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Role of Zinc in Chronic Gastritis

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ABSTRACT

Oxidative stress occurs in inflammation of gastric mucosa. The role of zinc in modulating oxidative stress has recently been recognized. Zn deficiency results in an increased sensitivity to oxidative stress and have a higher risk of musoca damage in inflammation. The aim of this study was to determine wheather chronic inflammation affects on the concentration of Zn²⁺ ions in gastric mucosa of patients with chronic gastritis. Forthy-three patients with chronic gastritis were enrolled. Patients were endoscoped. Histology and scoring of gastritis was performed following the guidelines of the updated Sydney system. Endoscopic finding of mucosa were scored according to a Lanza scoring system. The diagnosis of Helicobacter pylori (H. pylori) infection, histopathologic changes, intensity of inflammation and zinc concentration were determined from biopsies of gastric mucosa. The atomic absorption spectrophotometer was used to determine tissue concentrations of zinc. Twenty of 43 patients with chronic gastritis were uninfected by H. pylori. There was no statistically significant difference in tissue concentrations of zinc between H. pylori-positive and H. pylori-negative patients. From those infected patients 53.3% had chronic active gastritis. There was no statistically significant difference in tissue concentrations of zinc between patients with chronic active gastritis and patients with chronic inactive gastritis (p=0.966). Zn in antrum showed positive correlation with density of H. pylori in antrum (Spearman' rho =0.481, p=0.020), negative correlation with density of H. pylori in corpus (Spearman' rho = -0.492, p=0.017) and with zinc in corpus (Spearman' rho = 0.631, p=0.001). Tissue concentration of zinc was not affected by chronic inflammation of gastric mucosa in patients with chronic gastritis.

Key words: zinc, inflammation, gastritis

Introduction

Oxidative stress occurs in inflammation of gastric mucosa¹. The role of zinc in modulating oxidative stress has recently been recognized². Zn deficiency results in an increased sensitivity to oxidative stress and have a higher risk of musoca damage in inflammation. Zinc, as an essential mineral stimulate the activity of approximately 100 enzymes and supports a healthy immune system and is needed for wound healing and DNA synthesis. Zn is crucial for healing of gastric ulcers³. Interestingly, Zn *per se* can influence the course of infection and inflammation. For example, recent studies showed that dietary Zn supplementation attenuated Helicobacter felis-induced gastritis⁴ and that polaprezinc (zinc complex of L-carnosine), a new antiulcer agent, inhibited the develop-

ment of *H. pylori* – induced gastritis^{5,6}. Some studies suggested that decreased serum Zn concentration and elevated Cu/Zn ratio may be precancerous factor for development of gastric cancer⁷.

Oxidative stress is known to be important contributing factor in several chronic human disease. The role of zinc in modulating oxidative stress has recently been recognized⁸. It protect cells from damaging effects of oxygen radicals generated during immune activation⁹. Zinc negatively regulates gene expression of inflammatory cytokines such as TNF-alfa and IL-1beta which are known to generate reactive oxygen radicals (ROS). This may be one additional mechanism by which zinc may be func-

tioning as an antioxidant in humans¹. In addition nitric oxide induces zinc release from metallothionein, which may limit free radical membrane damage during inflammation^{10,11}.

Given evidence about oxidative stress in chronic inflammation and the role of zinc in the response to oxidative stress we hypothesized that tissue zinc could be affected in patients with chronic gastritis.

Methods

Patients and gastric biopsy specimen collection

A total 43 patients of either sex were recruited from those who underwent endoscopy for dyspeptic symptoms and found to be suffering from gastric disease such as gastritis. Endoscopic finding of mucosa were scored according to a Lanza scoring system. From these biopsies the diagnosis of *H. pylori* infection and its severity, histopathologic changes, zinc concentration and intensity of inflammation were determined. Biopsies were used to for histopathology and were used to measure tissue zinc concentrations. Patients who had received non-steroidal anti-inflammatory drugs and patients diagnosed with ulcer disease other gastric duodenal disease were excluded from this study.

The study was conducted in an ambulatory care Osijek University Hospital Center, Croatia. Local ethics committee approval was granted. Informed written consent was obtained from each patient before entrance into the study. Standards of Good Clinical Practice and The Declaration of Helsinki were followed.

Histopathologic examination

Histology was performed on two biopsies from the antrum and two from the corpus, following the guidelines of the Sydney system. Hematoxylin-eosin stain was used to grade gastritis and Giemsa stain to detect *H. pylori*. The diagnosis of gastritis was based on the pathologic findings of *H. pylori*, chronic inflammation, atrophy, polymorphonuclear (PMN) and intestinal metaplasia. The assessment of gastritis was performed according to the updated Sydney System²⁶. The grading of intensity of inflammation was based on the infiltration of mononuclear inflammatory cells in gastric mucosa to mild (1), moderate (2) and severe (3). The PMN infiltra-

tion as a sign of activity was categorized as mild (1), moderate (2) and severe (3) depends on amount of PMN and their spreading in structure of gastric mucosa.

Detection of H. pylori

The presence of *H. pylori* in biopsy was determined either by rapid urease test (CLO test) and histological analysis with Giemsa staining. Single samples from antrum and corpus were used for the CLO test which was considered positive if there was a change in color within 24 hours. Four categories of *H. pylori* infection were determined: 0, none; 1, mild, if low number of bacteria was present; 2, moderate, if higher number of dispersed bacteria was present; and 3, severe, if small colonies or aggregated bacteria were present. Patients were classified as *H. pylori* positive if both of tests were positive.

Determination of zinc concentration in gastric tissue

The biopsies, two mucosal samples for each individual were pooled. The sample digested with nitric acid and analysed by atomic absorption spectrophotometer.

Results

Twenty of 43 patients with chronic gastritis were uninfected by *H. pylori*. There was no statistically significant difference (Table 1) in tissue concentrations of zinc between *H. pylori*-positive and *H. pylori*-negative patients (Mann-Whitney test, in antrum Exact P=0.343; in corpus Exact P=0.092).

From those infected patients 53.3% had chronic active gastritis (Table 2). There was no statistically significant difference in tissue concentrations of zinc between patients with chronic active gastritis and patients with chronic inactive gastritis (p=0.966). Differences in total updated Sydney score (Table 3) were found between *H. pylori*-positive and *H. pylori*-negative patients (p<0.001 in antrum and p=0.008 in corpus). There was no statistically significant difference in tissue concentrations of zinc and Lanza score between both of groups (p>0.05). Infiltrates in antrum showed positive correlation with activities (Spearman' rho=0.504, p=0.014) and with density of *H. pylori* in antrum (Spearman' rho=0.527, p=0.010) in infected patients (Table 4). Zn in antrum showed positive correlation with density of *H. pylori* in

TABLE 1
ZINC LEVEL IN ANTRUM AND IN CORPUS OF GASTRIC MUCOSA OF *HELICOBACTER PYLORI* NEGATIVE AND *HELICOBACTER PYLORI* POSITIVE PATIENTS WITH CHRONIC GASTRITIS

<i>Helicobacter pylori</i> negative patients (n=20)	Zn level* (µg/mL) (antrum)	0.46 (0.35–0.66)
	Zn level* (µg/mL) (corpus)	0.40 (0.23–0.75)
<i>Helicobacter pylori</i> positive patients (n=23)	Zn level* (µg/mL) (antrum)	0.513 (0.36–0.675)**
	Zn level* (µg/mL) (corpus)	0.515 (0.25–0.705)**

* median (interquartile range)

** statistically not significant difference *H. pylori* positive patients vs. *H. pylori* negative patients (Mann-Whitney test, Exact P=0.343 antrum; Exact P=0.092 corpus)

TABLE 2
CHARACTERISTICS OF THE STUDY GROUP

	chronic active gastritis	chronic inactive gastritis
<i>H. pylori</i> positive	15	8
<i>H. pylori</i> negative	2	18
total number	17	26

TABLE 3
SYDNEY SCORE IN *HELICOBACTER PYLORI* NEGATIVE AND *HELICOBACTER PYLORI* POSITIVE PATIENTS WITH CHRONIC GASTRITIS

<i>Helicobacter pylori</i> negative patients	score* (antrum)	0 (0–3)**
	score* (corpus)	2 (1–3)**
<i>Helicobacter pylori</i> positive patients	score* (antrum)	8 (6–9)***
	score* (corpus)	7 (2–8)***

* median (interquartile range)

** statistically significant difference vs. *H. pylori* positive patients (Mann-Whitney test, Exact $P < 0.001$)*** statistically significant difference vs. *H. pylori* negative patients (Mann-Whitney test, Exact $P = 0.007$)

antrum (Spearman' rho = 0.481, $p = 0.020$), negative correlation with density of *H. pylori* in corpus (Spearman' rho = -0.492, $p = 0.017$) and with zinc in corpus (Spearman' rho = 0.631, $p = 0.001$). The relationship between severity of *H. pylori* infection and gastric infiltration by neutrophils was found (Fisher exact, $p = 0.001$). Zinc showed positive correlation with presence of intestinal metaplasia in *H. pylori*- positive gastric mucosa (Spearman' rho = 0.416, $p = 0.048$) and positive correlation with atrophy in antrum (Spearman' rho = 0.339, $p = 0.026$).

Discussion

The aim of this study was to determine if chronic inflammation affects the tissue levels of Zn in patients with chronic gastritis. Tissue concentration of zinc was not changed. There was no statistically significant difference in tissue concentrations of zinc between *H. pylori*-positive and *H. pylori*-negative patients but Zn in antrum showed positive correlation with density of *H. pylori* in patients with chronic gastritis.

TABLE 4
COMPARISON BETWEEN THE DEGREE OF THE INFLAMMATION AND PRESENCE OF *HELICOBACTER PYLORI* INFECTION IN GASTRIC BIOPSIES

Degree of inflammation	Presence of <i>Helicobacter pylori</i> infection	
	antrum*	corpus**
Absent	17.65% (3/17)	55.55% (5/9)
Mild	40.00% (2/5)	25% (4/16)
Moderate	84.62% (11/13)	73.3% (11/15)
Severe	87.5 % (7/8)	100% (3/3)

* Fisher Exact test, exact $p < 0.001$ ** Fisher Exact test, exact $p = 0.014$

Zn is an important anti-inflammatory factor in neutrophil-dependent mucosal injury. The metals are important for metabolism of *H. pylori* (Ni, Cu, Zn, Fe) and during the treatment of *H. pylori* infection (Bi, Al, Se). The daily Zn intake of *H. pylori* positive subjects is significantly higher than in *H. pylori* negative subjects emphasizes the intensive need of bacterium for zinc¹². In our results, the same Zn concentration in those with and without *H. pylori* infection but with chronic inflammation could be indicated that Zn is not utilized by *H. pylori*, and that there must be some other cause of the reduced mucosal resistance. The ability of zinc to retard oxidative processes has been recognized for many years. Little is known of the mechanisms regulating zinc ions homeostasis in gastric mucosa. It was hypothesized that hypoxic injury and the ensuing inflammatory response lead to accumulation of ions of zinc in cells of the glands and of the surface epithelium of mucosa. The consequences of increases in ions of zinc in inflamed gastric mucosa include suppression of acid secretion, enhancement of mucosal protective functions, restraint of glycolysis and mitochondrial respiration. In general, oxidant-induced increases in zinc would be viewed as protective mucosal function. On the other side, chronic zinc deprivation results in increased sensitivity to oxidative stress. In Ecuador where is high prevalence of zinc deficiency, degree of inflammation in *H. pylori*-induced gastritis appears to be modulated by gastric tissue zinc concentration. *H. pylori* infection together with lower zinc concentration in gastric mucosa would induce increased oxidative stress, which would be associated with increased inflammation¹³. Although the gastrointestinal tract is the major site for regulation of zinc homeostasis and the homeostasis of zinc could be affected by *H. pylori* infection, we was not found these association. It is possible to speculate that the oxidant-induced disturbances in tissue zinc was absent in our patients with chronic gastritis which may due to antioxidant properties of zinc.

From those infected patients 75% had chronic active gastritis. There was no statistically significant difference in tissue concentrations of zinc between patients with chronic active gastritis and patients with chronic inactive gastritis. We found the relationship between severity of *H. pylori* infection and gastric infiltration by neutrophils. These indicate that neutrophil accumulation in gastric mucosa is associated with inflammation-induced oxidative stress in *H. pylori* positive patients with chronic gastritis. Activated neutrophils produce reactive oxygen species via NADPH oxidase, nitrogen species and myeloperoxidase within gastric mucosa which induce oxidative stress. However, zinc and divalent cations are known to inhibit the human neutrophilic NADPH oxidase¹. When highly ROS are generated close to cell membranes, they oxidized membrane phospholipids lead to lipid peroxidation. Phospholipids are susceptible to oxidative damage by free radical attack which is a direct cell injury by oxidative stress. Total updated Sydney score were significantly higher in *H. pylori*-positive patients compared to *H. pylori*-negative patients. These indicate that inflammation-induced changes of gastric mucosa were more expressed in patients with *H. pylori* infection. It has been demonstrated that damage to the gastric mucosa during *H. pylori* infection is mainly caused by increased ROS and consequent oxidative stress^{18–21}. Our findings demonstrate that the zinc concentration was unchanged in gastric mucosa regardless to neutrophil accumulation in gastric mucosa. Neutrophils recruited to the site of inflammation generate ROS and damage mucosa. This would suggest that patients with unchanged gastric mucosa zinc concentrations have a lower risk of increased damage by chronic inflammatory. As zinc has powerful antioxidative role, in vivo zinc concentrations might be a good indicator of sensitivity to ox-

idative stress in gastric mucosa with chronic inflammation. It has been shown that Zn inhibit *H. pylori*-associated gastric mucosal oxidative inflammation⁵. A study by Ishihara et al.⁶ showed that Zn component of polaprezinc, antiulcer drug, significantly attenuated neutrophil activity, mononuclear infiltration and surface epithelial erosion in gastric mucosa in mongolian gerbils infected with *H. pylori*.

Other studies showed that patients with peptic ulcer have reduced level of Zn in plasma, but elevated in gastroduodenal mucosa, suggesting that healing of the ulcer lesion is associated with Zn shift from plasma to mucosa^{14,15}. Zinc has a beneficial effect during the initiation of experimental carcinogenesis. Histopathological studies showed that zinc treatment greatly restored normalcy in the colonic histoarchitecture with no apparent signs of abnormality in rats treated with 1,2 dimethylhydrazine¹⁶. High tissue zinc concentration was strongly associated with a reduced risk of developing esophageal squamous cell carcinoma¹⁷. Neutrophil accumulation within epithelial crypts and in intestinal mucosa directly correlates with clinical disease activity and epithelial injury in inflammatory bowel disease. In addition secondary products of neutrophils induced by oxidative stress may play a role in the development of intestinal inflammation. It is found that HNE (4-hydroxy-2-nonenal), a product of lipid peroxidation is involved in the immune response of plasma cells in early intestinal inflammation²².

The oxidant-induced disturbances in tissue zinc was absent in patients with chronic gastritis. These study promise novel insights into role of zinc as a signal of oxidative stress that occurs in gastric mucosa in response to injury followed by inflammation.

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ULOGA CINKA U KRONIČNOM GASTRITISU

SAŽETAK

Oksidativni stres se pojavljuje u upali sluznice želuca. Nedavno je uočena uloga cinka u oksidativnom stresu. Deficit cinka dovodi do povećane osjetljivosti na oksidativni stres te povećava rizik oštećenja sluznice tijekom upale. Cilj ovog istraživanja bio je odrediti da li kronična upala utječe na koncentraciju cinkovih iona u sluznici želuca bolesnika sa kroničnim gastritisom. U studiju je bilo uključeno 43 bolesnika sa kroničnim gastritisom kojima je napravljen endoskopski pregled. Histološka analiza i dijagnoza gastritisa napravljena je prema Sydney sistemu. Endoskopski nalaz sluznice bodovan je prema Lanza sistemu. U biopsijama tkiva sluznice želuca određena je dijagnoza *Helicobacter pylori* infekcije, histopatološka analiza, jačina upale i koncentracija cinka. Dvadeset od 43 bolesnika sa kroničnim gastritisom nije inficirano sa *H. pylori*. Razlika u koncentraciji cinka u tkivu sluznice između *H. pylori* pozitivnih i *H. pylori* negativnih bolesnika nije pronađena. Kod bolesnika sa *H. pylori* infekcijom 53,3% imalo je kronični aktivni gastritis. Statistički značajna razlika u koncentraciji cinka između bolesnika sa kroničnim aktivnim gastritisom i bolesnika sa kroničnim inaktivnim gastritisom nije pronađena ($p=0,966$). Pronađena je pozitivna korelacija koncentracije cinka sa *H. pylori* u antrumu (Spearman' $\rho=0,481$, $p=0,020$), negativna sa *H. pylori* u korpusu (Spearman' $\rho=-0,492$, $p=0,017$) i sa cinkom u korpusu (Spearman' $\rho=0,631$, $p=0,001$). Kronična upala ne mijenja koncentraciju cinkovih iona u sluznici želuca bolesnika sa kroničnim gastritisom.