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Chronic Statin Therapy and Histologic Gastric Changes

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ABSTRACT

Background: The additional benefits of certain frequently used chronic drugs such as statins or aspirin are investigated for their possible effect of influencing various types of cancer, including gastric cancer. The possible role of statins in the occurrence of pre-neoplastic gastric lesions has not been investigated. **Aim:** The study aims to determine the influence of chronic statin therapy on premalignant gastric lesions (glandular atrophy, intestinal metaplasia and dysplasia), adjusted with the most important aggressive environmental factors of the gastric mucosa (*Helicobacter pylori* [*H. pylori*] infection, low-dose aspirin [acetylsalicylic acid, ASA], biliary reflux, smoking, alcohol consumption). **Method:** The study included 566 patients with cardiovascular diseases who underwent an upper endoscopy: 222 patients with chronic statin therapy (atorvastatin 20–80 mg/day or rosuvastatin 5–20 mg/day for at least 6 months) and 344 patients without statin intake. A complete set of biopsies from the gastric antrum and corpus were routinely processed and examined, and demographical, clinical, and pathological variables were recorded. **Results:** Active *H. pylori* infection in gastric biopsies (p = 0.45), biliary reflux (p = 0.74), alcohol consumption (p = 0.43), or prior ulcer disease (p = 0.07; OR: 0.59; 95% CI: 0.33–1.04) were not associated with an increased risk for premalignant lesions, neither in the statin, nor the no-statin group. Smoking was associated with premalignant lesions in both groups (p = 0.01; OR: 2.24; 95% CI: 1.12–4.47; and p = 0.04; OR: 1.72; 95% CI: 1.01–2.94, respectively), while chronic use of ASA had no influence (p = 0.24, respective p = 0.35). In multivariate regression models, chronic treatment with statins had a protective effect (p = 0.006; OR: 0.59; 95% CI: 0.4–0.8), while smoking (p = 0.01; OR: 1.99; 95% CI: 1.17–3.39) and age >50 years (p <0.01, OR: 3.09; 95% CI: 1.84–5.21) were predictors for pre-neoplastic lesions. *H. pylori* infection, gender, alcohol consumption, biliary reflux, or prior ulcer disease were not associated with premalignant lesions (p >0.05). **Conclusions:** In the studied population, chronic statin treatment seems to be associated with a decreased risk for premalignant gastric lesions, while age over 50 years and smoking, regardless of gender or ASA consumption, remain the most important risk factors for premalignant gastric lesions.

Keywords: statins, gastric atrophy, intestinal metaplasia, premalignant lesions

INTRODUCTION

Statins are widely prescribed in patients with cardiovascular diseases.[1] A growing body of research investigated the effect of statins on gastrointestinal disorders, with controversial results.[1,2] Used to lower cholesterol levels and prevent the progression of atherosclerosis, statins are also known to reduce the incidence of different types of cancers, including gastric cancer, due to their anti-inflammatory and immunomodulatory effects.[3,4] Even though statins may be protective in the setting of cancer, their influence on the risk of gastrointestinal bleeding is a matter of concern, as the study results are controversial.[5] Currently, the roles of *Helicobacter pylori* (*H. pylori*) infection and of the carcinogenic cascade involving progression from chronic gastritis to glandular atrophy (GA), intestinal metaplasia (IM), dysplasia, and cancer are accepted, while the effect of statins on this cascade has not been investigated. In patients with cardiovascular disorders, the impact of chronic statin therapy on the histologic changes of the stomach, adjusted for known risk factors for endoscopic lesions, was not questioned.

AIM

Our study aims to determine the influence of chronic statin therapy on premalignant gastric changes (GA, IM, and dysplasia), adjusted with the presence of the most important aggressors of the gastric mucosa (*H. pylori*, age, low-dose aspirin, biliary reflux, smoking, alcohol consumption).

METHODS

We included 222 patients with chronic statin therapy (atorvastatin 20–80 mg/day and/or rosuvastatin 5–20 mg/day for at least 6 months), comprising the study group, and 344 patients without statin intake, comprising the control group. They were recruited from patients with cardiovascular diseases (hypertension, coronary artery disease, valvulopathy, heart failure, peripheral arterial diseases, or cerebrovascular diseases) who underwent an upper endoscopic examination for specific symptoms or for the assessment of bleeding risk. A minimum of 4 biopsy specimens (from the antrum, the corpus, and the gastric incisura) were taken and referred for routine histology examination. Chronic inflammation of the gastric mucosa, activity, *H. pylori* infection, GA, and IM were described and classified according to the Updated Sydney System. Demographical, endoscopic, histologic, and clinical data, as well as smoking and alcohol consumption were registered in a specially-created database. Patients were assigned as alcohol consumers if they were drinking more than 10 units/week and smokers if they were smoking more than 5 cigarettes/day, including those who have quit in the past 5 years. Low-dose aspirin exposure was considered chronic therapy in case of a dosage of 75–100 mg/day for at least 1 month prior to recruitment, and exposure to a proton pump inhibitor (PPI) (e.g., esomeprazole, pantoprazole, omeprazole) in case of consumption of regular daily doses for more than 1 month. Patients with duodenogastric reflux and visualization of bile pooling in the stomach on endoscopy were assigned as having biliary reflux. Patients with peptic ulcer disease in their medical records were considered as having peptic ulcer history. Patients with incomplete set of data, chronic exposure to other gastrotoxic drugs (non-aspirin, non-steroidal anti-inflammatory drugs, anticoagulants) were excluded. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 22, Chicago, IL, USA).

RESULTS

We analyzed the frequency of current *H. pylori* infection, prior ulcer disease, smoking, alcohol consumption, biliary reflux, and ASA or PPI consumption in patients divided according to the presence of premalignant gastric lesions in both groups. A homogenous distribution of age and sex in both the study and the control group was noticed (Table 1).

Coexisting *H. pylori* infection ($p = 0.45$; OR: 1.25; 95% CI: 0.69–2.23), biliary reflux ($p = 0.74$; OR: 0.90; 95% CI: 0.51–1.60), alcohol consumption ($p = 0.43$; OR: 1.27; 95% CI: 0.69–2.73), or prior ulcer disease ($p = 0.07$; OR: 0.59; 95% CI: 0.33–1.04) were not associated with increased risk for premalignant lesions neither in the study, nor the control group. Smoking habit proved to be an important risk factor for GA/IM in both statin ($p = 0.01$; OR: 2.24; 95% CI: 1.12–4.47) and non-statin users ($p = 0.04$; OR: 1.72; 95% CI: 1.01–2.94). Chronic use of ASA had no influence on premalignant lesions in the study group ($p = 0.24$; OR: 1.42; 95% CI: 0.78–2.60) or the control group ($p = 0.35$; OR: 1.29; 95% CI: 0.77–1.29). PPI consumption was associated with less frequent pre-neoplastic lesions in the statin group, but was borderline associated with an increased frequency in the non-statin group (Table 1).

We investigated the potential protective effect of statin use against premalignant lesions using multivariate regression analysis, through various study models. In all models, chronic treatment with statins proved to have a protective effect. Age over 50 years and smoking habit were risk factors for premalignant lesions in all models,

TABLE 1. Bivariate analysis of demographical and clinical variables on premalignant gastric changes in the study groups

	Statin group N = 222					No-statin group N = 344				
Variables	**With GA/IM N = 78**	**Without GA/IM N = 142**	**p value**	**OR**	**95% CI**	**With GA/IM N = 145**	**Without GA/IM N = 1199**	**p value**	**OR**	**95% CI**
Age >50 years	75 (96.1%)	135 (95%)				122 (84.1%)	126 (63.3%)			
Female gender	38 (48.7%)	64 (45%)				78 (53.7%)	116 (58.2%)			
H. pylori	28 (35.9%)	44 (31%)	0.45	1.24	0.69–2.23	45 (31%)	54 (27.1%)	0.43	1.20	0.75–1.93
Alcohol[a]	23 (29.5%)	35 (24.6%)	0.43	1.27	0.68–2.37	44 (30.3%)	50 (25.1%)	0.28	1.29	0.80–2.09
Smoking[b]	21 (26.9%)	20 (14.1%)	0.01	2.25	1.12–4.47	36 (24.8%)	32 (16.1%)	0.04	1.72	1.01–2.94
Ulcer history	42 (53.8%)	94 (66.2%)	0.07	0.59	0.33–1.04	92 (63.4%)	111 (55.8%)	0.15	1.37	0.88–2.13
Biliary reflux	29 (37.2%)	56 (39.4%)	0.74	0.90	0.51–1.60	58 (40.0%)	79 (39.7%)	0.95	1.01	0.65–1.56
ASA[c]	56 (71.8%)	91 (64.1%)	0.24	1.42	0.78–2.60	34 (23.45%)	38 (19.1%)	0.35	1.29	0.77–2.18
PPId	50 (64.15%)	108 (76.1%)	0.05	0.56	0.30–0.92	87 (60.0%)	97 (48.7%)	0.06	1.57	1.02–2.43

[a] >10 units/week; [b] >5 cigarettes/day, including those who have quit in the last 5 years; [c] use of low-dose aspirin (75–100 mg); dPPI- regular dosses of proton pump inhibitors; GA – glandular atrophy; IM – intestinal metaplasia

while *H. pylori* infection, gender, alcohol consumption, biliary reflux, or prior ulcer disease were not (Table 2). Chronic medication, such as ASA or PPI, had no effect on the development of premalignant lesions in the studied population.

DISCUSSIONS

The additional benefits of certain frequently used chronic drugs were investigated in several observational studies and meta-analyses, one of them suggesting that statin use significantly reduces the incidence of gastrointestinal cancer.[6]

Premalignant gastric lesions were observed in 39.5% of patients in the present study, GA representing 26.4%, IM 18.7%, and dysplasia 0.7%, higher than in other European populations, but comparable with Asian studies and similar with our previous reports.[7] Patients on statin therapy had a lower frequency of premalignant lesions than those in the no-statin group (35.4% vs. 42.1%, p = 0.33), but the difference was not significant.

H. pylori infection, smoking, alcohol consumption, family history, and the presence of premalignant lesions (especially GA and IM) are accepted as risk factors for gastric cancer.[8] Recently, a wide-territory retrospective cohort research showed an increased risk for gastric cancer associated with chronic PPI use, even after *H. pylori* eradication.[9,10] In this regard, we questioned the impact of chronic PPI use on GA/IM. On bivariate analysis, PPI therapy was associated with decreased risk for premalignant lesions in patients with statins, while in patients without statins a contrary effect was observed. Nevertheless, in multivariate regression analysis, after adjustment with the rest of factors, no effect of PPI was noticed. Therefore, the interaction between PPI and statins on the gastric mucosa should be further investigated in specially-designed studies.

Studies performed in an Asian population identified *H. pylori* infection, male gender, and age over 60 years as important risk factors for premalignant gastric lesions.[11] In our study, the presence of *H. pylori* in gastric biopsies was not associated with premalignant lesions in a statistically significant manner. The decreasing acid secretion in patients with GA and IM, which creates an inappropriate environment for *H. pylori*, and the lack of data regarding previous infection (serology) can explain the findings. On the other hand, the "age" of the infection, usually acquired during childhood, correlated with age over 50 years as the most important risk factor for GA/IM in all our studied models, supports the role of an old infection in premalignant gastric lesions in the studied population.

Once the premalignant lesions are installed, patients remain at high risk for the development of gastric cancer, even after *H. pylori* eradication.[9] This may explain why different chemo-preventive therapeutic strategies such as chronic use of aspirin and statins were studied. Recent meta-analyses investigating the potential role of aspirin showed its benefits against gastric cancer, mediated through the cyclooxygenase pathway.[9]

In our study, aspirin use had no influence on the development of premalignant lesions, similarly to the results of other randomized trials.[2,12,13]

Case-control or observational studies evaluating the interaction between gastric cancer and statin therapy

TABLE 2. Multivariate regression analysis of factors influencing premalignant gastric changes (GA/IM) in gastric mucosa

Model 1

Variables	p value	OR	95% CI	
			Lower	Upper
Gender	0.530	0.882	0.595	1.306
Age >50 years	0.000	3.098	1.842	5.213
Statin	0.006	0.593	0.408	0.860
H. pylori	0.237	1.257	0.860	1.837
Ulcer history	0.586	0.904	0.628	1.300
Biliary reflux	0.826	0.961	0.671	1.376
Smoking[a]	0.011	1.992	1.170	3.392
Alcohol[b]	0.972	1.009	0.610	1.669
Constant	0.000	0.290		

Model 2

Variables	p value	OR	95% CI	
			Lower	Upper
PPI[c]	0.561	1.116	0.769	1.620
H. pylori infection	0.116	1.363	0.925	2.006
Gender	0.533	0.886	0.607	1.295
Age >50 years	0.000	1.041	1.025	1.056
Smoking[a]	0.009	2.213	1.384	3.537
Statin	0.005	0.589	0.404	0.858

Model 3

Variables	p value	OR	95% CI	
			Lower	Upper
ASA[c]	0.415	1.185	0.787	1.785
Age >50 years	0.000	1.039	1.024	1.054
Gender	0.487	0.874	0.598	1.277
Smoking[a]	0.000	2.223	1.392	3.548
Statin	0.007	0.569	0.378	0.857

[a] >10 units/week; [b] >5 cigarettes/day, including those who have quit in the last 5 years; [c] use of low-dose aspirin (75–100 mg)

showed a neutral effect,[14,15] while others have noticed a reduced rate of gastric cancer,[16–18], or even an inverse effect.3 The present research identified a statistically significant protective role of statins (p = 0.006) against premalignant lesions in the studied population, while age over 50 years and smoking remain the most important risk factors for premalignant gastric lesions. Statin therapy might have a certain protective effect, but other factors related to the host's genetic susceptibility[19] and the complex interaction with environmental risk factors should be considered in further large models.

CONCLUSIONS

In the studied population, chronic statin treatment seems to be associated with a decreased risk for premalignant gastric lesions, while age over 50 years and smoking, regardless of gender or low-dose aspirin consumption, remain the most important risk factors for gastric glandular atrophy and intestinal metaplasia.

CONFLICT OF INTEREST

None for all authors.

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