

Gamma-Glutamyltransferase and C-Reactive Protein in Stable Chronic Obstructive Pulmonary Disease

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ABSTRACT

Systemic inflammation and oxidative stress are the most important features of chronic obstructive pulmonary disease (COPD). The presence of oxidative stress in the airways of smokers, the largest population of COPD patients, is a consequence of direct inhalation of cigarette smoke and increased inflammation-related production of reactive oxygen species. On the other hand, oxidative stress appears to be the key component of many processes associated with chronic inflammation. We intend to examine whether serum C-reactive protein (CRP) concentration and gamma-glutamyltransferase (GGT) activity might be used as auxiliary markers in monitoring level of oxidative stress and inflammation in clinically stable COPD. We also investigated influence of cigarette smoking on these two systemic parameters. Catalytic activity of GGT and concentration of CRP were determined in sera of COPD patients (N=109) and in healthy controls (N=51) by using standard spectrophotometric method and immunoturbidimetric method, respectively. Concentration of CRP and activity of GGT were increased in COPD patients, as compared to healthy controls ($p < 0.05$). We found a significant positive correlation between those two parameters in COPD patients ($r = 0.202$, $p = 0.0371$). Our results showed no difference in GGT activity ($p = 0.606$) or CRP concentration ($p = 0.573$) between groups of patients when subdivided according to the severity of the disease. Smoking did not have a significant impact on CRP and GGT values in COPD patients and healthy controls. We showed an increase of serum CRP and GGT values in COPD patients, and we suggest that serum GGT activity might also represent an inflammation/oxidative stress marker. It seems that COPD patients present higher serum CRP and GGT values than healthy subjects independently from their smoking habits.

Key words: chronic obstructive pulmonary disease, C-reactive protein, gamma-glutamyltransferase, smoking, systemic inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is the fifth most common cause of death in general population and the only chronic disease that has continuously showed an increase in mortality. It is a systemic inflammatory disease that begins with the impairment in the lung function and morphology, and progresses with an increase in airflow limitations, further destruction of

lung parenchyma and development of extra-pulmonary complications¹. The most important elements in the pathogenesis of COPD are inflammation and development of oxidative stress^{2,3}. In COPD, inflammation is occurring in the airways, pulmonary parenchyma, blood vessels and has generalised effects. The presence of oxidative stress in the airways of smokers, the largest population

of COPD patients, is a consequence of direct inhalation of cigarette smoke and increased inflammation-related production of reactive oxygen species. Cigarette smoke is a complex mixture of more than 4700 chemical compounds, including high concentrations of free radicals and other oxidants⁴. Oxidative stress appears to be the key component of many processes associated with chronic inflammation. It produces direct damaging effects to the lungs, and activates the molecular mechanisms that aggravate lung inflammation.

Association of impaired lung function and an increased concentration of CRP was first suggested by Kony et al⁵. Recently, serum CRP was used as a marker for the airways obstruction and inflammation in severe state of asthma and in COPD, irrespective of the smoking history or concomitant ischemic heart disease. However, administration of the inhaled corticosteroids produced a significant decrease in CRP levels^{6,7}. Based on these findings CRP was proposed as a supplementary marker for the inflammation of upper respiratory airways.

Glutathione (gamma-glutamylcysteinylglycine; GSH) is the most important cellular antioxidant. The membrane-bound enzyme gamma-glutamyltransferase (GGT) initiates metabolism and turnover of GSH, and plays an important role in GSH homeostasis⁸. Activity of GGT as a possible marker of oxidative stress that is present in the pathology of lung and other diseases has recently come into focus^{9,10}. However, depending on local conditions in the tissue, GGT might express both anti-oxidative and pro-oxidative function^{10,11}. Reference range for the serum activity of GGT are rather broad and higher GGT activities, although still within the reference range, might be used as an early and sensitive marker of oxidative stress^{12–17}. In addition, GGT regulates the catabolism of leukotriene C4 (LTC4) and its conversion into leukotriene D4 (LTD4), thus showing a pro-inflammatory effects. A positive correlation that was established between GGT activity, concentration of CRP and some other markers of inflammation has also put GGT on the list of putative markers for inflammation^{18,19}. The precise role of GGT in different physiological and pathophysiological conditions is currently under serious investigation.

The aim of this study was to examine serum CRP concentration and GGT activity in COPD patients and healthy individuals. We hypothesized that these two systemic parameters might be used as auxiliary markers in monitoring level of oxidative stress and inflammation in clinically stable COPD. We also investigated influence of cigarette smoking on CRP and GGT values.

Materials and Methods

Study design

The study included 109 patients with clinically stable COPD (33 smokers, 28 ex-smokers, 48 non-smokers) and the control group of 51 healthy subjects (18 smokers, 15 ex-smokers, 18 non-smokers). Smokers were defined as

current smokers who smoke more than 2 cigarettes/day and those who quit smoking up to 6 months before enrolment in the study; ex-smokers were defined as persons who smoked during their lifetime, quit smoking more than 6 months before enrolment in the study and have pack years value >1; non-smokers were defined as never smokers.

Inclusion criterion for the patients was a clinical diagnosis of COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Disease)¹ – clinical examination and FEV₁/FVC <0.70, as measured on first admission at the Department for Pulmology in the General Hospital »Dr. Ivo Pedišić«, Petrinja, Croatia. Exclusion criteria for both COPD patients and healthy subjects were presence of pulmonary diseases (except COPD for the patients), infective and inflammatory diseases, neoplastic pathologies, renal, gastrointestinal, endocrine and hepatic diseases, and excessive alcohol consumption (≥40 g/day).

All the patients were in the stable phase of the disease for at least 3 months without the need for hospitalization and therapy modification. Their medication therapy consisted of a combination of bronchodilators, anticholinergic agents, theophylline, and inhaled corticosteroids.

Spirometry was performed for all participants. Blood samples were collected between 7:00 a.m. and 9:00 a.m. Sera were separated by centrifugation at 3500 rpm for 10 min, and CRP concentration and GGT activity were determined immediately. Patients were classified according to the severity of disease, as suggested by GOLD¹. Stage II – moderate COPD (N=30): FEV₁/FVC <0.70, 50% ≤ FEV₁ <80% predicted value; stage III – severe COPD (n=50): FEV₁/FVC <0.70, 30% ≤ FEV₁ <50% predicted value; stage IV – very severe COPD (N=29): FEV₁/FVC <0.70, FEV₁ <30% predicted value or FEV₁ <50% predicted value and with chronic respiratory failure. The study was approved by the medical ethics committee of the Hospital, and informed consent was obtained from all study subjects.

Methods

Catalytic activity of GGT was determined by using standard spectrophotometric method, according to IFCC suggestion (Herbos Diagnostics, d.o.o., Sisak, Croatia), on automatic analyser Alcion (Abbott Diagnostics, Abbott Park, IL, USA)²⁰. Reference range for the serum activity of GGT: male 11–55 U/L, female 9–35 U/L. Determination of CRP concentration was performed by using immunoturbidimetric method on automatic analyser Dimension Xpand Plus (Siemens Healthcare Diagnostics, USA)²¹. Reference range for concentration of CRP: male, female ≥20 years: <5 mg/L.

Statistical analysis

Statistical analysis was performed with Med Calc 9.4.2.0. (MedCalc Software, Mariakerke, Belgium). All data were tested for normal distribution by Kolmogorov-Smirnov test and differences between the means by student t-test. Data for non-normally distributed varia-

bles were expressed as medians with interquartile range, and tested by Mann-Whitney test. Statistical analysis for multiple comparisons was analysed by one way analysis of variance (ANOVA) and Kruskal-Wallis test. Correlation coefficients were calculated using Pearson and Spearman correlation coefficient. Statistical significance was defined as $p < 0.05$. Each biochemical marker was tested using Receiver Operating Characteristic Curve (ROC), for pairs of diagnostic specificity and diagnostic sensitivity.

Results

Characteristics of COPD patients and healthy controls are presented in Table 1. Healthy subjects were of good general health, had normal lung function, as shown by FEV₁ (% predicted) and FEV₁/FVC values, and were younger than patients with stable COPD. We tested the influence of age on activity of GGT and concentration of CRP in sera and we found no correlation between age and CRP or GGT values neither in patients' group (CRP – $r_s = -0.0249$, $p = 0.7958$; GGT – $r_s = -0.0558$, $p = 0.5656$) nor in healthy subjects (CRP – $r = 0.08571$, $p = 0.5498$; GGT – $r = -0.04104$, $p = 0.7749$).

Significant differences in FEV₁ (% predicted), FEV₁/FVC and BMI were observed between the groups. In addition, COPD patients had a significantly higher number of pack years values than controls (Table 1).

We measured catalytic activity of GGT and concentration of CRP in sera and found a statistically significant increase in GGT activity (for 63%) and in CRP concentration (for 79%) in all COPD patients when compared to healthy controls ($p < 0.05$). Figure 1 represents catalytic activity of GGT and concentration of CRP in sera of COPD patients

TABLE 1
CHARACTERISTICS OF COPD PATIENTS AND HEALTHY CONTROLS

| | COPD (N=109) | Healthy controls (N=51) |
|---|-----------------|----------------------------|
| Age* | 71 (65–76) | 52 (46–56) |
| Male, N (%) | 82 (75) | 21 (41) |
| Female, N (%) | 27 (25) | 30 (59) |
| BMI adjusted for age (kg/m ²) | 21.0 ± 5.4** | 26.4 ± 4.5 |
| FEV ₁ (% predicted) | 41 ± 14** | 106 ± 15 |
| FEV ₁ /FVC (%) | 62.0 ± 10.6** | 86.2 ± 6.6 |
| Pack years* | 50 (32–75)** | 20 (15–30) |

COPD – chronic obstructive pulmonary disease, BMI – body mass index, calculated as the ratio weight (kg) divided by height (m²), FEV₁ (% predicted) – forced expiratory volume in 1 second, corrected for gender, age, body mass and height, FEV₁/FVC – FEV₁ as percentage of forced vital capacity, FVC, pack years (for smokers and ex-smokers) – duration of smoking multiplied by the number of cigarettes smoked per day, and divided by 20. Data shown are $\bar{X} \pm SD$, except for * where median and interquartile range are presented.

** $p < 0.001$ in comparison with controls

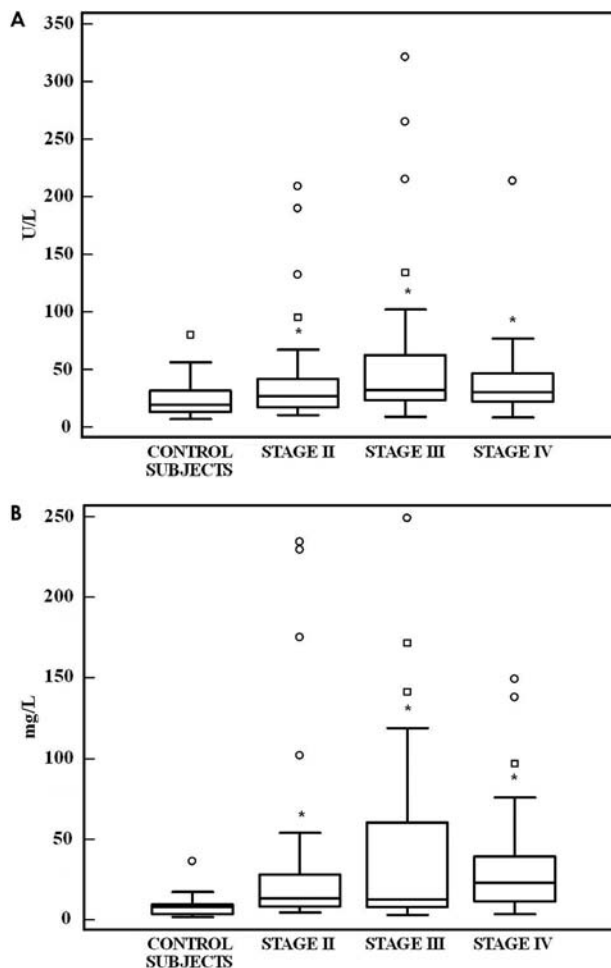


Fig. 1. Catalytic activity of GGT (A) and concentration of CRP (B) in sera of healthy controls and COPD patients subdivided by disease severity (GOLD grades). GGT – gamma-glutamyltransferase, CRP – C-reactive protein, COPD – chronic obstructive pulmonary disease, GOLD – global initiative for chronic obstructive lung disease, *significant difference in stages II, III and IV when tested against healthy controls, $p < 0.05$.

assigned to three stages according to the disease grades (GOLD II, III, and IV). Since data did not show normal distribution, results are presented as median and interquartile range. In all COPD stages we found a significant increase in GGT activity when compared to healthy controls ($p < 0.05$). Similarly, significantly higher CRP concentrations were found in all COPD stages when compared to healthy controls ($p < 0.05$). However, there were no significant differences either in GGT activity ($p = 0.606$) or CRP concentration between COPD stages ($p = 0.573$).

Each biochemical marker was further tested using ROC curve for diagnostic specificity and sensitivity (Figure 2). Analysis showed that cut-off value for serum CRP concentration of 11.86 mg/L exhibited a good diagnostic accuracy (AUC=0.808, $p = 0.0001$), with 94.12% specificity and 59.63% sensitivity. Serum GGT activity measurement (cut off value of 22 U/L) displayed a fair diagnostic accu-

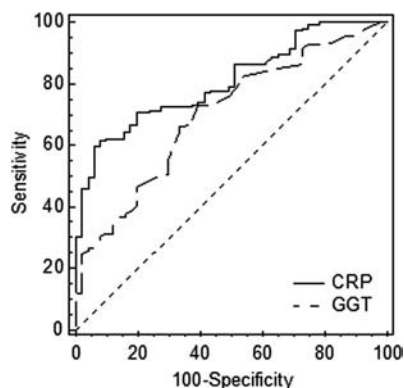


Fig. 2. ROC curve for serum CRP concentration and GGT activity in COPD patients. CRP – C-reactive protein, GGT – gamma-glutamyltransferase, COPD – chronic obstructive pulmonary disease.

racy (AUC=0.702, $p=0.0001$), with 60.78% specificity and 73.39% sensitivity. The cut-off value for GGT activity for all COPD patients, regardless of stage, was equal.

In order to test diagnostic specificity and sensitivity in particular GOLD grade, we performed ROC analysis with COPD patients divided into subgroups. ROC analysis of CRP data showed a good diagnostic accuracy for stage IV (cut off value 11.31 mg/L, AUC=0.865, specificity 92.16%, sensitivity 75.86%, $p=0.0001$). For stages II and III, CRP determination exhibited a fair diagnostic accuracy (stage II – AUC=0.791, specificity 94.12%, sensitivity 56.67%, $p=0.0001$; stage III – AUC=0.786, specificity 80.39%, sensitivity 68.00%, $p=0.0001$). ROC analysis for GGT measurement demonstrated a poor diagnostic accuracy for stage II (AUC=0.657, specificity 60.78%, sensitivity 63.33%, $p=0.0150$), and a fair diagnostic accuracy for stages III and IV (stage III – AUC=0.723, specificity 60.78%, sensitivity 78.00%, $p=0.0001$; stage IV – AUC=0.714, specificity 66.67%, sensitivity 72.41%, $p=0.0006$).

Spearman coefficient of correlation showed a significant positive correlation between serum CRP and GGT activity ($r=0.202$, $p=0.0371$) in COPD patients group.

As shown in Figure 3, smoking did not affect CRP concentration and GGT activity either in COPD patients or in healthy controls. Only GGT values between healthy smokers and healthy ex-smokers differed significantly ($p<0.05$). When COPD patients were subdivided both by disease severity and smoking habits, similar results were obtained (Table 2). Within a particular smoking category (smokers, ex-smokers, non-smokers), CRP and GGT were increased in patients as compared to healthy subjects, but no significant differences were present among COPD stages.

Discussion

We evaluated the possibility of applying serum CRP concentration and GGT activity as markers in monitoring level of inflammation and oxidative stress in COPD patients. Population-based studies have observed positive dose-response relations between serum GGT (mostly

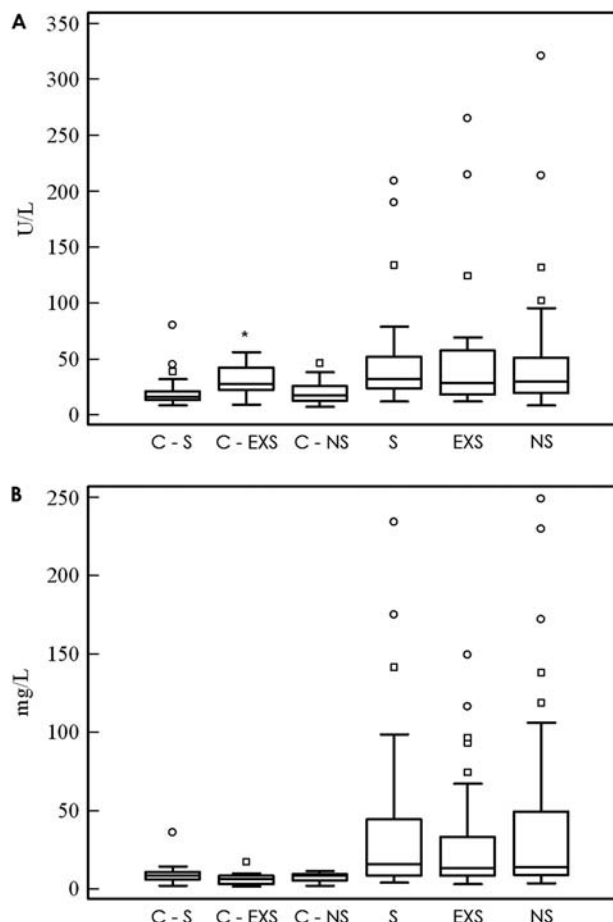


Fig. 3. Catalytic activity of GGT (A) and concentration of CRP (B) in sera of healthy controls and COPD patients subdivided by smoking history: control smokers (C-S), control ex-smokers (C-EXS), control non-smokers (C-NS), COPD smokers (S), COPD ex-smokers (EXS), COPD non-smokers (NS). GGT – gamma-glutamyltransferase, CRP – C-reactive protein, COPD – chronic obstructive pulmonary disease, *significant difference between healthy smokers and healthy ex-smokers, $p<0.05$.

within normal range) and markers of oxidative stress, and inverse association with serum and dietary antioxidant vitamins^{15,22,23}. Thus, it was suggested that serum GGT, even within its normal range, is a sensitive and early marker of oxidative stress¹⁸. In addition, GGT may be involved in the inflammation cascade¹³. It has been hypothesized that elevation in GGT might occur before an elevation in CRP, if oxidative stress leads to a subsequent inflammatory response¹⁸. It is well established that imbalance between oxidants and antioxidants is implicated in the pathogenesis of COPD, with oxidative stress being involved in amplification of chronic inflammatory processes¹.

In this study, we found an increase of CRP and GGT values in sera of the individuals with clinically stable COPD, as compared with healthy subjects. This is in agreement with previously published data for CRP^{7,24–28}, but in contrast with results for GGT obtained from the study using a limited number of COPD patients (29

TABLE 2
CRP CONCENTRATION AND GGT ACTIVITY IN SERA OF COPD PATIENTS SUBDIVIDED INTO GOLD STAGES AND HEALTHY CONTROLS, WITH RESPECT TO THEIR SMOKING HISTORY

| | COPD patients (N=109) | | | Healthy subjects (N=51) | |
|-------------|------------------------------|-------------------------------|-------------------------------|-----------------------------|---|
| | Stage II (N=30) | Stage III (N=50) | Stage IV (N=29) | | |
| CRP (mg/L) | | | | | |
| Smokers | (N=8) 16.09 (9.24–114.50) | (N=13) 10.11 (6.48–50.26) | (N=12) 22.27 (10.98–36.63) | (N=18) 8.41 (6.16–11.02) | a |
| Ex-smokers | (N=8) 13.90 (8.04–27.04) | (N=13) 10.57 (7.60–32.03) | (N=7) 27.60 (12.99–82.13) | (N=15) 6.38 (3.00–8.49) | b |
| Non-smokers | (N=14) 12.59 (7.69–20.86) | (N=24) 26.54 (10.34–71.39) | (N=10) 18.16 (7.93–38.45) | (N=18) 7.98 (4.57–9.30) | c |
| GGT (U/L) | | | | | |
| Smokers | (N=8) 37.5 (33.5–199.5) | (N=13) 28.0 (22.3–65.8) | (N=12) 30.0 (24.5–47.5) | (N=18) 16.0 (13.0–21.0) | d |
| Ex-smokers | (N=8) 16.5 (15.0–35.5) | (N=13) 37.0 (27.0–82.8) | (N=7) 28.0 (18.0–39.3) | (N=15) 28.0 (22.0–42.5) | |
| Non-smokers | (N=14) 26.0 (18.0–40.0) | (N=24) 32.5 (21.0–59.5) | (N=10) 43.5 (23.0–52.0) | (N=18) 18.0 (13.0–25.0) | e |

COPD – chronic obstructive pulmonary disease, CRP – C-reactive protein, GGT – gamma-glutamyltransferase. Data are expressed as median (interquartile range: 25th–75th percentile).

^a Significant difference between Stage IV and healthy smokers, $P < 0.05$

^b Significant difference between the multiple groups (COPD ex-smokers: Stage II, Stage III, Stage IV) compared with healthy ex-smokers, $p < 0.05$

^c Significant difference between the multiple groups (COPD non-smokers: Stage II, Stage III, Stage IV) compared with healthy non-smokers, $p < 0.05$

^d Significant difference between the multiple groups (COPD smokers: Stage II, Stage III, Stage IV) compared with healthy smokers, $p < 0.05$

^e Significant difference between the multiple groups (COPD non-smokers: Stage III, Stage IV) compared with healthy non-smokers, $p < 0.05$

COPD patients)¹⁷. As GGT activity has been commonly used as a marker for alcohol consumption or liver dysfunction, we excluded from this study all the individuals (healthy subjects and COPD patients) who excessively drunk alcohol beverages as well as those with confirmed liver diseases. In addition, we measured activity of alanine aminotransferase and aspartate aminotransferase in sera of the persons enrolled in the study, and found that enzyme activities were within the reference range both for healthy controls and COPD patients, indicating a normal liver function (data not shown).

Some authors have shown that serum GGT was positively associated with CRP and certain other systemic markers of inflammation, in a dose-dependent manner^{18,19,23,28}. However, those studies involved only healthy subjects. Best to our knowledge, this study is the first report exploring the relation between serum GGT and CRP in COPD patients, and we found a significant positive correlation between those two parameters.

Our results showed no significant difference either in GGT activity or CRP concentration when the patients were subdivided according to the disease grades (GOLD II, III, and IV). However, CRP rose with increasing severity of COPD in some other studies^{24,26,29}. Although stable

COPD is undoubtedly characterised by systemic inflammation process, it is still unclear whether it reflects the continuous intensification of the lung inflammation associated with the disease progression, or inflammation in the peripheral blood aggravates only during the exacerbation episodes. Thus, the amount of each inflammatory marker might not necessarily differ significantly among disease stages during the stable phase of the disease, and it would be interesting to monitor the values of those systemic parameters and their association during exacerbation.

Cigarette smoking is by far the most commonly encountered risk factor for COPD. In our study, smoking did not have a significant impact on CRP and GGT values in COPD patients and healthy controls. The only exception was difference in GGT activity between healthy smokers and healthy ex-smokers, but it is quite possible that a small number of participants within a particular group (18 and 15, respectively) affected the results obtained. Thus, it seems that COPD patients present higher serum CRP and GGT values than controls independently from smoking habits. The same conclusion was reached for GGT activity and CRP concentration in other studies^{7,17}, although Gan and co-workers demonstrated in-

fluence of smoking on CRP³⁰. As the understanding of the importance of risk factors for COPD has grown, so has the recognition that essentially all risk for COPD results from a particular gene-environment interaction. Little is known about the reason why some persons with the same smoking history develop clinically important COPD whereas others do not, and it was suggested that it is due to diversity in genetic predisposition to the disease¹. In a previous study which demonstrated increased CRP concentrations in COPD patients independent of smoking, the authors speculated that each person has an inherited inflammatory genetic profile, so called »phenotype of CRP responders«, and thus the differences may precede the exposure to the environmental factors⁷. However, although the most common, cigarette smoke is not the only trigger for COPD occurrence. Numerous other inhaled noxious agents may also contribute to respiratory symptoms and COPD by increasing the lungs total burden of inhaled particles and gases¹. Subjects enrolled in our study experienced a long-term and intensive exposure to air pollution from the nearby oil refinery and thermal power plant, and the number of COPD and asthma patients is rapidly growing in this area. The role of air pollution in causing COPD is unclear, although it is associated with adverse effects on lung function³¹. However, the concept of total personal exposure to the irritants, such as smoking and pollution, may be more relevant for developing COPD, in addition to the COPD susceptibility genes.

In this study, we included COPD patients with moderate, severe and very severe stage of the disease, except those with mild stage (GOLD I) who have not yet experienced a typical and strong symptoms of the disease and hence are often underestimated. In addition, both our healthy subjects and COPD patients have different smoking habits, and they were classified as smokers, ex-

-smokers and non-smokers. Many studies that analyse COPD patients combine ex-smokers either with current smokers or with never smokers, while in the others, when this subgroup is present separately, ex-smokers are defined differently. Hence, there is a need for a consensus in defining who meet criteria for the category of ex-smokers. This could contribute to more accurate exploring of the influence of smoking on both pulmonary and extra-pulmonary changes associated with COPD.

Our study has several shortcomings. First, relatively small sample size (109 COPD patients, 51 healthy controls) is restrictive for an unambiguous conclusions, and a larger epidemiological study will be needed to assess the association between increased CRP and GGT values. Second, we did not assess CRP and GGT in COPD patients suffering from exacerbation episode. Third, smoking habits of our subjects were self-reported, and measurement of the carboxyhemoglobin should be performed to confirm smoking status. Despite these potential limitations, we showed an increase of serum CRP and GGT values in COPD patients, thus supporting the hypothesis that serum GGT activity might represent an inflammation/oxidative stress marker in COPD, as already suggested in the case of cardiovascular diseases and metabolic syndrome¹⁰. However, more research is needed to better understand the pathophysiological role of both CRP and GGT in development and progression of COPD.

Acknowledgements

This work was supported by the Croatian Ministry of Science, Education and Sports (Grants No. 006-0061245-0977 and No. 0006612). The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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GAMA-GLUTAMILTRANSFERAZA I C-REAKTIVNI PROTEIN U STABILNOJ KRONIČNOJ OPSTRUKCIJSKOJ PLUĆNOJ BOLESTI

SAŽETAK

Sistemska upala i oksidativni stres su najvažnije značajke kronične opstruktivne plućne bolesti (KOPB). Prisutnost oksidativnog stresa u dišnim putovima pušača, najveće populacije pacijenata oboljelih od KOPB-a, je posljedica direktnog udisanja cigaretnog dima i upalom uvjetovanog pojačanog stvaranja reaktivnih kisikovih čestica. S druge strane, čini se da je oksidativni stres ključna komponenta mnogih procesa povezanih sa kroničnom upalom. Željeli smo ispitati da li se vrijednosti koncentracije C-reaktivnog proteina (CRP) i aktivnosti gama-glutamiltransferaze (GGT) u serumu mogu koristiti kao pomoćni markeri u praćenju razina oksidativnog stresa i upale u klinički stabilnoj KOPB. Također smo ispitali utjecaj pušenja na ta dva sistemska parametra. Katalitička aktivnost GGT-a i koncentracija CRP-a su određene u serumu pacijenata oboljelih od KOPB-a (N=109) i zdravih kontrolnih ispitanika (N=51) koristeći standardnu spektrofotometrijsku odnosno imunoturbidimetrijsku metodu. Koncentracija CRP-a i aktivnost GGT-a su bile povišene u pacijenata prilikom usporedbe sa zdravim kontrolama ($p < 0,05$). Pronašli smo statistički značajnu pozitivnu korelaciju između ta dva parametra u KOPB pacijenata ($r=0,02$, $p=0,0371$). Nismo pronašli razliku u aktivnosti GGT-a ($p=0,606$) i koncentraciji CRP-a ($p=0,573$) između grupa pacijenata podijeljenih prema stupnju težine bolesti. Pušenje nije imalo značajan utjecaj na vrijednosti CRP-a i GGT-a u KOPB pacijenata niti u zdravih kontrolnih ispitanika. Pokazali smo porast vrijednosti CRP-a i GGT-a u serumu pacijenata i pretpostavljamo da aktivnost GGT u serumu može također predstavljati marker upale/oksidativnog stresa. Čini se da se u serumu pacijenata oboljelih od KOPB-a nalaze više vrijednosti CRP-a i GGT-a nego u zdravih ispitanika, neovisno o njihovim pušačkim navikama.