

# Helicobacter Pylori-induced Chronic Inflammation Leading to Gastric Mucosal Erosions in Pakistani Citizens

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## ABSTRACT

**Aim:** To know the underlying processes by this causative organism inflicts damage to the mucosa of the stomach.

**Methods:** This descriptive cross sectional research work was conducted on three hundred individuals with clinical presentation of gastropathy who report in OPDs of Quetta, Rahim Yar Khan and Sahiwal from March 2014 to July 2016. From eighteen patients we got gastric biopsy specimens with chronic gastropathy resulting from Helicobacter pylori infection.

**Results:** The analysis of gastric biopsy depicted elevated protein complex that controls transcription of DNA, cytokines production and cell survival (NF- $\kappa$ B) with superoxide dismutase activities enhanced display of Poly ADP Ribose Polymerase-1 (PARP-1) and a marker for DNA damage or DNA damage response (H2AX). After recommended regime of drugs to eradicate Helicobacter pylori, analysis of gastric biopsy showed standard parameters of NF- $\kappa$ B with superoxide dismutase activities enhanced display of PARP-1 and gH2AX. That proved possible cause of gastropathy may be oxidative DNA insult and elevated parameters of poly ADP ribosepolymerase-1 (PARP-1).

**Conclusion:** This current research work recommend that in a situation where there is insult to lining epithelium of stomach, underlying cause is non-homologous end joining (NHEJ) and (ROS) Reactive oxygen species which inflicts unusual telomere end joining resulting to telomere shortening treatment.

**Keywords:** Bacterium H pylori, Nucleotide at end of chromosomes, Poly ADP ribosepolymerase-1 (PARP-1), Potentially active oxygen varieties

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## INTRODUCTION

Gastric inflammation is an invariable finding in patients infected with *H. pylori* and represents the host immune response to the organism<sup>1</sup>. The incidence of gastropathy which originates by the infectious process triggered by Helicobacter pylori (*H. pylori*) infection is quite high in moderated times because of the eatables not from natural sources but bakery items are preferred in the society today still one of prevalent infections in the world<sup>2</sup>. About 18% of the patients who receive infection due to this organism end up with the infection of the epithelium, lamina propria and muscularis also involving the submucosa ultimately results into chronicity of the gastric ulcers and the patient reports to the gastroenterologist with repetitive signs and symptoms of gastric ulcers<sup>3</sup>.

Another sequale of the infection caused by this organism is the tumour of the stomach<sup>4</sup>. Chronic infection established by *H. pylori* requires. Natural barriers which are combating the on slight of the *H. pylori* include the stomach mucosal pH of around 3<sup>5</sup>. Then very strong covalently linked components of the mucus layer of the stomach and the natural immunity

which interior of the stomach has are the defense mechanism of the stomach. Considering DNA level of the most virulent *H. pylori* strain contains the cag autogenicity location cagPAI which has power to modify "CagA" sequences of amino acids through variety number four of secretion system into damaged lining of stomach<sup>6</sup>. MAP kinase signaling happens to be introduced into damaged lining of stomach. Consequently pro-inflammatory transcription factor NF- $\kappa$ B turns potent<sup>7</sup>. In a situation when the infectious process is triggered by helictobactr pylori, connective tissue cells like macrophages, monocytes and dendritic cells engulf causative agent to produce cytokines which mediate color, rubor dolor, tumor and loss of function<sup>8</sup>. The cells of inflammation helps in recognition of helicobacter pylori by toll like receptors through lipoproteins flagellins and lipopolysaccharides but still *H Pylori* is able to destroy the innate immunity of the persons stomach and also damages the adaptive immunity which itself remains the great mystery<sup>9</sup>. One of the hypotheses in this regard is that the bacteria (*H pylori*) produces a tolerance in the toll like receptors to those bacterial antigens and also changes the nature of T cells. Different mediators are involved but it is supposed that interleukin 18 has some key role in causing the inflammation. It also produces different reactive oxygen species and nitric oxide (NO) which further causes the mucosal

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proliferation and disruption in the nuclear material of the cells.<sup>10</sup> It is also believed that enzymes that ribosylates the adenosine diphosphates has some role. Different inflammatory mediators like chemokines and cytokines, and different molecules of adhesion are activated by different transcriptional modifiers like poly ADP ribose polymerase. The telomeres which are the part of the nuclear material having a specific nucleotides sequence may get shortened by the attack of this bacteria which may restores to normal after the removal of the bacteria.

## MATERIAL AND METHODS

Three hundred patients with symptomatic acid peptic disease, received through out patients departments of Quetta, Rahim Yar Khan and Sahiwal from March 2014 to July 2016. Gastric biopsy specimens were obtained from 18 patients with chronic gastritis or peptic ulcer caused by *H. pylori* infection, nine males (age 28 to 57 years) and nine females (ages 32 to 65), who all had documented *H. pylori* infection were included for the study. Patients which were picked for the study were reported with pain in epigastric region and these patients also had different examinations like esophageal gastroduodenoscopy (EGD). Different signs of infection from helicobacter pylori were prominent in the patients who were picked for the study like regular diffused rubor or irregular reddish appearance of the mucosa. From the area of pylorus 6-8 biopsies were taken from the greater curvature of the stomach and also from the lesser curvature. The material taken from the biopsies were examined by different stains and techniques to produce the result. Drugs given for the treatment of such infected persons of Helicobacter pylorie are amoxicillin (one gram) twice a day for one week, clarithromycin (500 milligram) and nexium which is given in 40 milligrams. The infected patient needs to see the doctor one month after the treatment to confirm that the treatment was effective and the infected bacteria has been died. For this purpose there is again a need of some biopsies, the assay procedure of SOD (superoxide dismutase) to check the enzymes and another esophagogastroduodenoscopy.

The *H. pylori* cultured on chocolate agar plate at 7°C in a microaerophilic atmosphere of 10% CO<sub>2</sub> in air and 95% humidity. *H. pylori* were scraped from agar plates, washed twice with phosphate buffered saline, and resuspended in serum F12 Medium. Bacterial cells were added without use of antibiotic.

## RESULTS

The use of antibodies and other drugs in treating the helicobacter pylori results in decrease of neurofactors and decrease in PARP-1 function and hence reducing the inflammatory response of the tissue.

The neurofactors (NF- $\kappa$ B) has some definite role in the inflammatory response by increasing the production of various mediators (like chemokines, cytokines) which remain till the infection is in active state. The treatment results in decreasing these factors (NF- $\kappa$ B) in the tissue taken for biopsy showing that the treatment is effective. The repairment of the DNA damaged by oxidative species is corrected by PARP1 which is induced as a result of inflammation. The level of PARP1 and NF $\kappa$ b decreases to normal after the treatment of infection treatment also effects the ADP ribosylation of various proteins in the tissue which is increase during the infection. The nuclear material when studied from the biopsy revealed that there is a shortening of telomeres during the infection along with the production of various species (ROS, nitric oxide) that may cause the destruction of nucleic material of the DNA and telomeres shortening in the cells.

## DISCUSSION

It is believed that the bacteria helicobacter may sometimes prove so fetal and may cause carcinogenesis. In fact it is nominated by the WHO as the class 1<sup>11</sup>. There are many cases reported of development of cancer in the patients of *H. pylori*<sup>12</sup>. Though the main role of these bacteria is in development of chronic inflammation and various theories are proposed to study the causes that lead to development of cancer. Many factors are involved in the carcinogenesis including different compounds like reactive oxygen species, free radicals, compounds of nitrogen), decrease in the production of gastric contents and increase in mitosis of epithelium in an uncontrolled manner<sup>13</sup>. There is a little study on the role of damaged DNA of gastric cells in development of infection from *H pylori*. The inflammatory cells (activated neutrophils) produce free radicals that may result in dna damage by producing breaks in the DNA structure and may also produce adducts in the DNA structure. The correction of the damaged DNA is not easy and ultimately leads to carcinogenesis of gastric<sup>14</sup>. For the sake of repairment various signals are produced along with some proteins which may undergo phosphorylation and translocation the increases of different mediators, receptors upregulations and inflammatory cells helps in diagnosing the chronic inflammation<sup>15</sup>. It is believed that increase neuro factors activity and PARP1 and gH2AX is of great value. The reactive oxygen species produced as a result of chronic inflammation causes the disruption of DNA and damage to telomeres<sup>10</sup>. The poly adensine ribosyl polysome 1 causes increased change in Non homologous end joining on the

telomere that causes them to become function less. All is reversed and normalized once after the removal of bacteria<sup>16</sup>.

## CONCLUSION

After performing the study on specifically the effects on telomeres , it is found that the cells which are effected by the reactive oxygen species resulted in shortening of telomere The cells of the gastric mucosa are replaced regularly i.e., almost after every 3-4 days so the effected cells with damaged shortened telomere are replaced after some time but if the stem cells of the gastric mucosa are involved by the action of helicobacter pylori or reactive oxygen species , the shortening of the telomeres may disrupt and damage the genomic material of the stem cells resulting in permanent damage and also in the genesis of cancer, thus this study helped a lot in studying the telomere shortening caused by the helicobacter pylori and in carcinogenesis of stomach adenocarcinoma

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