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Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromsø Study 2001

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ABSTRACT

Background: Bronchial airflow limitation is a known predictor of raised C-reactive protein (CRP) level. The aim of this study was to explore this association in an elderly population, as well as the influence of other known and possible predictors of the CRP level, like smoking and the use of statins and inhaled corticosteroids.

Population and Methods: The study population consists of 3877 Norwegians aged 60 years or more who took part in the fifth Tromsø study in 2001, a cross-sectional study. The examinations included questionnaires, spirometry and the measurement of CRP.

Results: A geometric mean CRP value of 3.15 mg/L was found in subjects with severe airflow limitation (FEV_1 % < 50 predicted and FEV_1/FVC <70%), compared to 1.64 mg/L in subjects with normal spirometry, ($p < 0.001$), and 19% of the subjects with severe airflow limitation had a CRP value above 10 mg/L compared to 4.9% in those with mild airflow limitation or normal spirometry. Elevated body mass index (BMI), smoking, hormone replacement therapy, and increasing age, were also strong independent predictors of increased CRP. Statin use was a strong predictor of decreased CRP level, while the use of inhaled corticosteroids was not associated with decreased CRP values.

Conclusion: We found a strong link between bronchial airflow limitation and the circulating CRP level in an elderly population, independent of self-reported diseases, medication, smoking, and elevated BMI. The CRP value increased with increasing age in men, but not in women, which may be partly explained by a greater impact of COPD morbidity on the CRP level in men than in women. Measuring CRP may show to be a useful part of the diagnostic work-up in COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by inflammatory changes in all segments of the bronchial tree,¹ which can be traced by, among other biomarkers, the circulating C-reactive protein (CRP). Among COPD patients, raised CRP values are particularly found in severe cases,²⁻⁵ and in patients with frequent exacerbations.⁶ Increased CRP values are not only associated with the degree of bronchial airflow limitation,⁷⁻¹⁰ but is an independent prognostic factor in COPD patients.^{11, 12} Cigarette smoking is a known predictor of raised CRP level, but can only partly explain the association between the CRP level and the severity of airflow limitation.^{5, 10} COPD is an established risk factor of myocardial infarction, and since elevated CRP predicts cardiovascular events,^{7, 13, 14} CRP has been suggested to be a link between these conditions.¹⁵

The use of oral or inhaled corticosteroids has been shown to reduce the CRP level in COPD patients,^{5, 16} and reduces the frequency of exacerbations in severe disease.¹⁷ There is also evidence of a favourable effect of inhaled corticosteroids in COPD patients in terms of reduced risk of cardiovascular death.¹⁸ Statins reduce both CRP level and mortality in subjects with cardiovascular disease.¹⁹ The effect of statins on the inflammatory response in COPD is still unknown.

The aim of this population based study was to explore how the CRP level, in an elderly population, is associated with bronchial airflow limitation when analyzed together with other factors affecting the inflammatory response, like smoking, body mass index and the use of statins and inhaled corticosteroids.

METHODS

Subjects

The participants were inhabitants of Tromsø aged 60 years or more, who took part in a population survey between March 2001 and February 2002. The Tromsø Study is a repeated population based study in the municipality of Tromsø, a city in the northern part of Norway, with a current population of 64000. This fifth Tromsø Study was conducted by Institute of Community Medicine, University of Tromsø in cooperation with the National Health Screening Service. In the fourth survey in 1994, all inhabitants aged 55-74 years of age, and 5-10% of samples in other age groups between 25- 84 years, were asked to take part in a second, and more extensive medical examination (phase II). The attendance rate was 77%. In this fifth survey, all phase II participants from the fourth survey who still lived in Tromsø, were eligible to participate. In addition, all inhabitants aged 60 and 75 years were invited. A total of 5328 subjects aged 60 years or more were eligible and 4713 (88.5%) attended phase one, and 4519 (85%) attended also phase II. Spirometry was performed in 4102 subjects, 90% of the attendees and 77 % of those eligible for participation. Absence of staff and technical problems were reasons for spirometry not being performed in 10% of the attendees. At the time of data analysis, 54 subjects had withdrawn their consent to participate. Ninety women and 21 men (2.7% of all) were excluded due to inadequate spirometry.²⁰ Of the 3938 remaining subjects, CRP measurement was obtained in 3877 (72.8% of all eligible), and these were included in our analyses.

Examinations

A questionnaire including smoking habits, previous diseases, and daily medication was enclosed in the letter of invitation and collected at the following visit, where height and weight were measured. Participants who reported to be suffering from asthma and chronic bronchitis, were classified as “self-reported asthma” and “self-reported chronic

bronchitis/emphysema”, respectively, and they were grouped together as “self-reported obstructive lung disease”. Those reporting angina pectoris, myocardial infarction or cerebral stroke, were classified as “self-reported cardiovascular disease”.

The brand names of prescribed drugs used regularly during the four weeks preceding the study were reported and registered on the fifth level of the Anatomical Therapeutic Chemical (ATC) system, version 2000. Participants reporting a proprietary name of a statin (ATC group C10AA), were classified as statin users in the analysis. Use of inhaled and systemic corticosteroids were defined from self-report of brand names belonging to ATC groups R03BA and R03AK, and H02AB, respectively. Participants reporting use of antihypertensive treatment, were classified as users of antihypertensives, regardless of reported brand names. Use of systemic estrogens, (hormone replacement therapy, HRT) was only to be reported by women.

When attending the first examination, the participants got a second questionnaire, which should be submitted by post or delivered when they met for the phase II examination a few weeks later. One of the questions addressed recent airway infection: “Have you, during the last 3 weeks, had a common cold, a flu, bronchitis, pneumonia, sinusitis or other airway infection?”

Spirometry, carried out with the use of a “Sensormedics Vmax 20”, was part of the phase II examination. The American Thoracic Society-criteria for spirometry testing were followed.²¹ Reversibility test was not performed. Current drug therapy was not interrupted before the test. The European Community of Steel and Coal (ECSC)²² equations were used in the calculation of % predicted values. The subjects were allocated into five groups on the basis of lung function: Severe airflow limitation: $FEV_1/FVC < 70\%$ and FEV_1 % predicted < 50 (corresponding to GOLD stage 3 and 4), moderate airflow limitation; $FEV_1/FVC < 70\%$ and FEV_1 % predicted ≥ 50 and < 80 (corresponding to GOLD stage 2), mild airflow limitation: $FEV_1/FVC < 70\%$ and FEV_1 % predicted $\geq 80\%$ (corresponding to GOLD stage 1),

pulmonary restriction: $FEV_1/FVC \geq 70\%$ and FEV_1 1 % predicted <80 , and normal airflow: $FEV_1/FVC \geq 70\%$ and FEV_1 1 % predicted ≥ 80 .

On the examination day blood was drawn for CRP analysis. Sera were stored at -20°C until tested. CRP was measured by high (ultra) sensitive CRP method (particle-enhanced immuno-turbidimetric assay) in MODULAR P auto-analyser (Roche/Hitachi) with reagents from Roche Diagnostics GmbH, Mannheim, Germany. The analytical sensitivity (lower detection limit) of this assay is 0.03 mg/L, and the measuring range is 0.1-20 mg/L. The analytical coefficient of variation (CV) is 3.6%. The samples with CRP more than 5 mg/L, were analysed by immunoturbidometric method with in the same analyser and with reagents from the same manufacturer. The analytical sensitivity (lower detection limit) of the assay is 3mg/L, and the analytical coefficient of variation (CV) is 4.0%.

Statistical analysis

The CRP values were analysed according to gender, age, smoking habit, spirometry results, body mass index (BMI), self-reported diseases and medication. Differences between groups were analyzed using Mann-Whitney's and Chi-square tests. Pearsons' correlation was calculated between the CRP level and other variables. Because CRP values were skewed, geometric means were calculated, and explanatory variables were entered multivariable linear regression analysis with log-CRP as the outcome variable. The SPSS 12.0 for Windows (SPSS inc, Chicago, Illinois, USA) was used in the statistical analyses. A p-value <0.05 was considered significant. The Regional Committee for Medical Research Ethics in North Norway approved the Tromsø V survey. All the participants gave written informed consent.

RESULTS

Mean age in the study material was 69.4 years, and 54.1% of the 3877 included subjects were women. Among women, 47.2% were never smokers, compared to 18.2% among the men (table 1). BMI fell significantly with increasing age in men ($r = -0.154$, $p < 0.001$), while a weak positive correlation, statistically insignificant, was found in women. Moderate or severe airflow limitation was more frequently detected in men than in women, in 17.8% and 12.7%, respectively ($p < 0.001$), and this sex-difference was particularly pronounced among the subjects older than 70 years (table 1). Cardiovascular disease was reported almost twice as often in men than in women, while there were only small differences in self-reported obstructive lung disease and diabetes. Systemic oestrogens was reported more than double frequency in women aged 60 to 70 years compared to older women.

CRP by gender, age and life-style.

CRP values ranged from 0.12 to 220 mg/L, the mean value was 3.58 mg/L, the median value 1.66 mg/L, whereas the geometric mean was 1.81 mg/L. No significant difference in geometric mean CRP value was observed between men and women (table 2). A significant correlation between age and CRP level was found for men ($r = 0.072$, $p < 0.005$), but not for women ($r = 0.003$, NS). Current smokers had significantly higher CRP values than previous smokers, and CRP values were highly increased, with a geometric mean of 2.59 mg/L in subjects with BMI higher than 30 kg/m² (table 2).

CRP by lung function and reported diseases

Moderate to severe airflow limitation and pulmonary restriction were associated with increased CRP values, and the geometric mean was 3.15 mg/L in severe airflow limitation (table 2). In this subgroup, 18.9% had a CRP value above 10mg/L (figure 1). In the subjects with normal spirometry or mild airflow limitation the frequency was significantly lower, 4.9%

($p < 0.001$). Self-reported obstructive lung disease, cardiovascular disease, diabetes and recent airway infection were all associated with increased CRP values (table 2)

CRP and medication

Use of antihypertensive medication was associated with increased CRP values (table 2).

Among the 512 subjects who reported obstructive lung disease, 172 used inhaled corticosteroids. The geometric mean CRP in these 172 was 2.55 mg/L, compared to 2.26 mg/L in the 340 non-users (a non-significant difference). Oral corticosteroids were used in 23 of the subjects who reported obstructive lung disease. Their geometric mean CRP value was 1.99 mg/L, compared to 2.37 in the 489 non-users ($p < 0.001$). Among the oral corticosteroid users who did not report obstructive lung disease the geometric mean CRP was 5.15 mg/L. Significantly increased CRP values were detected in women who used HRT.

Statin use was associated with decreased CRP values. This was particularly the case in subjects who reported cardiovascular disease, but not obstructive lung disease, 1.54 mg/L and 2.30 mg/L, in users and non-users, respectively ($p < 0.001$, table 3). When both cardiovascular and chronic lung diseases were reported, the CRP values did not differ significantly between users and non-users of statins (table 3).

CRP in healthy subjects

The geometric mean CRP value was 1.26 mg/L in the 646 subjects who were never smokers, had a BMI < 30, had not reported chronic respiratory or cardiovascular disease, diabetes, or recent airway infection, and were not using oral corticosteroids.

Multivariate analysis

By multivariate analysis, age, male gender, smoking, BMI, diabetes, recent airway infection and use of HRT and oral corticosteroids, were significant predictors of increased CRP values,

whereas increasing FEV₁% predicted and use of statins were associated with decreased CRP values (table 4). Multivariate analyses excluding the subjects who reported recent airway infection, gave similar results, but cardiovascular disease became a significant predictor ($p < 0.05$), whereas previous smoking turned out to be an insignificant predictor.

DISCUSSION

We observed a strong association between reduced bronchial airflow and increased circulating CRP level among elderly subjects. Among subjects with severe airflow limitation, as many as 19% had a CRP value above 10 mg/l, in line with a population based study including younger individuals.⁸ The sensitivity of the CRP measurement, with a lower detection limit of 0.03 mg/L, made possible more valid results than in the study by Mannino et al.⁸ As described in previous studies, BMI^{7, 23}, current smoking,^{5, 10} and use of systemic oestrogens²⁴ were strong predictors of raised CRP values, and added to the effect of airflow limitation. Interestingly, self-reported cardiovascular disease did not turn out to be an important independent predictor of elevated CRP level in the multivariate analyses, even when controlled for statin use.

The reduced CRP values among the statin users, compared with non-users, were comparable to reductions found in clinical trials with statins in patients with cardiovascular disease.²⁵⁻²⁷ The decreased CRP level associated with statin use in those who reported both obstructive lung disease and cardiovascular disease or only obstructive lung disease did not reach statistical significance. Probably, there is no such strong effect of statins on inflammation linked to COPD, as has been demonstrated in cardiovascular disease. A reduced mortality in COPD patients who use statins has been found in a recent study.²⁸ The reduction found was not necessarily associated with statin effects on the inflammatory response in COPD, but may be explained by a very high prevalence of cardiovascular disease, known and unknown, in COPD patients.²⁸ With this strong tendency of co-morbidity in mind, the low frequency of statin use in subjects with severe airflow limitation (table 3) seems to be a clinical challenge.

It was surprising that the use of inhaled corticosteroids was not associated with decreased CRP level, not even when controlled for the degree of airflow limitation by multivariate analyses. Pinto-Plata and co-workers found significantly reduced CRP levels associated with inhaled corticosteroid use in an observational study of patients with severe

COPD.⁵ In a small-sized placebo-controlled clinical trial, Sin and co-workers found a striking effect of a daily dose of 1 mg of fluticasone on the CRP level among COPD patients among whom also patients with moderate and mild disease were included.¹⁶ One may speculate if the drug use in our study was associated with lower doses and compliance as compared to the clinical trials. Possibly, prescriptions of inhaled corticosteroid are associated with an increased severity of COPD beyond what can be measured by the spirometry, with higher CRP values previous to treatment than in those not treated with inhaled corticosteroids. Inhaled corticosteroids are recommended in patients with severe COPD and frequent exacerbations,²⁹ and CRP values have been found to be particularly increased in this subgroup.⁶

The use of oral corticosteroids was a strong predictor of raised CRP value. This can be explained by the use of this medication in other diseases than COPD, such as rheumatoid arthritis, ankylosing spondyloarthritis and inflammatory bowel diseases, in which the CRP value often is elevated.^{30, 31} Among those who reported obstructive lung disease, however, use of oral corticosteroids was associated with reduced CRP values.

A greater influence of age on the CRP level in men than in women was also reported by Albert and co-workers.²⁴ Our findings indicate different causes of increased CRP values in the two genders. The age dependency in men is probably linked to a greater increase in prevalence and severity of COPD with increasing age. The effect of smoking probably increases by age, since the number of pack-years have shown to play a role,³² and among the women ever smoking and HRT use became less frequent by increasing age (table 1). The similar average CRP values found in men and women, in spite of the higher frequency of cardiovascular disease and moderate to severe airflow limitation in men, can probably be explained by both the use of HRT²⁴ and the generally higher BMI values in woman than in men. Severe co-morbidity may have been a reason for non-participation in the survey, and the effect of age could thus have been somewhat underestimated.

As could be expected, a report of recent airway infection had a significant influence on the CRP level. This association was probably underestimated for two reasons. The participants were asked to report an airway infection that had taken place within the last three weeks. The CRP response lasts, however, usually not more than 14 days,^{33, 34} and a considerable proportion had probably reached their background CRP level when the blood was drawn. In addition, an unknown proportion of the participants answered the questionnaire several days before the blood sample was drawn. Some participants may therefore have experienced airway infection after answering the questionnaire, but prior to the blood sampling. Nevertheless, the prevalence of CRP values above 10 mg/L in severe airflow limitation, tells us that moderate elevated CRP values in exacerbations of COPD should be interpreted with caution, when used as a marker of bacterial infection,³⁵ and that knowledge about the background CRP value in COPD patients may be useful in that respect.

The ECSC reference values were used. Application of Norwegian reference values, which give higher estimates, would have resulted in a higher percentage of FEV₁ % predicted values below 80%. The Norwegian reference values developed by Langhammer and co-workers may, however, be too strict for our elderly population.²⁰ In the multivariate regression analysis the choice of reference values is of no importance. Somewhat higher values of FEV₁/FVC% and FEV₁ % predicted could have been obtained if reversibility testing had been performed, but probably with only a small effect on the association between spirometry and CRP values. The similar CRP results in those with mild bronchial obstruction (GOLD 1) and normal spirometry support the view that the GOLD criterion of FEV₁/FVC <70% for diagnosing COPD may lead to misclassification of healthy elderly.²⁰

We have shown that impaired lung function is a strong predictor of circulating CRP in the elderly, also when controlling for other known predictors. Measuring CRP value may show to be a useful part of the diagnostic work-up in COPD patients, not only during exacerbations, but also due to treatment opportunities offered by anti-inflammatory drugs.

However, effects of treatment with inhaled corticosteroids and statins on the CRP level and prognosis in COPD patients need to be studied further in clinical trials.

Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this work

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Legend to the figure

Figure 1

Distribution of CRP values by lung function* in 3857 subjects aged 60 years or more. The Tromsø Study 2001.

*Normal spirometry: $FEV_1/FVC \geq 70\%$ and $FEV1 \% \text{ predicted} \geq 80$

Pulmonary restriction: $FEV_1/FVC \geq 70\%$ and $FEV1 \% \text{ predicted} < 80$

Mild airflow limitation: $FEV_1/FVC < 70\%$ and $FEV1 \% \text{ predicted} \geq 80\%$ (GOLD stage 1)

Moderate airflow limitation: $FEV_1/FVC < 70\%$ and $FEV1 \% \text{ predicted} \geq 50\%$ and $< 80\%$ (GOLD stage 2)

Severe airflow limitation: $FEV_1/FVC < 70\%$ and $FEV1 \% \text{ predicted} < 50\%$ (GOLD stage 3 and 4),

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