Gastric acid and salivary bicarbonate. Is there a relationship in duodenal ulcer patients?

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Abstract

Purpose: Since saliva protects the oesophageal and oral mucosa against hydrogen ions, the aim of the study was to establish the relationship between the secretion of gastric acid and salivary bicarbonate.

Material and methods: The study involved 43 Helicobacter pylori positive duodenal ulcer patients receiving: 1. omeprazole alone (O), 2. omeprazole and amoxicillin (OA) or 3. omeprazole, amoxicillin and tinidazole (OAT). In each study group the examination was performed twice, before and at the end of a two-week treatment, both under basal conditions and during a gastric secretory test with pentagastrin. Concentrations of gastric hydrogen ions and salivary bicarbonate were evaluated by the titration method.

Results: In all therapeutic groups analysed separately, the secretion of gastric acid as well as salivary bicarbonate decreased at the end of the treatment, however only in OA and OAT groups the differences in bicarbonate reached statistical significance. As the changes in the concentration and output of both salivary bicarbonate and gastric acid had the same direction, the three therapeutic groups (O, OA, OAT) were subjected to combined analysis. It showed that under basal conditions and during stimulation with a gastric catheter or catheter and pentagastrin, bicarbonate concentration and output were higher before than at the end of the treatment. However, no direct correlation between gastric acid secretion and salivary bicarbonate was found in groups subjected to either separate or combined analysis.

Conclusions: The results of our study provide evidence for the partial involvement of hydrogen ions of gastric origin in the regulation of salivary bicarbonate secretion in duodenal ulcer patients.

Key words: duodenal ulcer, gastric acid, salivary bicarbonate.

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Introduction

Saliva exerts many physiological actions in the oral cavity and oesophagus. A crucial one is the protection of oesophageal mucosa against refluxed gastric acid [1,2]. Attempts have been made several times to determine the correlation between the secretion of gastric acid and saliva, but the results have not been conclusive; the correlation was found to be either positive or none [3,4]. The effect of gastric acid on salivary secretion may occur as a result of gastroesophageal reflux and reflex regulation of salivary secretion associated with stimulation of pH-sensitive receptors located in the lower oesophagus [1,5,6]. In duodenal ulcer patents, this regulation is responsible for 25% of total salivary secretion [7].

In the neutralisation of gastric acid refluxed to the oesophagus bicarbonate ions play an essential role; they originate either from the oesophageal submucosal mucus glands or saliva. Since in this action saliva is most important [1,2], the aim of the study was to establish the relationship between the secretion of gastric acid and salivary bicarbonate.

We designed our study for duodenal ulcer patients as their gastric acid secretion is relatively high and additionally it can be easily decreased or increased, using omeprazole and pentagastrin. By distinguishing therapeutic groups of similar initial (pH = 2) but different final gastric acidity (pH = 4 and pH = 7) [8,9], we expected to answer the question what gastric acidity, if any, is involved in this regulation.

Material and methods

Patients

Forty-three duodenal ulcer patients (33 men, 10 women; mean age 38 years, range 20-64 years; 23 smokers and 20 non-smokers) entered the study. The qualifying criteria included: duodenal bulb ulcer 5-10 mm in diameter, H. pylori infection of gastric mucosa and normal routine laboratory tests. The exclusion criteria were as follows: ulcer related to non-steroidal anti-inflammatory drugs, treatment with other drugs than antacids within the previous two weeks, gastro-duodenal surgery, complicated duodenal ulcer, oesophagitis, pregnancy and lactation, salivary gland diseases and poor general condition.

Study groups

Patients were allocated to one of the three therapeutic groups receiving a two-week oral treatment with: 1. omeprazole alone (2x20 mg) (15 subjects), 2. omeprazole (2x20 mg) and amoxicillin (2x1000 mg) (14 subjects) and 3. omeprazole (2x20 mg) in combination with amoxicillin (2x1000 mg) and tinidazole (2x5000 mg) (14 subjects).

Saliva collection

Saliva was collected twice, before treatment (under basal conditions and during a gastric secretory test with pentagastrin) and at the end of treatment (day 13 – saliva collection under basal conditions; day 14 – collection during a gastric secretory test with pentagastrin). Saliva collections at the end of the treatment were performed 12 hours after the evening doses of drugs, starting always at 8.00 a.m. On the day of the examination the subjects remained in a fasting state, having refrained from eating since the previous evening and from drinking since midnight. They were required to refrain from smoking in the morning hours prior to saliva collection. On examination, subjects were in a sitting position, expectorating the saliva to volumetric caps every 15-30 seconds. Each time, a total saliva collection period was 135 minutes. As saliva secretion during the first few minutes varied greatly, the initial 15-min fraction was discarded. The remaining part was mixed carefully and frozen at a temp. of -25^{0}C.

Collection of gastric contents

The tip of a gastric catheter (5 mm in diameter) was inserted transnasally to the antral region of the stomach. During the examination all subjects were in a sitting position. Residual gastric contents were removed for 15 min and discarded. Then, the contents were collected for 60 min without additional stimulus and the collection was continued for another 60 min following a subcutaneous administration of pentagastrin (Peptavlon, Zeneca) at a dose of 6 μg/kg. Gastric secretion was assessed twice, before and at the end of the two-week treatment. In subjects in whom saliva was collected under basal conditions, gastric acid secretion was not monitored. For them we used the results of gastric secretory test performed a day later.

Assay of salivary bicarbonates

One ml of saliva, previously unfrozen at room temperature was used to determine bicarbonate concentration. Measurements were performed using the titration method [10], with a pH-meter (HI-9321, Hanna Instruments) scaled on standard buffers. At first, it was found that freezing and unfreezing had no effect on bicarbonate concentration, and the values did not differ from those obtained in the freshly collected saliva. Salivary bicarbonate concentration was expressed in μmol/ml, output in μmol/min.

Assessment of gastric secretion

Gastric secretion of hydrogen ions was determined using the titration method. Basal and maximal acid secretion were assessed directly after the collection with 0.1 MNaOH solution, starting from the initial pH to pH 7.0 [11]. The secretion of gastric juice was expressed in ml/hour, concentration of hydrogen ions in pH units and output in mmol/hour.

Assessment of H. pylori infection

During diagnostic gastroscopy which preceded qualifying patients for the study, 6 gastric mucosa specimens, 3 specimens from the gastric antrum and 3 from the gastric body were collected. In one specimen of each series, H. pylori infection was determined with a rapid urease test (CLO-test), in the remaining two, the histological method was used (staining with Giemsa method); the outcome of both tests for H. pylori was positive in all subjects.

Statistical analysis

The results were expressed as means ± S.E. The Wilcoxon's test for paired values was used for statistical analysis. The level of significance was accepted for $p < 0.05$.

The study was approved by the Bioethics Committee, Medical University of Białystok. All the subjects gave informed consent to the participation in the study.

Results

Under basal conditions, concentration and output of salivary bicarbonate were lower at the end of the treatment than at the baseline; however, significant differences were found only in patients treated with OA regimen (9.23 ± 1.04 vs 6.23 ± 0.60 μmol/ml and 3.38 ± 0.60 vs 2.29 ± 0.38 μmol/min, $p = 0.007$ and $p = 0.021$, respectively) and with OAT regimen (7.24 ± 0.54 vs 5.92 ± 0.49 μmol/ml and 3.75 ± 1.04 vs 2.52 ± 0.70 μmol/min, $p = 0.006$ and $p = 0.011$, respectively) (*Fig. 1* and *2*). In the omeprazole group, the differences were not significant.

During the first hour of the gastric secretory test (the catheter tip inserted transnasally to the stomach) no statistically significant differences were found in the concentration and output of salivary bicarbonate between the baseline and the end of the two-week treatment in all study groups (*Fig. 1* and *2*).

In the second hour of the gastric secretory test (the catheter inserted to the stomach with a simultaneous pentagastrin stimulation), bicarbonate concentration at the end of the treatment decreased as compared to the baseline, but only in OA and OAT groups the differences were significant (8.75 ± 1.19

Figure 1. **Salivary bicarbonate concentration under basal conditions and during a gastric secretory test with pentagastrin before (1) and at the end (2) of a two-week treatment (means ± S.E.)**

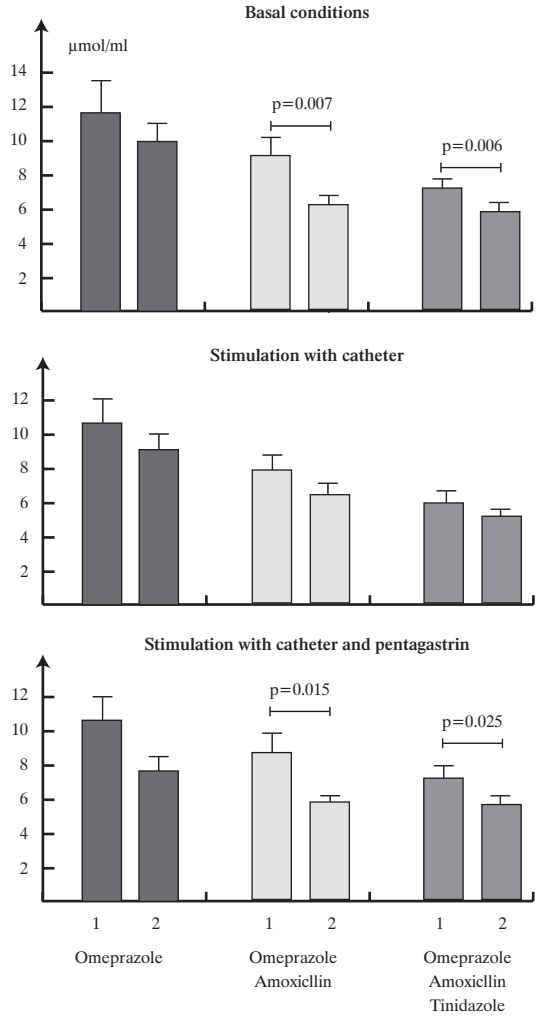
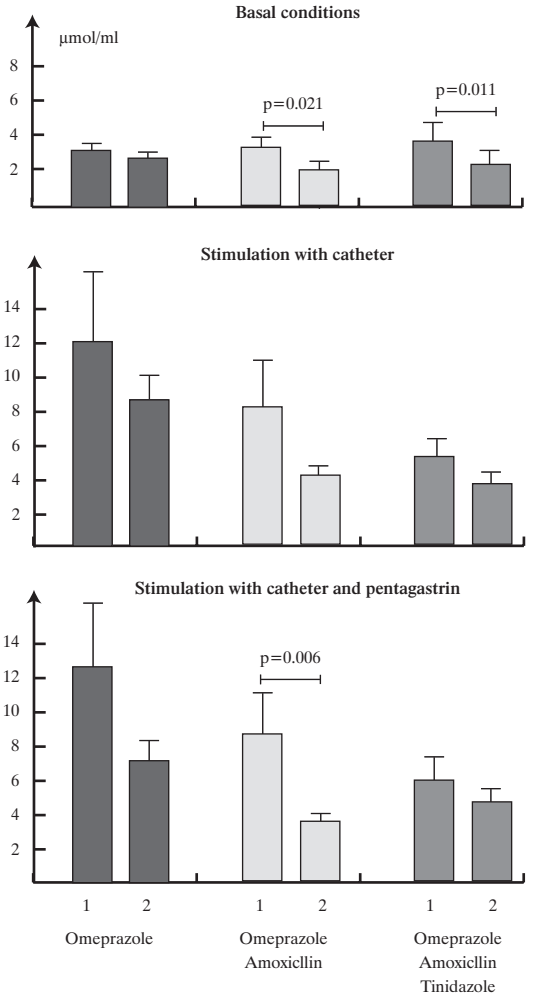


Figure 2. **Salivary bicarbonate output under basal conditions and during a gastric secretory test with pentagastrin before (1) and at the end (2) of a two-week treatment (means ± S.E.)**



vs 5.75 ± 0.38 μmol/ml and 7.41 ± 0.68 vs 5.65 ± 0.56 μmol/ml, p = 0.015 and p = 0.025, respectively). At this time bicarbonate output was also lower but the difference was significant only in OA-treated group (8.08 ± 2.49 vs 3.23 ± 0.52 μmol/min, p = 0.006) (*Fig. 1* and *2*).

At the end of the treatment, in the first and second hour of the gastric secretory test, the volume of gastric content was lower, while pH was higher; the highest pH was observed in the group treated with omeprazole alone (*Tab. 1*). The output of hydrogen ions was lower at the end of the treatment in all therapeutic groups; this concerned both the first and second hour of the gastric secretory test.

As the changes in the concentration and output of both salivary bicarbonate and gastric acid had the same direction, the three therapeutic groups were subjected to combined analysis. It showed that under basal conditions and during stimulation with a gastric catheter or catheter and pentagastrin, bicarbonate concentration and output were higher before than at the end of the treatment (*Tab. 2*). However, no direct correlation between gastric acid secretion and salivary bicarbonate was found in groups subjected to either separate or combined analysis.

Discussion

The present findings indicate that in duodenal ulcer patients gastric antisecretory therapy may contribute to the decrease in salivary bicarbonate secretion. The saliva collection performed 12 hours after taking the final dose of omeprazole may exclude a direct effect of the drug; its serum concentration 8 hours after administration cannot be determined [12]. Serum amoxicillin concentration is also short-lasting (approximately 4 hours) [13], while tinidazole concentration is high not only during the treatment but also for a few consecutive days following its termination [14]. The same direction of changes in the concentration and output of salivary bicarbonate at the end of the treatment in all therapeutic groups suggests, however, that the direct effect of tinidazole on the examined saliva indices is insignificant as well.

Table 1. **Gastric secretion (mean ± S.E.)**

		O		OA		OAT	
		1	2	1	2	1	2
Basal	volume (ml/h)	76.6 ± 13.7	44.8 ± 6.6 [a]	90.6 ± 15.3	37.4 ± 4.4 [b]	76.9 ± 16.8	34.5 ± 3.5 [b]
	pH	2.12 ± 0.28	7.21 ± 0.34 [b]	1.80 ± 0.43	4.26 ± 0.45 [a]	1.76 ± 0.35	3.65 ± 0.55 [a]
	output H^+ (mmol/h)	4.63 ± 1.19	0.19 ± 0.19 [a]	4.54 ± 0.97	0.88 ± 0.17 [a]	4.28 ± 1.12	0.59 ± 0.15 [a]
Pentagastrin	volume (ml/h)	195.6 ± 15.5	93.9 ± 24.1 [a]	184.9 ± 18.9	80.9 ± 15.6 [a]	212.9 ± 14.3	67.2 ± 12.1 [b]
	pH	1.43 ± 0.13	4.89 ± 0.48 [b]	0.98 ± 0.10	2.59 ± 0.36 [b]	0.94 ± 0.28	2.07 ± 0.45 [a]
	output H^+ (mmol/h)	19.2 ± 2.03	3.35 ± 2.11 [b]	18.51 ± 1.92	4.43 ± 1.05 [b]	24.2 ± 2.60	3.98 ± 1.25 [b]

O – omeprazole; OA – omeprazole, amoxicillin; OAT – omeprazole, amoxicillin, tinidazole
1 – before treatment; 2 – end of a two-week treatment
[a] $p<0.01$, [b] $p<0.001$ vs before treatment

Table 2. **Salivary bicarbonate; joint analysis of three therapeutic groups (mean ± S.E.)**

	basal conditions		stimulation with catheter		stimulation with catheter and pentagastrin	
	1	2	1	2	1	2
concentration (μmol/ml)	9.47 ± 0.8	7.44 ± 0.51 [b]	8.28 ± 0.66	6.97 ± 0.48 [a]	8.95 ± 0.68	6.39 ± 0.38 [c]
output (μmol/min)	3.44 ± 0.39	2.55 ± 0.28 [a]	8.05 ± 1.65	5.17 ± 0.65 [a]	8.58 ± 1.53	4.80 ± 0.51 [b]

1 – before treatment; 2 – end of a two-week treatment
[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$ vs before treatment

The mechanism by which gastric acid could modify salivary bicarbonate secretion is unclear. There are no data available for the regulation done through the gastro-salivary reflex. However, the obtained results may be easily explained through the oesophago-salivary reflex. Previous findings have provided evidence that the decrease in the oesophageal pH to 2.1 causes a two-fold increase in the salivary bicarbonate secretion, while at pH 1.3 the increase is even three-fold [1]. It is unknown at what pH the stimulation of salivary bicarbonate secretion is totally extinct; this is likely to occur at pH 2.2 [5]. A reduction in the oesophageal pH related to the gastric reflux is sporadic in healthy subjects, while relatively frequent in patients with duodenal ulcer [15]. Since erosive oesophagitis is a result of gastroesophageal reflux, duodenal ulcer patients with coexistent erosive oesophagitis were not recruited. Unfortunately, the intraoesophageal pH was not monitored and thus it is unknown whether the changes in the intraoesophageal pH took place during saliva collection. As at the end of the treatment gastric pH measured under basal conditions was higher than 3.5 in all therapeutic groups, stimulation of the salivary glands via the oesophago-salivary reflex must have been completely inhibited. Therefore, it can be assumed that in our study only sufficiently low gastric pH before treatment could affect salivary bicarbonate and thus explain their higher values at that time.

Assuming that oesophago-salivary reflex is involved in the regulation of salivary bicarbonate secretion, it seemed rational to collect saliva not only under basal conditions but also during a gastric secretory test with pentagastrin. The intragastric catheter inserted transnasally disturbs the function of the lower oesophageal sphincter and thus promotes gastric reflux to the oesophagus [16,17], while pentagastrin by increasing gastric acid secretion makes stimulation of pH sensitive receptors in the lower oesophagus more efficient during gastroesophageal reflux [5]. The present findings indicate that the catheter had no significant effect on the concentration and output of bicarbonate assessed at the end of the treatment, compared to the baseline, in any of the three therapeutic groups. Since the catheter in the oesophagus could trigger local defence mechanisms by increasing the secretion of oesophageal submucosal glands, similar in composition to that of the oral salivary glands [18-21], the stimulation of oesophageal chemoreceptors by the gastric refluxate could be then attenuated. The higher output of bicarbonate in subjects tested with than without catheter may be explained by the enhanced salivary secretion resulting from catheter stimulation of mechanoreceptors located in the throat and oesophagus.

In the second hour of the gastric secretory test patients with a constantly maintained catheter additionally received pentagastrin as a secretory stimulus. The effect of decreased intragastric pH on the concentration and output of salivary bicarbonate was however manifested in the way similar to that observed in patients without additional stimuli. This is likely related to the fact that pentagastrin, apart from the stimulatory effect on gastric secretion, increases the secretion of the salivary glands as well as submucosal glands of the oesophagus [6,22], and causes an increase in the lower oesophageal sphincter tension, protecting against gastroesophageal reflux [23].

It cannot be excluded that the lack of significant differences

in the concentration and output of bicarbonate before and at the end of the treatment in some of the subgroups analysed separately, may be associated with a small number of patients and a relatively wide dispersion of the results. Nevertheless, in joint analysis of all groups, the concentration and output of salivary bicarbonate as well as the secretion of gastric acid, decreased significantly at the end of the treatment both under basal conditions and when stimulation with a catheter or catheter and pentagastrin was used. No correlation found between the secretion of gastric acid and salivary bicarbonate could be related to the fact that the regulation tested may be responsible only in part for total salivary bicarbonate secretion.

According to some authors, the increase in salivary bicarbonate output, associated with a decrease in intraoesophageal pH, is only related to the increase in salivary secretion and results from the induction of oesophago-salivary reflex [1]. The present findings suggest that in duodenal ulcer patients not only the output but also the concentration of bicarbonate is the subject to changes, and thus mechanisms other than oesophago-salivary reflex can also be involved in the regulation described above. The limitation of our study is a lack of observation documenting salivary bicarbonate secretion after the cessation of antisecretory therapy. However, on the basis of our former studies, we can speculate that it will increase reaching or even exceeding the pre-treatment values [24].

The results of our study provide evidence for the partial involvement of hydrogen ions of gastric origin in the regulation of salivary bicarbonate secretion in duodenal ulcer patients and suggest that disturbed regulation of salivary bicarbonate in some of these patients may predispose to the development of oesophagitis.

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References

1. Brown CM, Snowdon CF, Slee B, Sandle LN, Rees WDW. Effect of topical acidification on human salivary and oesophageal alkali secretion. Gut, 1995; 36: 649-53.

2. Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WJ, Teeter BC. Effect of esophageal emptying and saliva on clearance of acid from the oesophagus. N Engl J Med, 1984; 310: 284-8.

3. Blum AL, Woodal JW. Salivary secretion in duodenal ulcer patients. Gut, 1972; 13: 713-7.

4. Nagwani PL, Naik SR, Sachdev S, Srivastava PN, Chuttani HK. Correlation of salivary and gastric acid secretions in duodenal ulcer patients in tropics. Gut, 1979; 20: 585-9.

5. Dutta SK, Matossian HB, Meirowitz RF, Vaeth J. Modulation of salivary secretion by acid infusion in the distal esophagus in humans. Gastroenterology, 1992; 103: 1833-41.

6. Namiot Z, Sarosiek J, McCallum RW. Secretory function of the esophageal mucosa in opossum. The role of cholinergic, peptidergic and histaminergic pathways. Ann Acad Med Bialostocensis 2004; 49: 80-4.

7. Namiot Z, Stasiewicz J, Kralisz M, Kożuszyńska-Topór M, Markowski AR, Aljanaby FK, Kemona A, Górski J. Omeprazole therapy and salivary flow rate in duodenal ulcer patients. Med Sci Monit, 2001; 7: 276-81.

8. Namiot Z, Stasiewicz J, Kożuszyńska-Topór M, Markowski AR, Kemona A, Bucki R. Helicobacter pylori eradication and gastric acid secretion. Can antibacterial therapy be postponed? Gastroenterol Pol, 1999; 6: 107-10.

9. Labenz J, Tillenburg B, Peitz U, Idstrom JP, Verdu EF, Stolte M, Borsch G, Blum AL. Helicobacter pylori augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology, 1996; 110: 725-32.

10. Izutsu KT. Theory and measurement of the buffer value of bicarbornate in saliva. J Theor Biol, 1981; 90: 397-403.

11. Abernethy RJ, Gillespie IE, Lawrie JH, Forrest APM, Payne RA, Barabas A, Johnston IDA, Burns GP, Hobbs KEF, Clegg RT, Duthie HL, Fitzgerald JD. Pentagastrin as a stimulant of maximal gastric acid response in man. A multicenter pilot study. Lancet, 1967; 1: 291-5.

12. Cederberg C, Thomson ABR, Manachai V, Westin JA, Kirdeikis P, Fisher D, Zuk L, Marriage B. Effect of intravenous and oral omeprazole on 24-hour intragastric acidity in duodenal ulcer patients. Gastroenterology, 1992; 103: 913-18.

13. Goddard AF, Jessa MJ, Barrett DA, Shaw N, Idstrom J-P, Cederberg C, Spiller RC. Effect of omeprazole on the distribution of metronidazole, amoxicillin, and clarithromycin in human gastric juice. Gastroenterology, 1996; 111: 358-67.

14. von Konow L, Nord CE. Concentrations of tinidazole and metronidazole in serum, saliva and alveolar bone. J Animicrob Chemother, 1982; 10: 165-72.

15. Verma S, Jackson J, Floum S, Giaffer MH. Gastroesophageal reflux before and after Helicobacter pylori eradication. A prospective study using ambulatory 24-h esophageal pH monitoring. Dis Esophagus, 2003; 16: 273-78.

16. Brown CM, Snowdon CF, Slee B, Sandle LN, Rees WD. Measurement of bicarbonate output from the intact human oesophagus. Gut, 1993; 34: 872-80.

17. Vaderholzer WA, Klauser AG, Muhldorfer BE, Muller-Lissner SA. Effect of gastric inhibitors and cisapride on gastric volume in healthy volunteers. Eur J Gastroenterol Hepatol, 1992; 4: 635-8.

18. Namiot Z, Sarosiek J, Rourk RM, Hetzel DP, McCallum RW. Human esophageal secretion: mucosal response to luminal acid and pepsin. Gastroenterology, 1994; 106: 973-81.

19. Sarosiek J, Scheurich CJ, Marcinkiewicz M, McCallum RW. Enhancement of salivary esophagoprotection: rationale for a physiological approach to gastroesophageal reflux disease. Gastroenterology, 1996; 110: 675-81.

20. Sarosiek J, Yu Z, Namiot Z, Rourk RM, Hetzel DP, McCallum RW. Impact of acid and pepsin on human esophageal prostaglandins. Am J Gastroenterol, 1994; 89: 588-94.

21. Rourk M, Namiot Z, Edmunds MC, Sarosiek J, Yu Z, McCallum RW. Diminished luminal release of esophageal epidermal growth factor in patients with reflux esophagitis. Am J Gastroenterol, 1994; 89: 1177-84.

22. Loguercio C, de Sio I, Romano M, del Vecchio Blancho C, Coltorti M. Effect of somatostatin on salivary secretion in man. Digestion, 1987; 36: 91-5.

23. Giles GR, Mason MC, Humphries C, Clark CG. Action of gastrin on the lower oesophageal sphincter in man. Gut, 1969; 10: 730-4.

24. Namiot Z, Stasiewicz J, Markowski AR, Namiot DB, Jaroszewicz W, Kemona A, Górski J. Helicobacter pylori eradication and salivary flow rate and composition; a 12-month follow-up study in duodenal ulcer patients. Gastroenterol Pol, 2004; 11: 225-9.