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C-reactive protein in patients with COPD, control smokers and nonsmokers.

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Abstract:

Background: Patients with chronic obstructive pulmonary disease (COPD) have elevated serum levels of C reactive protein (CRP). This finding may be related directly to COPD and its associated systemic inflammation or secondary to other factors like concomitant ischemic heart disease (IHD), smoking status. The aim of this study was to evaluate IHD and smoking as potential causes of elevated CRP in COPD and to test the association between inhaled corticosteroids (ICS) use and serum CRP levels.
Methods: Cross-sectional analyses comparing cohorts of 88 COPD patients with 33 smokers (S) and 38 non-smoker (NS) controls. Clinical assessments included a complete medical history, pulmonary function, 6-minute walking test (6MWT), cardiopulmonary exercise test (CPEX) and high-sensitivity serum CRP.
Results: Serum CRP levels were significantly higher in COPD patients 5.03 (1.51) mg /L than in controls (adjusted odd ratio, 9.51; 95% confidence interval, 2.97-30.45) but similar in both control groups (S: 2.02 (1.04mg/L) and NS: 2.24 (1.04) mg/L). There was no clinical or exercise evidence of unstable IHD in any of the subjects. CRP levels were lower in COPD patients treated with ICS 3.7 (3.0) mg/L vs. 6.3 (3.6); this association was confirmed in an adjusted regression model ($p<0.05$).
Conclusion: CRP levels were elevated in COPD patients without clinically relevant IHD and independent of cigarette smoking. CRP was reduced in COPD patients using ICS. We conclude that CRP may be a systemic marker of the inflammatory process that occurs in patients with COPD.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a complex, chronic inflammatory disease of the lungs involving several types of inflammatory cells and a variety of inflammatory mediators. The relationship between these cell types, cytokines and the sequence of events that conclude with progressive airflow limitation and destruction of lung parenchyma remain largely unknown.[1]

Although primarily affecting the lungs, the chronic inflammatory process of COPD does have systemic repercussions. Inflammatory markers, including C reactive protein (CRP), lipopolysaccharide binding protein (LBP), the soluble TNF transmembrane receptor 75 (sTNF-R75) and soluble adhesion molecules are elevated in the systemic circulation of patients with COPD.[2] [3] [4] The impact of the systemic manifestations of COPD on prediction of mortality using a multidimensional index have been recently reported.[5]

CRP is a marker of inflammation that has been associated with an increased risk of incident myocardial infarction, stroke, unstable angina and sudden coronary death.[6] CRP contributes to the recruitment of circulating leukocytes, the uptake of low density lipoprotein (LDL) cholesterol by macrophages and ultimately to a destabilization of vascular wall atheroma.[7] Inflammation has also been thought to play a role in the development of systemic hypertension.[8]

Population studies have shown an association between COPD and increased mortality from ischemic heart disease.[9][10] Sin and Man[11] and Mannino and co-workers[12] studied participants of the Third National Health and Nutrition Examination Survey (NHANES III) and concluded that a low-grade systemic inflammation, measured by a single determination of CRP, was present in patients with airway obstruction and was associated with increased risk of cardiac injury. However, it is not clear from these studies if the elevation of CRP is due to the presence of concomitant IHD or the systemic inflammatory processes associated with COPD. Limited information regarding other causes of elevated CRP like major infection, trauma, acute hospitalization, lupus, inflammatory bowel disease (IBD) [6][11][12] and the use of a low sensitivity assay to measure CRP were important limitations of those studies.[11][12] Indeed, none of the study protocols ruled out the presence of unstable angina or exercise-induced cardiac ischemia.

In a recent study Sin et al. [13] reported that the withdrawal of inhaled corticosteroid (ICS) resulted in a significant increase in CRP levels. However, no other information exists about the association between CRP level and use of different types of inhaled corticosteroids (ICS) prescribed at different dosages.

Using a cohort observational design, we recruited patients with moderate-to-severe COPD and two control groups without COPD (smokers and nonsmokers) and tested them using a high sensitivity CRP assay. We determined the presence of IHD and exercise induced ischemia and excluded patient with history of angina, infection, trauma, recent hospitalization, connective tissue disorders, malignancy and IBD. The study design allowed us to determine the effect of smoking on CRP levels in subjects with and without airflow obstruction, as well as to assess the stability of CRP levels over time. We also evaluated the influence of inhaled corticosteroids on the levels of CRP.

METHODS

Study population

This report is based on a cross-sectional analysis of a cohort study at the Caritas St Elizabeth's Medical Center (CSEMC). Subjects were recruited between June 1999 and June 2001 from different sources: pulmonary clinic, pulmonary function test laboratory, local press advertisement, and referral by patients already enrolled. Control subjects consisted of responders to an advertisement in the local press and the hospital. They had no history of COPD, confirmed by spirometry performed during the screening process. The study was approved by the Institutional Review Board at CSEMC and all participants signed the informed consent. The cohort consisted of three groups: 1) COPD patients (COPD): smokers or ex-smokers, with advanced disease (FEV_1 <55% predicted). 2) Control smokers (S): current smokers with FEV_1/FVC and FEV_1 > 70%. 3) Control non smokers/ex-smokers (NS): defined as patients with (FEV_1/FVC and FEV_1 > 70%) and one of this two characteristics: patients who never smoked or patients with smoking abstinence for more than 15 years and less than 20 pack-years of smoking history. Smoking status was confirmed by measuring the level of carboxyhemoglobin in every subject. Inclusion criteria were as follows: age >35, stable disease for at least 2 months and ability to complete the protocol. Exclusion criteria for patients and controls included myocardial infarction within the past 6 months, angina (Canadian Class I to IV: chest pain with strenuous exercise, walking > 2 blocks, walking 1-2 blocks or at rest), congestive heart failure, ventilator dependency, malignancy, hepatic cirrhosis, end-stage renal disease, rheumatoid arthritis, orthopedic condition precluding performance of walking or cardiopulmonary exercise test, neurological or psychiatry illness that interfered with participation in the study, tuberculosis or any systemic infection or inflammatory process that could be associated with increased CRP values.

Interview and Physical exam: One physician (VPP) interviewed all the patients using a designed questionnaire that includes direct questions on 40 co-morbid conditions, respiratory symptoms, current medications, anthropometrics and detailed physical exam. All subjects completed the St. George's Respiratory Questionnaire.[14]

Pulmonary Function Test and Dyspnea: Patients performed spirometry, lung volumes and diffusion capacity test following ATS standards.[15] Functional dyspnoea was scored using the modified Medical Research Council scale.[16]

Six-minute walk Test: Patients performed two-times the 6-minute walk test following the ATS guidelines[17], with some modifications: namely, a person walked next to the patient and provided encouragement every 30 seconds. Oxygen saturation was monitored, and supplemented to patients whose oxygen saturation decreased more than < 85% with the oxygen tank carried by the monitor. The longer of the 2 walks was used for the analysis.

Cardio-pulmonary exercise test: Exercise testing was performed on a cycle ergometer while breathing room air (Vmax 29, Sensormedics; Yorba Linda CA). Patients completed the following protocol: 2 minutes rest, 3 minutes no-load work followed by a 16 watts/ minute exercise with continuous 12 lead electrocardiogram (EKG) monitoring. Patients were exercise until exhaustion or evidence of IHD was present (clinical or by EKG). Minute ventilation (VE), oxygen uptake (VO2), and carbon dioxide output (VCO2) were measured breath by breath. The electrocardiogram was interpreted by an independent

physician to evaluate the presence of exercise-induced ischemia. Patients with evidence of IHD were excluded and referred to cardiology.

C reactive protein: Blood samples were obtained while the patients were at rest, before any other test was performed. Concentrations of CRP were determined using a high sensitivity chemiluminescent inmunoassay (DPC Immulite,) following the manufacturer instructions. The analytical sensitivity of this high sensitivity assay is of 0.1 mg/L. Samples were identified by a barcode, thus samples from controls and COPD patients were randomly distributed among assays plates.

Statistical Methods: Normally distributed data were summarized using arithmetic means and standard deviations (SD). Variables judged to be skewed were log-transformed and summarized using geometric mean and associated standard deviation. Between-group differences in the main descriptive variables were analyzed, depending on their nature, using student's t-test for independent samples or chi-square statistics (including Fischer's exact test).

First, we tested the association between the level of CRP and disease status (COPD and non-COPD) and adjusted for potential covariates. Logistic regression model was fitted with the disease status as a response variable. Several variables were selected as covariates, based on our preliminary knowledge that they can affect the CRP: age, gender, smoking history (pack-years), smoking status (never/former/current smoker), BMI and history of ischemic heart disease. Odds ratio accompanied by the 95% Wald confidence intervals was reported.

Second, we tested reproducibility of CRP values over time. We selected a subgroup of subjects with longitudinal follow-up (total N= 78; COPD= 36, control smoker= 21, control non/ex-smoker= 21) and repeated collection of serum samples (two samples, each collected at a respective visits; mean lag time between two visits = 17.7 $\pm$7.5 months). Reproducibility was explored using the Bland-Altman plot expressing the change within a subject and mixed linear models (adjusted for age, gender, smoking history, BMI, FEV1 and inhaled corticosteroid use). The zero hypothesis (no evidence for the lack of reproducibility) was tested as the absence of change over successive measurements.[18]

Third, we searched for best predictors of CRP value in COPD patients only. We used CRP levels as a response variable fitted in the generalized linear model. Predictor variables were selected based on our presumption they are associated with COPD severity and patients' functions (FEV_1 predicted, DLCO predicted, 6-MWT, history of COPD exacerbations, MRC dyspnoea scale and SGRQ). Additionally, known covariates, age, gender, smoking history (smoking status and packyears), history of ischemic heart disease and BMI, were also included.[19][20] Predictors judged to show little contribution to the model (p=0.15) were dropped from the full model.

Finally, we explored whether anti-inflammatory treatment with steroids can influence CRP level in COPD patients. The effect of medication, inhaled corticosteroids and oral steroids use [binary variable], was tested using linear mixed models adjusted for age, gender, smoking status, FEV_1 predicted and BMI.

Between-group differences were considered to be statistically significant at 5% level. The SAS v8.01 statistical software package was used for analyses.

RESULTS:

The baseline characteristics of the 88 COPD patients, 33 control smokers and 38 control non-smokers are shown in Table 1.

Table 1 **Demographics and clinical characteristics of the study population**

Variable	**COPD patients**	**Control Smokers (S)**	**Control Non Smokers (NS)**	**p value**
Number	88	33	38	
Gender % (M:F)	59:41	61:39	66:34	
Age (years)	66 (9)	62 (6)	67 (7)	*****: < 0.05 †: < 0.001
BMI (kg/m^2)	27.04 (5.43)	26.54 (5.63)	28.94 (4.43)	
Smoking (packs/year)	53 (3)	44 (2)	5(6)	*: < 0.05 † ‡: <0.001
IHD (%)	12.5	3.0	10.5	
MI (%)	10.1	3.0	2.6	
CRP (mg/L) All subjects	5.0 (1.5)	2.0 (1.0)	2.2 (1.0)	*,‡: < 0.001
CRP (mg/L) Subjects with IHD excluded	5.0 (1.5)	2.0 (1.1)	2.3 (1.1)	*,‡: < 0.001

Results are expressed as mean (SD). CRP values expressed as mean GeomMean (SD). p value non significant unless stated. IHD (%): percentage of patients with ischemic heart disease. MI (%):percentage of patients with myocardial infarction.
***** Comparison COPD and Control smoker (S) † Comparison between Smokers (S) and Non Smokers (NS)‡ Comparison between COPD patients and Non smoker (NS)

Patients with COPD were older and had longer smoking histories than control smokers (S). IHD had the same prevalence in COPD and non-smokers subjects but it was less frequent in smokers. There was also no difference among the groups in the prevalence of other screened comorbidities (data not shown). The majority of COPD patients were treated with inhaled short acting beta-agonists and anticholinergics (75% and 70%, respectively). Inhaled corticosteroid (60%) and long-acting-beta2-agonists were also prescribed (41%). Patients received theophylline (25%) and oral corticosteroids (16%) less frequently.

The CRP level was significantly higher in COPD patients (Geometric mean 5.03 (1.51) mg /L) compared to S 2.02 (1.04) mg/L and NS 2.24 (1.04) mg/L, (Table1, Figure 1) and this difference persisted even after adjustment for age, gender, smoking, IHD history and BMI in a multivariate logistic regression model. The adjusted odds ratio (OR) for increased CRP levels (in log scale) comparing COPD and control subjects was 9.51

(95% confidence interval [CI] 2.97-30.45). No difference was observed between control smokers and non-smokers. Likewise, among COPD patients, the mean CRP value in smokers (14%) and ex smokers (83%) was not significantly different (Geometric means 5.1 (3.2) vs. 4.3 (3.3), respectively). There was also no difference in CRP level after patients with known IHD were excluded from the analysis (Table 1).

The results of the pulmonary function tests, dyspnoea score and exercise capacity assessments are summarized in Table 2.

Table 2 **Results of the pulmonary function test, dyspnoea level and exercise capacity of the study population**

Variable	COPD patients	Control Smokers (S)	Control Non Smokers (NS)
FEV_1 (%)	37 (11)	91 (15)	92 (17)
FEV_1 /FVC (%)	42 (11)	73 (6)	75 (6)
TLC (%)	130 (23)	101 (18)	102 (20)
FRC (%)	174 (38)	99 (25)	105 (29)
DLCO (%)	52 (21)	89 (22)	96 (20)
MRC	2.2 (0.9)	0.5 (0.7)	0.2 (0.4)
6MWT (m)	375 (99)	546 (75)	558 (102)
Watts	64 (29)	119 (37)	131 (41)
VO_2 peak (mL/kg/min)	10 (4)	20 (5)	21 (7)

Results are expressed as mean (SD); geometric means are presented for non normally distributed variables.
All variables shown in table 2 were significantly different when comparing COPD patients and controls. There was no difference observed between the two control groups.

The CRP levels remained essentially unchanged in a subgroup of patients (36 with COPD and 42 control smokers and non/ex smokers) re-tested at a subsequent visit (mean lag time between visits: 17.7 (7.5) months). Coefficient of variance for variability within subjects was 14.6%. Using the mixed linear regression model with adjustment for known covariates no statistically significant difference was detected for the change of the CRP level over time (Figure 2). Also, the Bland-Altman plot with upper and lower limits (1.96 SD) shows a good consistency of data (difference between visit 1-visit 2), with only 6 outliers (Figure 3).

The correlation of CRP with potential predictors of severity and functioning of COPD, and the ability of covariates to predict CRP levels was tested in the cohort of COPD patients only. The final models describing predictive variables, their parameter estimate (regression coefficient) contribution to the sum of squares statistics and significance are shown in the Table 3. This analysis showed that the 6MWT, age and BMI significantly predict CRP level in COPD patients; CRP level increases with increasing BMI and decreasing 6MWT and age. Gender, smoking history, FEV_1 % predictive and history of COPD exacerbation in interaction with other predictors in the model contribute in

predicting the CRP level, though none of them appear to be an independent predictor with a 5% level of statistical significance. The most important, clinically relevant predictor was 6MWT (6MWT decreases with increased CRP). Neither smoking status, MRC scale, DLCO nor history of IHD had shown an effect on CRP levels.

Table 3 Multivariate regression model evaluating the predictors of CRP levels in the COPD cohort

Variables	Parameter Estimate	SE*	Type III SS #	Significance
Age	-0.02	0.01	1.38	0.009
Gender	-0.16	0.10	0.51	0.107
Pack-Years	0.18	0.12	0.43	0.141
BMI	0.04	0.01	2.84	<0.001
FEV_1 % predicted	0.81	0.43	0.67	0.065
6MWT	-1.14	0.44	1.29	0.012
COPD exacerbation_history	-0.16	0.10	0.52	0.106

SE(Standard Error) for the Parameter Estimate # Type III Sum of Squares
(All of the effects are examined simultaneously, i.e. the magnitude of each main effect or interaction is examined after controlling all the other main effects and interactions.
The Total Sum of Squares was 6.83. The R-Square estimate = 0.31.
The following variables were included in the full model, but excluded, because they failed the significance limit P<0.15: history of IHD, DLCO % predicted, SGRQ Composite score.

Fifty three patients with COPD (60 %) were using metered-dose inhaled corticosteroids (ICS). The baseline characteristics of both groups are shown in Table 4. The ICS used by the patients, dosage and percent of users included Fluticasone: 440-880 μg (45%), Flunisolide: 1000-4000μg (29%), Budesonide: 800-1200 μg (16%) and Triamcinolone: 400-1600 μg (10%). The CRP level in ICS users was statistically lower compared to that of patients not using ICS when tested by Student's t-test (Geometric Mean 3.7 (3) vs 6.3 (3.6) respectively, $p<0.05$)(Figure 4). The only statistical significant difference between the ICS users and nonusers was higher pack year history in ICS non-users (Table 4). Further analyses, using a linear mixed regression model adjusted for age, gender, BMI, smoking history, FEV_1 predicted value and oral steroid use, showed a trend for a decrease in CRP level in ICS users compared to non-users ($p<0.05$) (Data not shown).

Table 4. Demographics and clinical characteristics of ICS users and non-users.

	ICS yes	ICS no
N	53	25
Age (y)	66 (9)	64 (9)
Gender (% men)	60	56
Smoking (Pack/year)	48 (3)	59 (1)
Current smoker (%)	13	12
IHD (%)	13	12
MI (%)	11	8
BMI (kg/m^2)	26.7 (5.2)	27.58 (6.4)
FEV1 (% predicted)	37 (11)	35 (11)
6MWT (m)	388 (96)	345 (111)

Results are expressed as mean (SD). (Geometric Mean for log transformed variables). IHD: Ischemic heart disease. MI: Myocardial infarction. BMI: Body mass index. FEV_1: Forced expiratory volume in the first second. 6MWT: six-minute walk test distance.

DISCUSSION

In this study we confirm that CRP is elevated in patients with moderate to severe COPD. This elevation seems to be independent of clinically significant ischemic heart disease. It was also independent of cigarette smoking and reduced in patients using ICS, likely reflecting the systemic inflammatory process in patients with severe disease.

Several epidemiologic studies have found a significant relationship between pulmonary function and cause-specific mortality due to IHD.[9][10][11][12] Sin and Man[11], using population-based data from the Third National Nutrition and Examination Survey (NHANES III), studied 6629 patients including 2070 with mild, moderate and severe COPD. Using a low sensitivity CRP method (lowest detectable level 0.22 mg/dl) and a coding scheme to calculate a cardiac infarction injury score with a resting EKG, they concluded that moderate and severe COPD was associated with a higher level of CRP and increased occurrence of ischemic changes on electrocardiogram. Similarly, Mannino and coworkers[12] also using data from NHANES III, described an association between severity of COPD and level of CRP. A recognized limitation of both studies is that participants might have undiagnosed or asymptomatic IHD that is associated with lower levels of pulmonary function and high short-term mortality risk.[9][21]

Our study expands these observations. First, we excluded the presence of clinically significant or sub-clinical IHD using a comprehensive medical examination and exercise test with continuous EKG monitoring instead of a resting EKG alone.[11] We also excluded other conditions associated with increased CRP including acute and chronic infection, chronic inflammatory diseases (rheumatologic, gastrointestinal) and known malignancies. A follow up questionnaire and physical exam over one year after the initial encounter further exclude any of these conditions as responsible for an elevated

CRP. Second, we used a high sensitivity CRP test to obtain more accurate values than the 2 previous studies.[11][12]

We observed no difference in the mean CRP value between control smokers and non-smokers, despite the fact that the former group was younger than the later. Similarly, there was no difference among the patients with COPD who were current smokers and ex-smokers. These findings may be due to the lack of power to determine a difference between the 2 groups, the absence of inflammatory response in the group of smokers or persistent inflammation in COPD patients even after smoking cessation as seen in human lung samples.[22] A recent study[23] did report an association between cigarette smoking and a high CRP concentration ($p< 0.001$) but the data was not shown. In that study, it was unclear if COPD was ruled out in the group of smokers who had an elevated CRP value. The observation that CRP values were not different between smoker and non-smoker controls, and between smoker and ex-smoker patients with COPD may also suggests that the elevation of CRP may represent a phenotype of CRP responders. Little is known about the reason why some persons exposed to cigarette smoke develop clinically important COPD whereas others do not. We speculate that there may be individuals with an "inherited" inflammatory genetic profile (a proportion of our control, never smoker population had a CRP above 3 mg/L). If they are "exposed" to environmental factors (smoking, pollution), they have a higher risk of developing COPD.

Although our study fails to provide a mechanism, it does point out that the differences may precede the exposure to the trigger (cigarette smoking). It would be extremely interesting to determine CRP levels in teenagers before or around the time they begin to smoke to gain some insight about the presence in the general population of possible "inflammatory" phenotypes.

The CRP value in patients with COPD was lower in ICS users compared to non-users (Figure 4). These results are in concordance with a recent publication by Sin et al, who demonstrated that withdrawal of inhaled corticosteroids in patients with mild and moderate disease was associated with an increased in baseline CRP level by 71%.[13] It may be interesting to study larger groups of COPD patients treated with ICS[24][25] or withdraw from ICS[26] and determine if the changes in the number of COPD exacerbations and quality of life observed in those studies correlate with changes in the CRP level.

The mean CRP level in COPD patients in our study was similar to the results reported by Mannino et al.[12] It contrast, the values reported in epidemiologic studies of controls and patients who eventually developed IHD is at least three times lower.[23] This finding further supports the concept that CRP elevation in patients with severe COPD cannot be attributed only to concomitant IHD. CRP is a marker of systemic inflammation and has been associated with increased risk of incident myocardial infarction and stroke.[6][8] As suggested by others,[11][13] it is possible that the persistent systemic inflammation in patients with COPD may contribute to the pathogenesis of atherosclerosis and cardiovascular disease and explain a high risk of cardiovascular mortality in mild and moderate COPD. If we use the CRP values of <1, 1-3 and >3 mg/L reported to represent low, moderate and high risk groups for future cardiovascular events,[6][19][20] almost

60% of the COPD patients in our study would be categorized as high risk (data not shown).

One important finding of our study is that the value of CRP remained unchanged in the great majority of the patients retested after adjustment to age, gender, BMI and FEV_1 % predicted. This finding is in concordance with a recent report [23] that included 379 patients who provided paired blood for CRP analysis (mean time between samples was 12 years) and a within-person correlation of 0.59 (95 % confidence interval 0,52 to 0.66). Similar correlations have also been reported in other studies of normal subjects.[27] and we now reported it in COPD patients with COPD.

There was no association between selected pulmonary function test measurements (FEV_1, DLCO) and CRP level in COPD patients. A probable explanation is that our study was limited to patients with moderate to severe disease with a narrow range of these parameters likely failed to show any association. However we found an association between the CRP level and the BMI, and 6MWT that may prove clinically important. Probably, these clinical parameters reflect the systemic repercussions of COPD and the CRP level is a measure of the systemic inflammation observed in COPD patients.

Our study had some limitations. The population of patients with COPD included in the cohort was selected and therefore excluded patients in the community with milder forms of COPD. There were patients with known IHD in the COPD and control groups. However, there was no difference in the mean CRP level when these patients were excluded. We carefully sought to exclude clinically important ischemic heart disease, the biggest confounder of the studies published to date. The patients studied underwent a complete medical interview, a physical exam and a cardiopulmonary exercise test with electrocardiographic monitoring to rule out possible unstable IHD and those with "silent" or subclinical IHD. However, the sensitivity and specificity of the exercise test in asymptomatic patients is unknown and may never be known because a coronary angiography, the "gold standard" to diagnose coronary artery disease, is not indicated in asymptomatic patients. [28] Patients with recent acute exacerbation of COPD, arthritis, clinical evidence of acute or chronic infection or other chronic inflammatory process were also excluded from the analysis. Our findings are in agreement with the larger epidemiological studies and serves to complement them. Finally, we would like to point out that even though a large proportion of patients with COPD do die from cardiac reasons,[13] many will die from COPD.[5] To simply state that concomitant heart disease is the reason for the elevated CRP in patients with COPD may not fully explain the findings here reported and underestimate its importance as an independent biomarker of COPD.

In conclusion, we confirmed that CRP levels are significantly elevated in patients with COPD and this elevation is not related to smoking *per se* or to concomitant clinical or subclinical ischemic heart disease. The value of CRP remains stable over time in normal individuals and in patients with COPD, and was lower in patients treated with ICS.

Ethics Approval: The study was approved by the Institutional Review Board at CSEMC and all participants signed the informed consent

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Figure legends

Figure 1
The mean CRP value (Geometric Mean) distribution with interquartile range in COPD patients, control smokers and control non-smokers. The C reactive protein (CRP) values were higher in patients with COPD than in control smokers (S) and non smokers (NS). The value was similar for the latter two groups.

Figure 2
Intra-individual change in CRP level between visit 1 and visit 2 in subjects (COPD and control cohorts) with repeated measurement of CRP (mean lag time between visits = 17.7 (7.5) months). Each line connects measurement of an individual subject.

Figure 3
Bland-Altman plot of CRP reproducibility between two measurements.
The C reactive protein (CRP) level remained stable over the 18 months of the mean follow up time.

Figure 4
The mean CRP value (Geometric Mean) distribution with interquartile range in ICS users and non-users.
The C reactive protein (CRP) value was lower in users than non-users of inhaled corticosteroids (ICS).

Figure 1

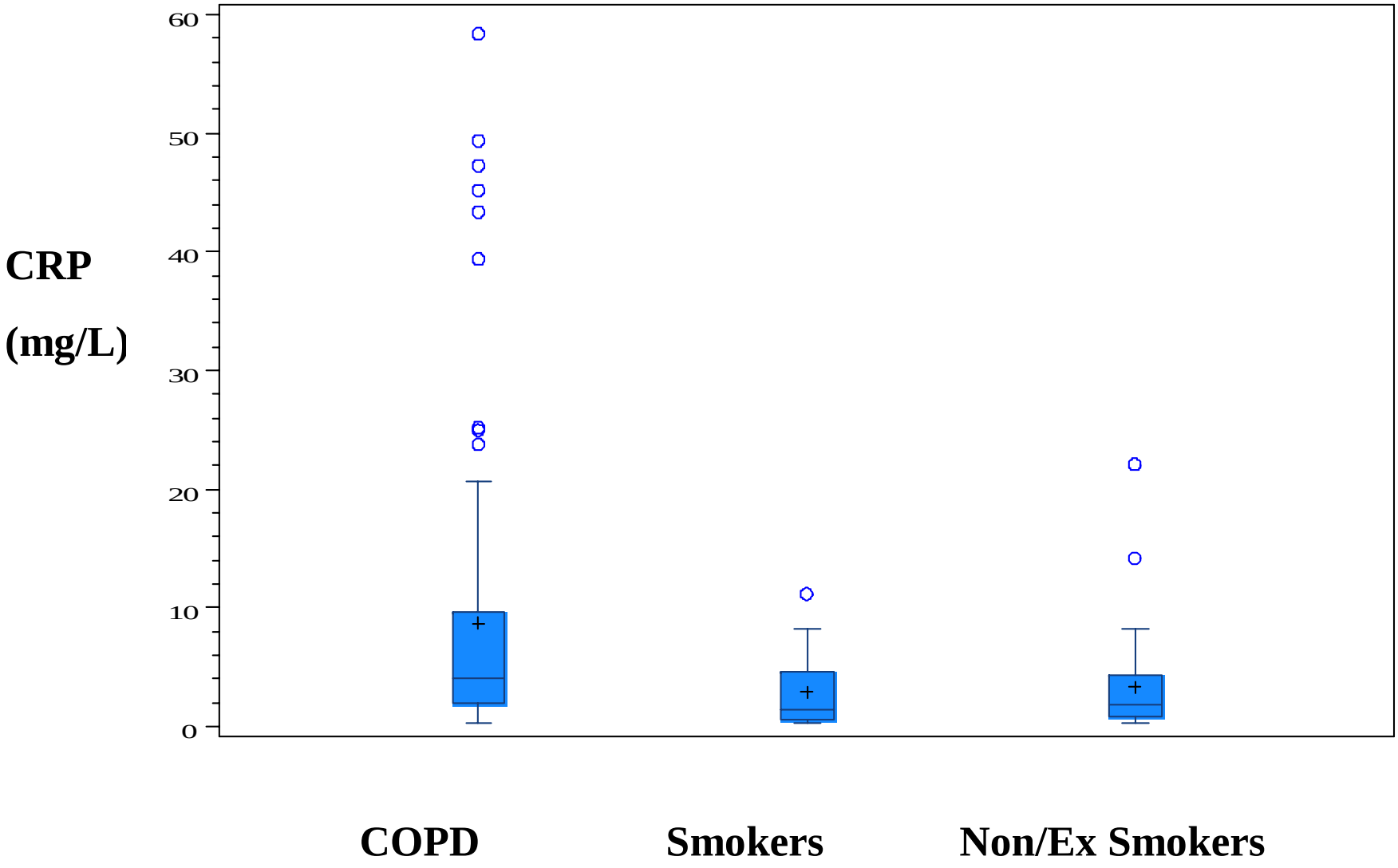
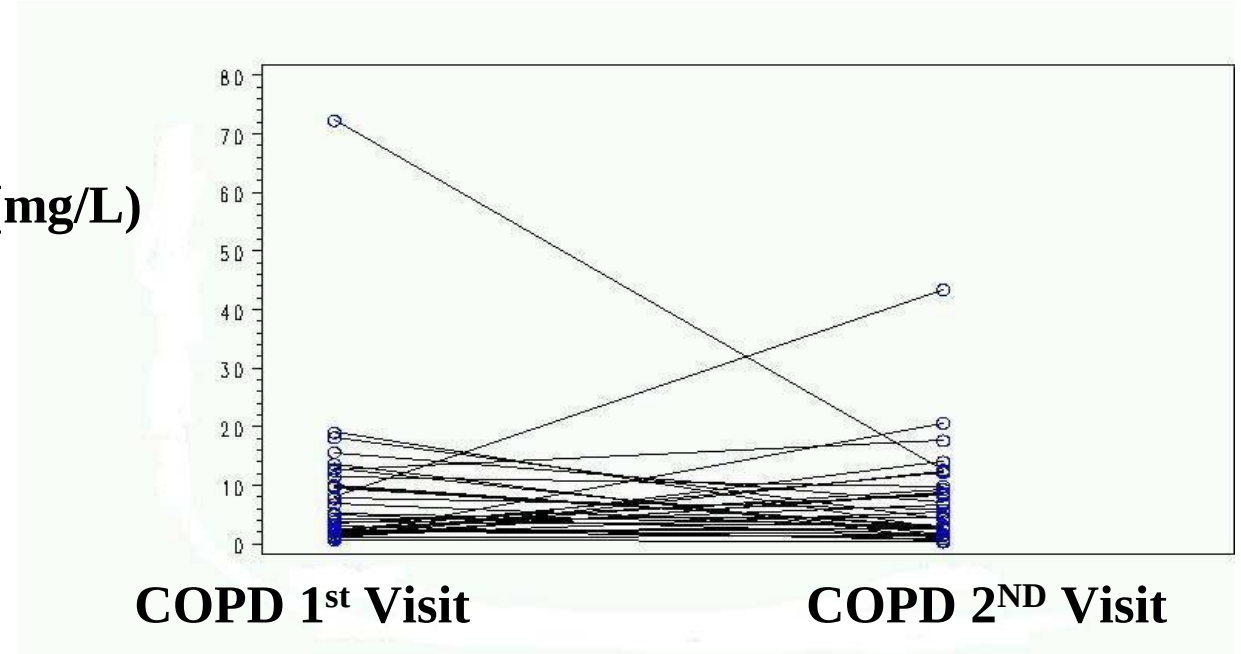


Figure 2



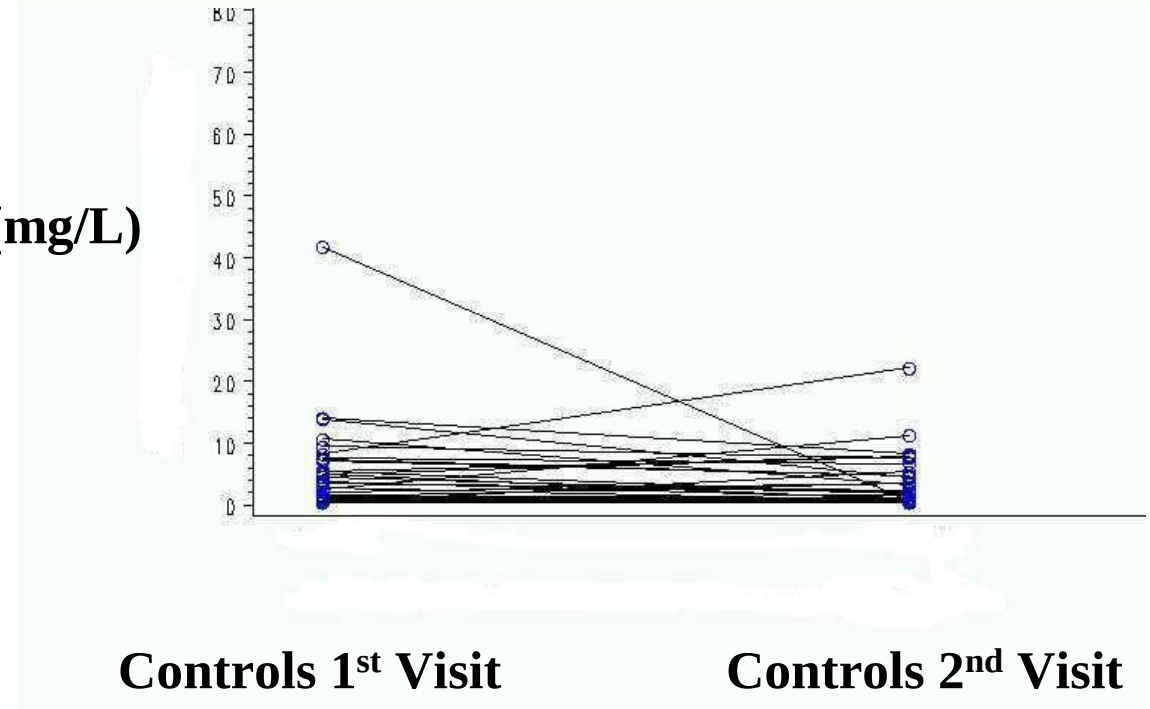


Figure 3

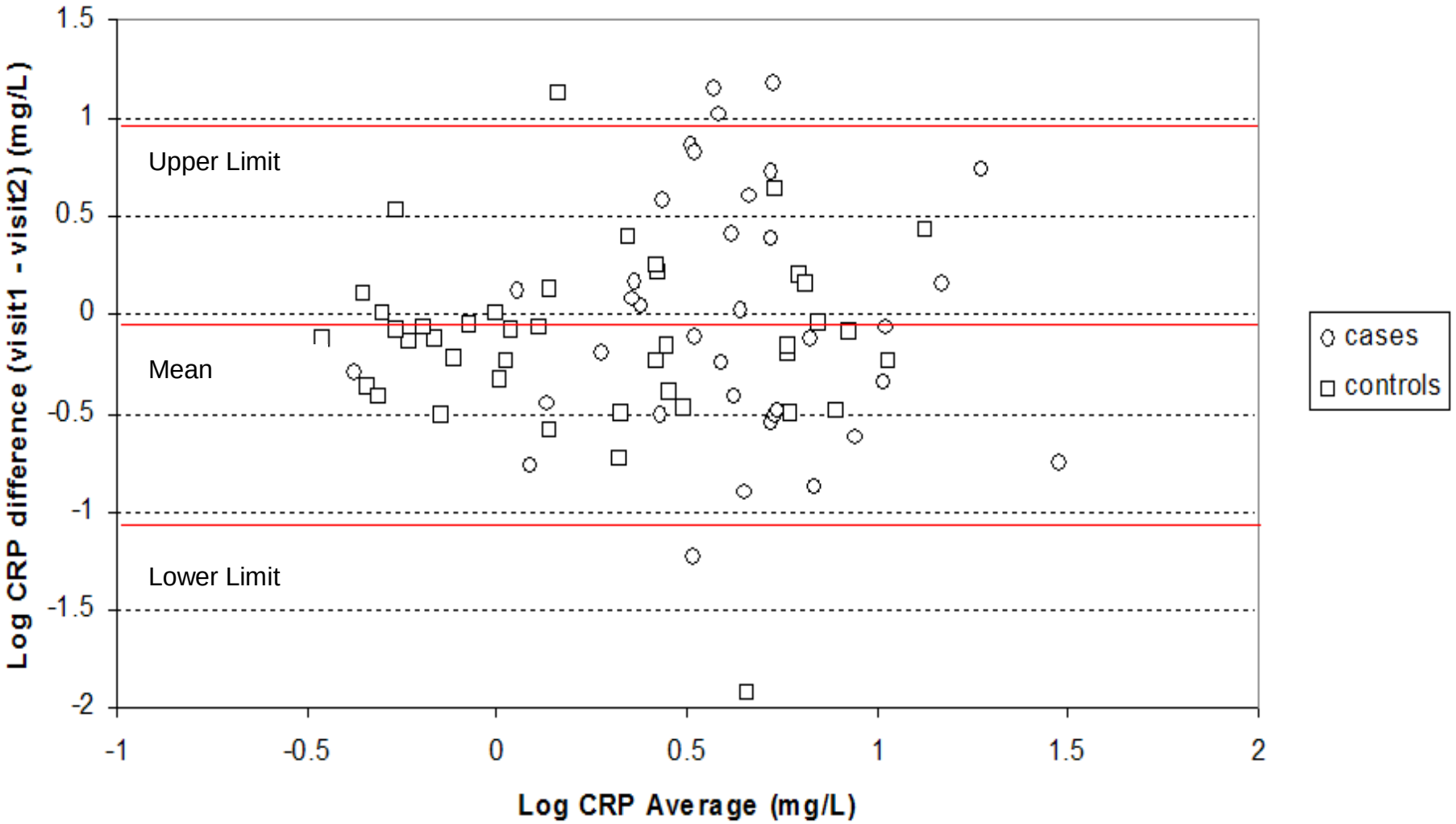


Figure 4