# Upper Digestive Mucosal Changes in Patients Taking Low-dose Aspirin

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**Objective:** The benefits of antiplatelet therapies for treatment and prevention of cardiovascular diseases have been demonstrated in the last years, but these therapies increase the risk of mucosal damage in the gastrointestinal tract. We aimed to evaluate endoscopic mucosal lesions in patients not referred for endoscopy, with a new recommendation for long term low-dose aspirin, who have not taken the drug before endoscopy and in patients taking long-term low-dose aspirin.

**Material and methods:** Two-hundred twenty-five patients who had accepted an endoscopy were included (90 with low-dose aspirin, 135 with recommendation for low-dose aspirin). With few exceptions, there were no statistically significant differences in patient groups regarding social habits, chronic diseases, ulcer history, concomitant drug or digestive symptoms.

**Results:** Severe Lanza scores were significantly more frequent in patients with low-dose aspirin than in patients without aspirin (60% vs. 30.4%, p<0.01). In patients with chronic low-dose aspirin, H. pylori infection was significantly less frequent than in patients not taking this therapy (38.9% vs. 50.4%, p=0.05), while gastric atrophy and/or intestinal metaplasia were more frequent (48.9% vs. 36.3%, p=0.04). Active infection with H. pylori in taken biopsies was associated with more severe lesions, including ulcers, in both groups, while gastric atrophy and/or intestinal metaplasia were significantly associated with severe endoscopic lesions in patients with low-dose aspirin.

**Conclusions:** Patients with recommendation for long term treatment with low-dose aspirin frequently present severe mucosal endoscopic lesions and multiple risk factors for gastrointestinal complications before starting the treatment. Patients taking low-dose aspirin on a daily basis present more severe endoscopic lesions when an active H. pylori infection and premalignant histological changes are present.

**Keywords:** aspirin, gastritis, Helicobacter pylori

## Introduction

The benefits of antiplatelet therapy for the treatment and prevention of cardiovascular diseases have been amply demonstrated within the last two decades. These therapies, however, have recognizable risks, especially gastrointestinal complications such as ulceration and related bleeding [1]. Worldwide prescriptions for low-dose aspirin increased during the last years, and the same tendency is expected to be present in our region. Due to the high number of patients on chronic therapy with potential gastrotoxic risks, the absolute number of gastroduodenal mucosal lesions detected by endoscopy at one time, even if they are not so frequent, can play an important role in further severe complications. The most important risk factors for gastrointestinal complications in patients with antiplatelet therapy were summarized in recent papers [1] and were based in most cases on Western studies. These factors include a history of peptic ulcer or ulcer complication, Helicobacter pylori (H. pylori) infection, concomitant use of NSAIDs, concurrent use of other antiplatelet or anticoagulants, advanced age, dyspeptic symptoms [1]. Despite the conflicting results of studies among non-aspirin non-steroidal anti-inflammatory (NSAID) drugs, infection with H. pylori was demonstrated to be an important risk factor for ulcer and ulcer bleeding in low-dose aspirin users [2,3,4]. It is very well known that the prevalence of H. pylori infection and the type and distribution of gastritis present important differences among Western and Eastern populations [5,6]. In our patients receiving antithrombotic therapy there are no specific studies to determine the risk factors for gastro-duodenal mucosal lesion occurrence.

In this study we aimed to identify the most important factors associated with endoscopic mucosal injury in patients with low-dose aspirin.

## Methods

We performed a prospective observational study among the patients of the 3rd Medical Clinic in Tîrgu Mureș, from January 2009 through September 2010. Patients with cardiovascular disease who have been receiving daily low-dose aspirin for more than one month or who were going to start a chronic therapy with low-dose aspirin and who accepted to be evaluated by endoscopy, irrespective of their symptoms, were enrolled.

We obtained for each patient clinical and demographical data using medical records: age, underlying disease, peptic ulcer history, concomitant drugs – gastroprotective therapy (proton pumps inhibitors – PPI, selective antagonist H2 receptors), anticoagulants (acenocumarolum, low-weight molecular heparin (LWMH), other antiplatelet therapy (clopidogrelum), NSAIDs, corticosteroids. Drugs that were prescribed regularly during low-dose aspirin, including the month before endoscopic examination, were defined as concomitant drugs. The presence of anemia was based on hemoglobin values in medical records. We also investigated the presence of digestive symptoms: abdominal pain, reflux symptoms, nausea, vomiting. A peptic ulcer history was confirmed by inclusion in the medical records and/or endoscopic findings of gastro-duodenal mucosal scars.

**Table I. Clinical and demographical characteristics of the patients**

| | Patients with low-dose aspirin (n=90) n (%) | Patients without low-dose aspirin (n=135) n (%) | p |
|---|---|---|---|
| Men | 50 (55.5%) | 58 (42.9%) | NS |
| Women | 40 (44.5%) | 77 (57%) | |
| Mean age | 66.4±7.7 | 54.9±14.9 | |
| Smoking | 18 (20%) | 41 (30.3%) | NS |
| Alcohol consumption* | 42 (46.6%) | 48 (35.5%) | NS |
| Diabetes mellitus | 39 (43.3%) | 27 (20%) | <0.01 |
| Arthritic diseases | 58 (64.4%) | 72 (50.3%) | NS |
| Renal diseases | 22 (24.4%) | 19 (14%) | NS |
| Respiratory diseases | 26 (28.8%) | 34 (25.9%) | NS |
| Peptic ulcer history | | | |
| Clinical diagnosis (symptoms) | 38 (42.2%) | 48 (35.5%) | NS |
| Confirmed by Rx or UDE | 15 (16.7%) | 35 (25.9%) | NS |
| Concomitant drug consumption | | | |
| NSAIDs | 50 (55.5%) | 62 (45.9%) | NS |
| Clopidogrel | 10 (11.1%) | 3 (2.2%) | <0.01 |
| Anticoagulants | 19 (21.1%) | 18 (13.3%) | NS |
| PPI | 39 (43.3%) | 54 (40%) | NS |
| Digestive symptoms | | | |
| Abdominal pain | 31 (34.4%) | 52 (38.5%) | NS |
| Pyrosis | 29 (32.2%) | 49 (36.3%) | NS |
| Belching | 10 (11.1%) | 20 (14.8%) | NS |
| Nausea | 33 (36.7%) | 45 (33.3%) | NS |
| Anemia | 18 (20%) | 19 (14%) | NS |

*>10 units/week; UDE = upper digestive endoscopy; NSAIDs = non-steroidal anti-inflammatory drugs; PPI = proton-pump inhibitors; NS = not statistical significant

The exclusion criteria were: patients with underlying unstable disease (instable ischemic heart disease, recent open heart surgery – by-pass), patients with obvious signs of upper digestive bleeding (hematemesis, melena), patients referred for upper digestive endoscopy (UDE) from other specialists or family doctors, patients with malignancy, patients after upper gastrointestinal tract surgery and patients with severe end-stage disease.

Upper digestive endoscopy was performed for all included patients. The extent of gastroduodenal mucosal injury was expressed using the modified Lanza score: 0 – no lesions, 1 – mucosal hemorrhages only, 2 – one or two erosions, 3 – numerous (3–10) areas of erosions, 4 – large number of erosions (>10) or ulcer. For each patient 4 biopsies were taken (2 from antrum and 2 from corpus) and also from any incidental lesion detected during the investigation. Biopsy specimens were fixed in formalin, embedded in paraffin and examined with hematoxylin-eosin staining, improved toluidine-blue staining and Giemsa staining. H. pylori infection was considered negative if H. pylori was absent from all biopsy sites and positive if at least one of the histology tests was positive. The degree of mucosal inflammation, activity of H. pylori infection, glandular atrophy, and intestinal metaplasia was classified into 4 grades according to the Updated Sydney System.

To evaluate differences in the prevalence of injury, we used $\chi^2$ test or Fisher's exact probability test. We compared the median Lanza score using Mann-Whitney test. All analyses were performed using the EpiInfo program.

**Table II. The frequency of endoscopic Lanza score in patient groups**

| | Lanza score | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | | 1 | | 2 | | 3 | | 4 | |
| Low-dose aspirin | No. | % | No. | % | No. | % | No. | % | No. | % |
| Yes | 12 | 13.3 | 24 | 26.7 | 25 | 27.8 | 11 | 12.2 | 18 | 20.0 |
| No | 58 | 43.0 | 36 | 26.7 | 11 | 8.1 | 10 | 7.4 | 20 | 14.8 |

| | Grouped Lanza score (p <0.05) | | | |
|---|---|---|---|---|
| | Lanza score 0 or 1 | | Lanza score 2, 3 or 4 | |
| Low-dose aspirin | No. | % | No. | % |
| Yes | 36 | 40.0 | 54 | 60.0 |
| No | 94 | 69.6 | 41 | 30.4 |

## Results

From a total of 857 patients evaluated, a number of 225 patients were included in the study: 90 patients with chronic low-dose aspirin and 135 patients with a recent recommendation for low-dose aspirin therapy. Clinical and demographical characteristics of the patients are presented in Table I.

The mean age in the low-dose aspirin group was about 66 years, significantly higher than in patients without chronic therapy with aspirin. There were no statistically significant differences in social habits (smoking and alcohol consumption). Chronic disease had comparable prevalence in both group, aside from diabetes which was more frequent in patients with low-dose aspirin. Diabetes is a risk factor for cardiovascular disease, consequently diabetic patients are more prone to be treated with low-dose aspirin.

Ulcer history, another important risk factor for gastrointestinal complications in patients with low-dose aspirin, was present in comparable proportion in both groups (42.2% in the low-dose aspirin group vs. 35.5% in the no-aspirin group), with no statistical significance.

About 50% of the patients from both groups presented concomitant NSAID consumption started at least four weeks before endoscopy, generally in recommended daily doses, but the difference between groups was not statistically significant. The clopidogrel consumption was more prevalent in patients with low-dose aspirin due to the recommendation for combining antiplatelet therapy in patients after an acute coronary syndrome. About 40% of all patients used gastroprotective therapy during their life, more frequently without medical recommendation, the difference between groups not being statistically significant.

**Table III. Histological aspects in the studied groups**

| | Low-dose aspirin | | p |
|---|---|---|---|
| | Yes | No | |
| H. pylori positive | 35 (38.9%) | 68 (50.4%) | 0.05 |
| Reactive gastritis | 14 (15.6%) | 20 (14.8%) | 0.51 |
| Gastric atrophy/intestinal metaplasia | 44 (48.9%) | 49 (36.3%) | 0.04 |

**Table IV. The correlation between important endoscopic lesions and histological aspects (H. pylori infection and premalignant gastric lesions) in patients groups**

| | Low-dose aspirin group (n=90) | | | No low-dose aspirin group (n=135) | | |
|---|---|---|---|---|---|---|
| | H. pylori positive (n=35) | H. pylori negative (n=55) | p | H. pylori positive (n=68) | H. pylori negative (n=67) | p |
| Lanza score 2, 3, 4 | 22 (62.8%) | 32 (58.8%) | NS | 20 (29.4%) | 9 (13.4%) | 0.01 |
| Ulcer | 10 (28.5%) | 6 (10.9%) | 0.04 | 13 (19.1%) | 3 (4.4%) | 0.01 |
| | Gastric atrophy/intestinal metaplasia | | p | Gastric atrophy/intestinal metaplasia | | p |
| | Yes (n=44) | No (n=46) | | Yes (n=49) | No (n=86) | |
| Lanza score 2, 3, 4 | 33 (75%) | 21 (45.6%) | <0.01 | 18 (36.7%) | 23 (26.7%) | NS |
| Ulcer | 13 (29.5%) | 4 (8.6%) | 0.01 | 9 (18.3%) | 11 (12.7%) | NS |

Digestive symptoms were present in both groups in comparable proportion. Abdominal pain with any location, pyrosis and belching were present in more than one third of the patients, with no statistically significant differences.

The mean Lanza score in patients with chronic low-dose aspirin was significantly higher than in patients who were going to start this chronic treatment (1.98 vs. 1.24, p=0.0001). If we studied the frequency of each Lanza score in the same patient group, clinically significant Lanza score (2, 3, 4) were significantly more frequent in patients with long term low-dose aspirin than in patients without (60% vs. 30.4%, p <0.05) (Table II).

If we study separately the ulcer occurrence, the patients with chronic low-dose aspirin had significantly more ulcers than patients who were going to begin this therapy (20% vs.14.8%, p <0.05).

H. pylori infection in gastric biopsies was less frequent in patients taking daily low-dose aspirin than in patients without chronic therapy, but the difference did not reach statistical significance (38.9% vs. 50.4%, p=0.059). Low-dose aspirin consumption was not associated with more frequent reactive gastritis than in patients not-taking aspirin (15.6% vs. 14.8%). Active and inactive gastritis had similar proportion in both groups (77.8% vs. 72.6%) (Table III). The premalignant gastric lesions (gastric atrophy and/or intestinal metaplasia) were significantly more prevalent in patients with low-dose aspirin compared with patients not taking this therapy (48.9% vs. 36.3%) (Table III).

Even if the clinically significant Lanza scores (2, 3 or 4) were more frequent in H. pylori negative patients with low-dose aspirin than in those with active H. pylori infection, the difference was not statistically significant (62.8% vs. 58.8%) (Table IV). On the other hand, the ulcer occurrence was significantly more frequent in H. pylori positive patients with aspirin in comparison with H. pylori negative patients taking the same medication (28.5% vs. 10.9%, p=0.04) (Table IV).

Gastric premalignant lesions, which generally occur in evolution of H. pylori infection, were also associated with more severe endoscopic changes in patients with chronic low-dose aspirin therapy. In this group, severe Lanza scores were significantly more frequent when gastric atrophy and/or intestinal metaplasia were present in biopsies, than in patients without these histological changes (75% vs. 45.6%, p <0.01). Ulcer occurrence was also more frequent in patients with premalignant features in gastric biopsies taking aspirin, than in patients without these aspects (29.5% vs. 8.6%, p= 0.01) in biopsy samples (Table IV).

In patients without aspirin therapy, H. pylori infection was significantly associated with a more severe Lanza score (29.4% vs. 13.4%, p=0.01) and more ulcers 19.1% vs. 4.4%, p=0.01), while premalignant lesions were not (36.7% vs. 26.7%, p>0.05, and 18.3% vs. 12.7%, p>0.05 respectively) (Table IV).

## Discussion

The mean age of the patients taking low-dose aspirin in our study was similar with that determined in other studies which investigated gastrointestinal effects of antiplatelet therapies – 66 years in our study, 68 years in a Japanese study published in 2009 [7].

The proportion of patients with cardiovascular diseases and gastrointestinal symptoms without recommendation for UDE from a cardiologist or general practitioner, could be explained by the high frequency of dyspeptic symptoms in the general population (40%) [8,9]. The high prevalence of H. pylori infection in our population [10] could be another explanation for these results. The presence of uninvestigated symptoms should also be a reason for acceptance for UDE in some of the patients in our study, so these results could be influenced by the selection of patients.

There are no statistically significant differences in the frequency of symptoms among patients with or without chronic low-dose aspirin therapy. Even if dyspepsia can occur in patients taking aspirin, there is a poor correlation between symptoms and endoscopic changes in patients taking any gastrotoxic medication [11]. In low-dose aspirin consumers the symptoms could be present in one third of patients without endoscopic changes and in one fifth from those having an endoscopic ulcer [12]. This proves the weak correlation between symptoms and endoscopic lesions in patients with gastrotoxic medication.

The majority of studies regarding patients with low-dose aspirin study bleeding complication, while the studies which determine the frequency of mucosal lesions occur-

rence are not so frequent or, are very inhomogeneous. Nevertheless, the presence of a lesion at one moment could be a risk factor for further severe bleeding lesions during long term aspirin treatment [13]. In our study about one third of the patients who were going to start a long-term aspirin treatment, presented a clinically significant Lanza score and a half presented H. pylori infection, both important risk factors for further gastrointestinal complications.

The prevalence of ulcer in asymptomatic low-dose consumer was higher in our study in comparison with that calculated in other studies, maybe due to the fact that patients with concomitant drugs were not excluded and the general prevalence of H. pylori infection in our population [2]. Other factors could be the mean age of patients in our study, the selection of hospitalized patients with multiple concomitant diseases. The proportion of ulcer in patients without low-dose had probably the same explanation.

Our study and other endoscopic studies generally show a negative correlation between H. pylori infection and aspirin use in patients referred for endoscopy, possible due to the inhibitory effect of the growth of the germ, which enhances the susceptibility to antimicrobial agents and sometimes cleares the infection [13].

Even if H. pylori infection and aspirin are widely known aggressive factors for gastric mucosa, not all epidemiological studies of the last years demonstrated that their association increases the risk for ulcer [5]. Western endoscopic studies have shown that ulcers were more frequent in patients with H. pylori infection and low-dose aspirin treatment [14,15], while in Eastern studies this correlation has not been proved [11,16]. One explanation for these differences could be the predominant type of gastritis in the studied population. Antral predominant gastritis determines an increased acid secretion, consequently more severe lesions in low-dose aspirin consumers. On the other hand, in patients with predominant corpus gastritis, which is more frequent in Eastern population, a low amount of acid secretion determines probably less frequent mucosal lesions in low-dose aspirin consumers [16]. Nevertheless, there have been few studies regarding association between the risk of endoscopic gastro-duodenal lesions and gastric histological changes [17].

In our study the presence of active H. pylori infection was not significantly associated with a Lanza score of 2, 3 or 4 in patients with long term aspirin, but only ulcer was. If we take into account all mucosal lesions (including erosions, submucosal haemoragies), the differences are not statistically significant, probably because they are generally related with aspirin ingestion. The most severe lesion, ulcer, probably occurs in patients with chronic aspirin ingestion who have also another aggressive risk factor, H. pylori. Our results are comparable with those presented in other studies which assessed the frequency of ulcer in patients taking low-dose aspirin with or without H. pylori infection [14,17].

The presence of gastric atrophy and/or intestinal metaplasia with any gastric site was significantly associated with endoscopic lesions in our study population. These results are probably due to the commonly encountered antral and corpus premalignant lesions. More detailed endoscopic and histological studies are needed to determine if corpus atrophy is a condition which could protect aspirin consumers against gastric complications, but our study does not seem to sustain this observation.

## Conclusions

Patients with recommendation for long term treatment with low-dose aspirin for cardiovascular diseases frequently present severe mucosal endoscopic lesions and multiple risk factors for gastrointestinal complications before starting the treatment. Patients taking low-dose aspirin on a daily basis present more severe endoscopic lesions when an active H. pylori infection and premalignant histological changes are present. In order to avoid further gastrointestinal complications, specialists who recommended long term low-dose aspirin need to carefully assess known risk factors for gastrointestinal complications in their patients.

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