Endoscopic and histopathologic aspects of drug induced gastro-duodenal lesions

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Introduction: The gastro-duodenal layer is permanently exposed to environmental aggressive agents and it benefits form complex physio-pathological mechanisms that are able to prevent self-digestion and maintain its integrity. Those mechanisms have been researched form more then 200 years, and have been completed with the discovery, by Robert ae all in the 1980's, of the cryoprotection complex, mediated by prostaglandin (PG) synthesis.

Lesions of the gastro-duodenal layer occur when aggressive agents affect a mucosa with intact defense mechanisms (Zollinger-Ellison syndrome) or when the they became inefficient (lesions associated with gastrotoxic drugs like NSAID, antithrombotic drugs, and *H. pylori* infection). The severity of the endoscopic lesions varies form erosive gastritis to ulcers complicated with upper digestive hemorrhages.

Aim : This thesis aims to investigate the effects of independent risk factors like biliary reflux, *H. pylori* infection, and the use of gastrotoxic drugs (NSAID, antithrombotic therapy) on the endoscopic lesions' s. severity or the occurrence of the premalignant gastric lesions (gastric atrophy/intestinal metaplasia) in patients with multiple comorbidities like cardiovascular, chronic kidney and pulmonary disease and the history of partial gastrectomy for peptic ulcer disease.

Investigating the effect of statin's therapy on gastroduodenal endoscopic lesions development, adjusted by known risk factors for ulcer disease (like gastrotoxic drug consumption, H.pylori infection and comorbidities), was another objective of this study.

The third part of the thesis aims to identify the incidence and risk factors involved in premalignant gastric lessons development, and to determine the effect of chronic statins therapy against gastric atrophy/intestinal metaplasia development.

Methods: Studies were conducted between 2012-2016, on 1755 subjects that underwent upper digestive endoscopy examination in the II Internal Medicine Clinique. Information's regarding symptoms, demographical data, medication and past medical conditions were obtained after applying questioners and consulting medical charts, for each patients included in the study. Upper digestive endoscopy was conducted, several biopsies were taken and refereed for proper histopathological examination, according to the Updated Sydney System recommendation, to each subject included in the study. The degree of chronic mucosal inflammation and the presence on *H. pylori* infection were appreciated and evaluated according also to Updated Sydney System. For statistical analysis SSP, Chicago IL. version 22, Fisher exact test and Pearson Chi square test were used and variables expressed in relative (%)and absolute value.

In the first study, 76 patients with previous gastric surgery were included: 21 patients with gastric ulcer (marginal ulcer or ulcer of the rest of the gastric remnant-study group) and 55 controls (nonulcer group), and we analyzed the effect of known risk factors for ulcer recurrence after more than 15 years post gastrectomy.

A consecutive series of 564 patients, with known cardio and cerebrovascular comorbidities, who underwent upper digestive endoscopy, were stratified according to the severity of endoscopic lesions and recruited for the second study. Patients with statin therapy were included in the study group (n=220), while patients without statins in the control group (n=344). Lanza classification was used for endoscopic lesion severity staging (Lanza 0/1-without endoscopic lesions; Lanza 2/3/4-moderat/severe endoscopic lesions), in both groups.

For the third study, we have enrolled 566 patients with chronic cardiovascular diseases who underwent an upper endoscopy, for digestive symptoms, anemia or prior major cardiovascular surgery. Into the study group, 222 patients with chronic statin therapy (atorvastatin 20–80 mg/day or rosuvastatin 5–20 mg/day for at least 6 months) were included, and 344 patients without statin intake, were the control group.

Results: In patients with history of subtotal gastrectomy, *H. pylori* infection tended to be higher in the control group than in the ulcer group (14.5% vs. 4.8%, $p = 0.43$), without statistical significance. Alcohol consumption (over 100ml pure alcohol/week) had a significant positive association with ulcer ($p = 0.008$), while smoking ($p= 0.064$), low-dose aspirin ($p = 0.063$), and biliary reflux ($p = 0.106$) had a tendency toward statistical signification for positive association, with moderate/severe endoscopic lesions. A high incidence of chronic comorbidities was noticed in both groups, with a statistically significant association between ischemic heart disease and gastric stump ulcers occurrence (p=0.02; OR:3.22; 95% CI1.28-8.35). On univariate analysis, smoking ($p = 0.048$, OR = 3.15, 95% CI: 1.01-9.93) and low-dose aspirin consumption ($p = 0.067$, OR = 2.63, 95% CI: 0.95-7.68) were significantly associated with ulcer. According to the multivariable regression model, alcohol consumption (OR = 6.68, 95% CI: 1.29-41.14) and biliary reflux (OR = 6.12, 95% CI: 1.36-38.26) remained significantly associated with increased odds of stump ulcer. Chronic kidney disease was also associated, with a tendency towards statistical significance (p=0.081), with the risk for gastric stump ulcer recurrence.

In the second study, we correlate the influence of chronic statin therapy (at least 6 months) with factors including age up to 50 years, Helicobacter pylori infection, smoking and drinking habits, ulcer history, gastrotoxic drug consumption (low-dose aspirin [ASA], anticoagulants), and comorbidities. Male gender represented a risk factor ($p<0.01$) for mild/severe endoscopic lesions only in the statin group. The estimated risk for developing mild/severe endoscopic lesions with ASA intake decreased from 6.26 to 3.40 ($p<0.01$) when statin therapy was associated. Patients without statins and ischemic coronary artery disease ($p<0.01$; OR=2.99; 95% CI:1.88-4.73), heart failure ($p=0.01$; OR=2.13; 95% CI:1.36-3.34), systemic atherosclerosis ($p=0.04$; OR=2.30; 95% CI:1.44-3.67) had a statistically significant increased risk for developing mild/severe endoscopic lesions in comparison with patients in the statin group. *H pylori* infection was more frequent in patients with mild/severe endoscopic lesions *vs.* no lesions, in both groups, but the difference was not statistically significant ($p>0.05$). In multivariate regression analysis models, smoking ($p<0.01$; OR=2.69; 95% CI:1.73-4.16), ASA ($p<0.01$; OR=4.54; 95% CI:2.83-7.16), and coronary artery diseases ($p=0.01$; OR=1.80; 95% CI:1.15-2.82) were independent risk factors for mild/severe endoscopic lesions, while chronic statin therapy ($p<0.01$; OR=0.31; 95% CI:0.19-0.51) was associated with a protective effect in all models.

The third study, regarding the risk factors for premalignant gastric lesions occurrence, 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 ($p >0.05$) development.

Conclusions: Biliary reflux and alcohol abuse, are the most important predictors for developing recurrent gastric stump ulcers, meanwhile H. pylori infection or gastrotoxic drug consumption are not associated with an increased risk for ulcers in patients after more than 15 years after partial gastrectomy.

In patients with physiological stomach, age over 50, smoking and chronic comorbidities like ischemic heart disease, systemic atherosclerosis, chronic lung and kidney disease, diabetes melitus and therapy with aspirin in low doses were important predictors for moderate /severe endoscopic lesions development. A protective effect of chronic statine therapy, against moderate/ severe endoscopic lesions, especially in patients with cardiovascular diseases and ASA consumption, was noticed in our study.

In one of our study, chronic statine therapy was associated with a protective effect against premalignant gastric lesions, while age over 50 and smoking, regarding sex or aspirin use, are se most important predictors for gastric atrophy/ intestinal metaplasia development.