepatitis B and C, *Human papillomavirus* (HPV), *Chlamydia trachomatis* (Ctr), and *Helicobacter pylori* (*H. pylori*) are strongly associated with

hepatocellular carcinoma, cervical cancer, cervical and ovarian cancer, and gastric cancer, respectively (2, 4). Contrary to other DNA lesions, DSBs are difficult to repair and its improper fixation can result in an accumulation of mutations, which might ultimately lead to the development of cancers (1, 5).

H. pylori is a spiral shaped Gram-negative microaerophile pathogen that inhabits and infects the stomach (6, 7). It infects 50% of the world's population, causing asymptomatic gastritis in 85% of cases, peptic ulcers in 15%, and gastric carcinoma in less than 1% of cases; outcomes of the bacterium infections that are determined by the interaction between different *H. pylori* strains and their virulence factors, host DNA, and environmental factors (8, 9). The establishment of infections and their maintenance is achieved via virulence factors including the cytotoxin-associated gene A (CagA) and the vacuolating toxin gene (Vac-A) (7, 10-12). Remarkably, *H. pylori* infection is associated with damage of the genetic material either through the direct effect of the bacterial virulence factors or indirectly due to the stimulation of the inflammatory immune response (13-15). Cag-A acts by subverting the cellular signaling pathways, inducing the inflammatory immune response, and mediating epigenetic changes (11, 16), while the Vac-A gene exerts its toxicity on the host cell by the formation of vacuoles inside the cell (12). It was confirmed that Cag-A positive strains can activate neutrophils and macrophages, which can lead to the release of proinflammatory cytokines (e.g. TNF- α , IL-1 β , and IL-8), the release of reactive oxygen species, and nitric oxide (4, 10, 15). Such chemicals can attack the host cell DNA, leading to altered DNA base pairing, blocking DNA transcription and replication, and triggering oxidative stress

leading to genetic instability (17) implicated in DNA single-strand breaks (SSBs) and DSBs (4, 10, 15).

In response to DSBs, infected cells initiate a complex DNA damage repair (DDR) cascade (18) that is regulated by different key proteins, including ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) proteins. They mediate the H2AX histone phosphorylation at ser 139 to form γ H2AX (19). γ H2AX acts as a signal to recruit proteins such as the tumor suppressor p53 that have a role in DNA integrity and repair through the activation of ChK1 and ChK2 transducers inducing cell cycle arrest or apoptosis (20-22). Therefore, γ H2AX is considered a biomarker on DSBs, and its level is correlated with DNA damage and repair. In practice, γ H2AX is widely used as an indication of DNA lesions due to the genotoxicity of chemicals and radiation exposure, as well as a bio-dosimeter for tumor radio- and chemotherapy treatment efficacy (23). The present study is the first work aimed to evaluate the degree of DNA damage in nonmalignant chronic gastritis biopsy samples and associate its occurrence with *H. pylori* infection among Jordanian patients.

MATERIALS AND METHODS

Sample collection

A sum of 75 formaldehyde-fixed paraffin-embedded (FFPE) gastric biopsies were collected from the antrum region, 25 control samples (15 males and 10 females) with negative to *H. pylori* and 50 samples (35 males and 15 females) from patients with chronic *H. pylori* pangastritis).

Samples were collected from the library of two referral hospitals in the middle and the Northern parts of Jordan including the King Hussein Medical City and Al-Karak

Governmental Hospital respectively. The inclusion criteria for gastritis were the age range between 15 to 80 years and the confirmed *H. pylori*-infected gastric glands from the histopathology reports of the selected samples. In addition to that, samples were selected from those collected between 2015 and 2017. All samples with a history of antibiotic therapy during the last three months before the study and any gastric abnormalities including surgery and malignancy were excluded from the study. Patient records indicated symptoms such as vomiting, dysphagia, and epigastric pain. The control samples were selected based on the absence of *H. pylori* infection and any other gastric pathologies.

Detection of *H. pylori* by histological examination

Samples that were fixed in 10% formaldehyde and embedded in paraffin wax were sectioned into 4 μ m thickness using a microtome (Leica, Germany). The sections were routinely stained with hematoxylin and eosin and were diagnosed by the pathologists in the departments.

***H. pylori* detection by polymerase chain reaction (PCR)**

Genomic DNA from all samples was extracted and purified using QIAamp DNA FFPE Tissue Kit (Qiagen, Cat Number 56404) and according to the manufacturer's instructions. Briefly, After removing paraffin from sections using xylene, samples were incubated with lysis buffer along with Proteinase K. The lysate is then applied to the elution column to bind DNA. The column was washed two times to remove cellular debris and proteins. Finally, DNA was eluted

from the column using high purified elution buffer and stored at -20 °C for further analysis. Infections with *H. pylori* were confirmed by detecting the 150 bp fragment 16S rRNA product specific for bacterium species using PCR (Applied Biosystems thermal cycler, USA). The Forward and the reverse primers used in the PCR reaction are 5'-GAAGATAATGACGGTATCTAAC-3' and 5'-ATTTCACACCTGACTGACTAT-3' respectively. The final volume of 25 μ l PCR reaction included 12.5 μ l master mix (Thermo Scientific, USA, Cat Number k0171), 3 μ l of DNA with a total concentration of 80 ng, 1 μ l of each primer, and water to complete the remaining volume. The amplification protocol including an initial denaturation step at 98 °C for 30 sec, 40 cycles of denaturation at 98°C for 7 sec, annealing at 57 °C for 30 sec, and extension at 72 °C for 30 sec with a final extension cycle at 72 °C for 7 min. The DNA bands were pictured using the Thermo Fischer Scientific gel documentation system. *H. pylori* strain P12 was used as a positive control.

Detection of γ H2AX and *H. pylori* urease by immunohistochemistry

The γ H2AX as an indicator of DNA damage and *H. pylori* urease stained for marker and bacteria using immunohistochemistry as described elsewhere (24). Xylene was used to deparaffinize the tissue sections and graded series of ethanol (100, 95 and 85%) were used for rehydration. The antigens were recovered from tissues using the antigen retrieval buffer (Dako, USA) after heating at 95°C for 15 min. Using 3% hydrogen peroxide, the tissue peroxidase activity was blocked for 30 min incubation at room temperature. After that, tissue samples were blocked in 1% bovine serum albumin in

phosphate buffer saline for 1 hour at room temperature. Primary antibodies including mouse Anti- Phospho-Histone- γ H2AX Antibody (Ser 139) (Sc-517348, Santa cruz, USA), polyclonal rabbit anti-*H. pylori* urease antibody (sc21016, Santa Cruz, USA), and the white DNA staining 4',6-Diamidino-2-phenylindole dihydrochloride (DAPI) (Sigma-Aldrich) were incubated with tissue samples for two hours at room temperature.

The primary antibodies were used at 1:100 dilutions. The primary antibody-labeled tissues were washed with PBS and treated for 60 min at RT with secondary fluorescent anti-rabbit Cy3 labeled (Red) (Goat, 1:100, Jackson Immuno Research Laboratories) and Anti-mouse Cy2 labeled (green) (Goat, 1:100, Jackson Immuno Research Laboratories) antibodies diluted in 1% BSA.

RESULTS

Confirming *H. pylori* infection in gastric biopsies using PCR.

H. pylori infection in the histopathologically diagnosed biopsies was confirmed using PCR with specific primers to the bacterial 16S rRNA gene (Figure 1). All biopsies from chronic *H. pylori* pangastritis patients revealed the presence of 150 bp fragments specific products for the *H. pylori* 16S rRNA gene (n=50). Meanwhile, all control samples were negative for *H. pylori* DNA.

γ H2AX expression levels in *H. pylori* positive and control tissue samples.

Fluorescence immunohistochemistry analysis revealed a strong signal of γ H2AX in the gastric gland epithelial cells from patients with confirmed *H. pylori* infections (Figure 2a). In contrast, none of the control cells showed signals for γ H2AX irrespective

of sectioning sites (Figure 2b). Intriguingly, quantification of fluorescence signal intensity verified that the γ H2AX signal was localized to the nuclei of infected cells with significant levels compared to the undetectable γ H2AX signal in negative control gastric biopsy specimens (Figure 3).

DISCUSSION:

H. pylori infection has been associated with DNA damage in various studies. Several mechanisms have been proposed for how *H. pylori* can cause DNA damage. One mechanism is through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by the bacteria (25). These molecules can damage DNA and other cellular components, leading to mutations and other genetic changes. Another mechanism is through the activation of host immune cells, which can also produce ROS and RNS in response to *H. pylori* infection (25). The immune response can also cause chronic inflammation, which can contribute to DNA damage. Several studies have found evidence of DNA damage in individuals with *H. pylori* infection (26). Overall, while the exact mechanisms by which *H. pylori* causes DNA damage are still being studied, there is evidence to suggest that this infection can contribute to genetic changes that may increase the risk of developing gastric cancer.

Cancer as a leading cause of death worldwide, has been associated with the malfunctioning of the host cell genome (27). In addition to gastric cancer, many cancers are generally associated with chronic pathogenic infections to the other where inflammation and direct DNA damage may be critical events that promote carcinogenesis (28). In contrast to the well-established relationship between viral infections and carcinogenesis, bacterial

infections are still controversial, in the development of human cancer (27, 29). Different molecular and epidemiological studies implicated bacterial infections with carcinogenesis (28). In particular, *H. pylori* has been demonstrated as an etiological agent of gastric cancer in 1% of infected people (1, 7). Besides environmental, diet and host genetic factors, different mechanisms have implicated *H. pylori* in gastric cancer including virulence factors as CagA and VacA that activate cellular proliferation, alterations in protooncogenes and tumor suppressor genes, inflammation processes, and DNA damage (7, 20, 21, 26). DNA damage predisposes the cell's genetic material to instability and formation of DSBs; unrepaired DSBs might lead to cellular transformation and tumorigenesis. Hence, human DNA repair machinery is a very important barrier against human malignancies (2). *H. pylori* infections are considered strong causes of DSBs with only 15% of the infected people developing a peptic ulcer and fortunately less than 1% developing gastric carcinoma (1). The tumorigenic outcome of *H. pylori* infections is either due to the direct effect of the bacterial toxins or indirectly due to the inflammation process which is accompanied by genomic instability; approximately 25% of all malignancies are attributed to inflammation (6, 8, 10-12). Likewise, to *H. pylori*, other pathogens contribute to DSBs as a result of the induction of the inflammatory pathways. *Salmonella enterica* serovar Typhi and *Bacteroides fragilis* are associated with carcinoma of the gallbladder and colon, respectively (13, 16, 30). Worth noting, several intracellular bacterial pathogens including *C. trachomatis* and *Listeria monocytogenes* also implicated in DSBs through the stimulation of reactive oxygen species release and the inhibition of the

downstream repair checkpoint (4, 17). Such genomic instability associated with infection is characterized by continuous DNA damage and repair subsequently triggering the DNA damage response (DDR) (6). In addition, mammalian cells infected with *E. coli*, producing cytolethal distending and colibactin toxins, have been shown to activate the classical DDR (14, 15). The DDR induces a series of proteins including the production of γ H2AX as a marker of DNA damage by histone H2AX modification at Ser 139 (18, 19). One important tumor suppressor gene associated with DDR and downregulated upon γ H2AX activation is p53 which might induce cell cycle arrest or induce apoptosis if the DNA damage is irreparable (20-22).

The level of expression of γ H2AX in *H. pylori*-infected cells detected herein was in line with and confirmed our previous findings where p53 protein expression was significantly downregulated in gastric mucosa upon *H. pylori* infection and increasing the risk for transformation associated with *H. pylori* infection (20). In this study, the expression of γ H2AX was found to be significantly high in the infected gastric biopsies compared to the undetectable signal in the control biopsies which appeared to be correlated with *H. pylori* infection. The loss of p53 and the detection of nuclear γ H2AX signal set the cells in high stress that might play a role in malignant transformation. It has been demonstrated that DSBs was induced by *H. pylori* in gastric epithelial cells *in vitro*, which can be counteracted by lycopene (21, 22). The mechanisms by which *H. pylori* induces DSBs include the chromosomal ends alteration resulting in telomeres loss and chromosomal instability leading to gastric carcinogenesis (31). These alterations were associated with the inhibition of the DDR due

to *H. pylori*; it inhibits recruiting several factors involved in nonhomologous end-joining and homologous recombination repair systems, such as ATR, MRE11, and NBS1 (31). Furthermore, chronic infection with *H. pylori* also alters two DNA repair mechanisms including mismatch repair and base excision repair (16).

CONCLUSION

DSBs and elevation of γ H2AX levels are associated with *H. pylori* infection which considered an early molecular event in gastric malignancies might play a significant role in gastric carcinoma development beside

other predisposing factors such as environmental and genetics factors. The expression γ H2AX and recruiting DDR proteins contribute to promoting host cell viability during infection and have a role in infection persistence (32). Despite the process by which DSBs are induced by *H. pylori* infection remains unclear, the expression of γ H2AX may be used as an important marker for the diagnosis and prognosis of gastric malignancies. Further investigations are recommended to reveal the mechanism by which *H. pylori*-induced DSBs might take place in gastric cells among Jordanian patients and how it combines impaired repair and prosurvival signaling.

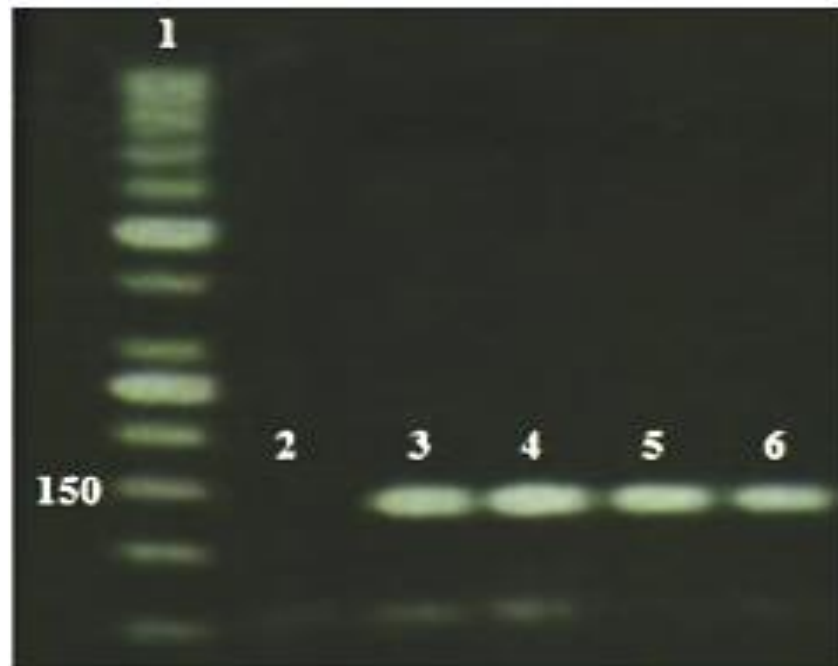


Figure 1: 16S rRNA Gel electrophoresis of *H. pylori* from the gastric biopsy samples. Lane 1: 150 bp DNA ladder, lane 2: negative control, lane 3: positive control, lane 4 to 6: representative gastric biopsy samples. PCR: polymerase chain reaction, bp: base pair.

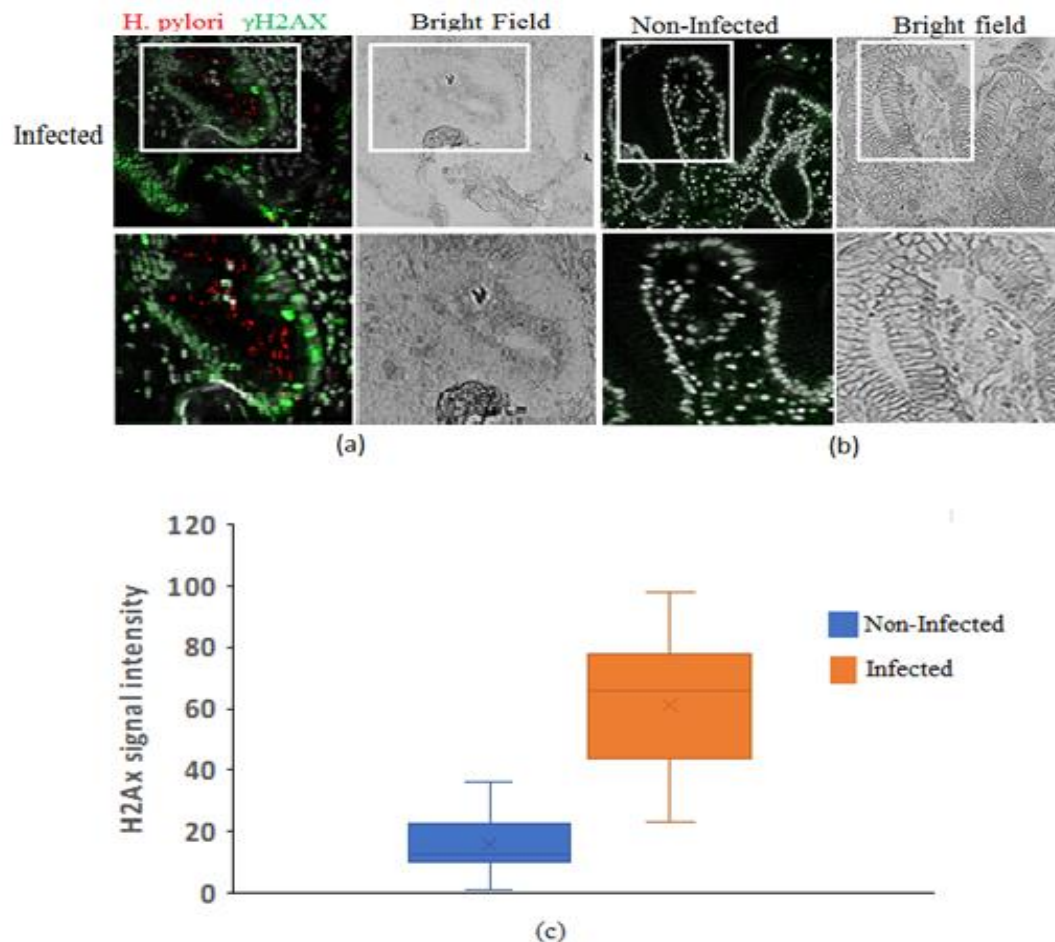


Figure 2: γ H2AX levels in *H. pylori*-infected and noninfected gastric glands. (a) Significant γ H2AX (green) expression signal localized in the nuclei of the infected gastric glands. DAPI (white) was used for DNA staining. (b) Negative control gastric biopsy specimens exhibiting negative nuclear γ H2AX signal. (c) Quantification of γ H2AX intensities in gastric samples revealed increased γ H2AX signal in the mucosal cells in infected samples compared to the undetectable signal in the negative control gastric biopsy specimens. Mean pixel intensities of γ H2AX per nucleus were quantified from confocal images with Image J.

Conflict of interest

The authors declared that they have no competing interest.

Authors' contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Ethics statement

Ethical approval to conduct the present study was obtained from the ethics committee of the Faculty of Medicine, University of Mutah. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed consent

Not applicable

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γH2AX كمؤشر لتكسر الحمض النووي المزدوج في التهاب المعدة المزمن المصاب بـ بكتيريا هيليكوباكتر بيلوري بين المرضى الأردنيين: دراسة استرجاعية

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الملخص

الخلفية والأهداف: يعد فسفرة سيرين 139 H2AX (γH2AX) علامة حيوية للاستجابة المبكرة لكسر الشريط المزدوج (DSB) ولرصد تلف الحمض النووي وحله. هدفت هذه الدراسة إلى قياس معدل تعبير γH2AX المرتبط بعدوى الملوية البوابية لدى المرضى الأردنيين المصابين بالتهاب المعدة المزمن.

المواد والطرق: تم تصميم دراسة الحالات والشواهد بأثر رجعي لتقييم معدل تعبير γH2AX في ظاهرة أنسجة المعدة في الأشخاص المصابين بشكل مزمن بالبكتيريا الحلزونية. تم اختيار ما مجموعه 75 عينة من خزعة المعدة المضمنة في البارافين من المكتبة، بما في ذلك 50 عينة مصابة بالعدوى المزمنة بالبكتيريا الحلزونية و 25 عينة سلبية للبكتيريا الحلزونية وأي أمراض معدية أخرى. تم استخدام PCR والكيمياء المناعية لتأكيد تشخيص خزعات المعدة المصابة وغير المصابة ببكتيريا الملوية البوابية، وتم تحليل معدل تكوين γH2AX في الغشاء المخاطي باستخدام تحليلات تلطيخ كيميائي مناعي.

النتائج: أثبت PCR والكيمياء المناعية الإصابة بالبكتيريا الحلزونية في خزعات المعدة للمرضى المصابين (ن = 50) وغياب عدوى الملوية البوابية في العينات السلبية (ن = 25). تم اكتشاف إشارة نووية قوية لـ γH2AX في العينات الإيجابية باستخدام الكيمياء المناعية مقارنة بالإشارة غير المكتشفة في العينات غير المصابة من الغشاء المخاطي في المعدة.

الخلاصة: تظهر النتائج التي توصلنا إليها أن عدوى الملوية البوابية تكون مصحوبة بمستويات عالية من DSBs. قد يلعب هذا دوراً في زيادة خطر بدء الورم المرتبط بنقل الملوية البوابية.

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