

REVIEW

Open Access

Surfactant protein D, Club cell protein 16, Pulmonary and activation-regulated chemokine, C-reactive protein, and Fibrinogen biomarker variation in chronic obstructive lung disease

Sofie Lock-Johansson¹, Jørgen Vestbo^{2,3} and Grith Lykke Sorensen^{1*}

Abstract

Chronic obstructive pulmonary disease (COPD) is a multifaceted condition that cannot be fully described by the severity of airway obstruction. The limitations of spirometry and clinical history have prompted researchers to investigate a multitude of surrogate biomarkers of disease for the assessment of patients, prediction of risk, and guidance of treatment. The aim of this review is to provide a comprehensive summary of observations for a selection of recently investigated pulmonary inflammatory biomarkers (Surfactant protein D (SP-D), Club cell protein 16 (CC-16), and Pulmonary and activation-regulated chemokine (PARC/CCL-18)) and systemic inflammatory biomarkers (C-reactive protein (CRP) and fibrinogen) with COPD. The relevance of these biomarkers for COPD is discussed in terms of their biological plausibility, their independent association to disease and hard clinical outcomes, their modification by interventions, and whether changes in clinical outcomes are reflected by changes in the biomarker.

Keywords: COPD, Biomarker, SP-D, CC-16, PARC/CCL-18, CRP, Fibrinogen

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide [1] and is forecasted to be the 3rd leading cause of death globally in 2030 [2]. There is an unmet need for easily obtained biomarkers that can identify subtypes of COPD, predict outcomes of COPD, and that can evaluate and facilitate targeting in management of COPD. To aid in the evaluation and development of biomarkers for COPD, Sin & Vestbo have formulated 5 criteria as an extension from the criteria for a biomarker proposed by Bucher et al. [3]. These criteria are: biological plausibility, independent association to disease, hard clinical outcomes, modification by interventions, and whether changes in clinical outcomes are reflected by changes in the biomarker [4]. The aim of this review is to summarize observations for a selection of investigated biomarkers for COPD, with guidance from these criteria. The selected biomarkers are recently validated

with regards to sensitivity, accuracy, precision and reproducibility [5]. Surfactant protein D (SP-D), club cell protein 16 (CC-16, previously named Clara cell protein), and pulmonary and activation-regulated chemokine (PARC/CCL-18) are categorized as pulmonary inflammatory markers, while C-reactive protein (CRP) and fibrinogen are systemic inflammatory markers.

SP-D

SP-D is a member of the collectin family [6] and is primarily produced in type II pneumocytes [7-9].

Biological plausibility

SP-D plays an essential role in pulmonary innate immune defense [10] and SP-D deficient mice exhibit abnormal accumulation of apoptotic macrophages. These animals also exhibit increased cytokine activation accompanied by lymphocyte infiltration and emphysema development [11-15], suggesting a protective role for SP-D in the pathogenesis of COPD. Several single nucleotide polymorphisms (SNPs) in the SP-D gene (*Sftpd*) have shown to associate with serum SP-D levels.

* Correspondence: glsorensen@health.sdu.dk

¹Institute of Molecular Medicine, University of Southern Denmark, JB Winsloews Vej 25.3, Odense 5000, Denmark

Full list of author information is available at the end of the article

In a twin-study, the coding SNP rs721917 was associated with lower SP-D levels in serum [16]. This finding was replicated in a cohort consisting of 1,719 COPD subjects in the “Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints” Study (ECLIPSE), where 28 SNPs were shown to influence serum SP-D. However, the strongest effect occurred with a promotor SNP (rs1885551), where the minor allele associated with lower serum SP-D [17]. In addition, three *Sftpd* SNPs (including rs721917) have been associated with forced expiratory volume (FEV₁)% predicted [17], and five SNPs in *Sftpd* have been associated with an increased risk of COPD development in a Genome Wide Association study (GWAS) [18]. Lastly, a Japanese study reported one *Sftpd* SNP in association with emphysema [19].

Independent association to disease

SP-D has been measured in bronchoalveolar lavage fluid (BALF) and in blood. Among smokers, most studies have reported reduced levels of SP-D in BALF [20-23] and increased circulating levels [16,22,24,25]. Some studies have noted significant decreases in SP-D in BALF from COPD patients compared with current smokers [22] while others have not [20,21]. SP-D exists in different molecular forms (full-length, nitrosylated and cleaved). Yet, attempts to construct assays for the breakdown products of SP-D have not provided additional information regarding COPD [26].

Factors associated with increasing circulating SP-D in healthy subjects include age, BMI and male gender [16,27,28]. Circulating SP-D has been correlated with a variety of pulmonary pathologies [29], and a small comparative study showed that serum SP-D levels could not distinguish COPD from the other pulmonary pathologies [30].

A recent population-based study demonstrated a correlation between serum SP-D and reduced pulmonary function in tobacco smokers [31], suggesting that serum SP-D may serve as a marker for subclinical cigarette smoke induced lung damage. In concordance with this, in a relatively small COPD study, an inverse correlation between serum SP-D and FEV₁/forced vital capacity (FVC) ratio was found in smokers [22]. This result was however not replicated in the ECLIPSE multi-center cohort study [25,32], nor in a Swedish twin study [33], both of which contained non-smoker control subjects in addition to smoker control subjects.

In the ECLIPSE cohort, higher serum SP-D levels were reported among COPD patients relative to current and former smokers. COPD subjects who had serum SP-D concentrations in the upper 5th percentile of non-smokers had (i) increased risk of exacerbations over the following 12 months [25], and (ii) increased serum SP-D concentrations during exacerbation of COPD compared

with stable COPD [34,35]. Data from the ECLIPSE cohort have further demonstrated that baseline serum SP-D levels were associated with a decline in lung density as measured by low-dosage high-resolution computed tomography [36].

Hard clinical outcomes

Further reports from the ECLIPSE cohort found that baseline serum SP-D levels were associated with 3-year all-cause mortality [37].

Modification by interventions and correlations between changes in clinical outcomes and biomarker changes

Three cohort studies have showed that treatment with oral corticosteroids resulted in suppressed serum SP-D levels [25,38,39], whereof one showed that serum SP-D correlated with symptom relief and change in FEV₁% predicted [38].

In summary, results from GWAS and animal studies suggest a strong link between SP-D levels and COPD. Smoking highly influences systemic SP-D levels and may be an explanation of the inconclusive findings of association between severity of COPD and systemic SP-D levels. SP-D has so far not proven to be a reliable prognostic tool in advanced COPD; however, stratification for tobacco smoking is warranted in such analyses and has been lacking. Although large studies have found associations between SP-D levels and early loss of pulmonary function as well as mortality and decline in lung density in COPD, these findings need to be further validated and the data representing intervention effects on SP-D are sparse.

CC-16

CC-16 is predominantly secreted from non-ciliated club cells [22] and is localized to both terminal bronchial epithelia [40] and respiratory bronchiolar epithelia [41,42]. An identical protein, human urinary protein 1 (P1), is secreted in the urogenital tract [43]. Systemic levels of CC-16 correlate well with BALF levels, and appear to be unaffected by the release of P1 from the urogenital tract in healthy subjects [44,45]. Circulating CC-16 levels reflect different chronic pulmonary pathologies, with circulating CC-16 levels being positively associated with severity in sarcoidosis and asbestos-exposed workers [45-49]. However, circulating levels are negatively associated with the severity of asthma [50], cystic fibrosis (CF) [51] and lung cancer [45].

Biological plausibility

CC-16-deficient mice challenged with hyperoxia showed augmented pulmonary inflammation [52], and *in vitro* studies have indicated that CC-16 inhibits phospholipase

A₂ activity [53] suggesting an anti-inflammatory role of CC-16.

Candidate gene studies have reported an association between a SNP in the *SCGB1A1* gene (Chromosome 11, A38G). Carriers exhibited reduced CC-16 plasma levels and an increased risk of asthma in a child cohort with European ancestry [54]; this association between asthma and SNP A38G was further replicated in adults [55]. However, in a Chinese population, no association between this SNP and COPD was found [56]. In a GWAS where serum CC-16 levels were measured in 1951 COPD subjects, associations between 11 SNPs on chromosome 11 (one of which was located in the *SCGB1A1* gene) and serum CC-16 were found. These 11 SNPs were further evaluated in an additional 2,939 COPD cases and 1,380 smoking controls, and one SNP, located near the *AHNAK* gene, was associated with both COPD risk and frequency of exacerbation during a 2-year follow-up. However, in the same study, this finding could not be replicated in two additional control/COPD populations [18].

Independent association to disease

Confounding factors that increase systemic levels of CC-16 in healthy subjects include age [57,58], BMI (though with conflicting findings) [33,59], and a decline in glomerular filtration rate [60].

Several studies have shown that circulating levels of CC-16 are lower in healthy smokers relative to non-smokers, while other studies, examining the amount of smoking, have been inconclusive [50,61-63].

In the ECLIPSE study, CC-16 levels were reduced in former and current smokers with COPD relative to current smoking controls [63]. This finding was consistent with findings from previous smaller studies [33,45,64]. When stratifying COPD patients into GOLD groups and by current smoking, lower serum CC-16 levels were seen in current smoking COPD patients relative to former smokers in GOLD2 and GOLD3 but not in GOLD4. In former-smoking COPD patients, a significant inverse correlation was observed between CC-16 and COPD severity. Additionally, CC-16 could distinguish between patients with or without reversibility in former smoking COPD patients [63]. The evaluation of FEV₁ decline over time in the ECLIPSE cohort showed a weak positive association between serum CC-16 and annual rate of decline in FEV₁ [2]. This was recently validated in a cohort consisting of 4,724 COPD subjects, where reduced levels of CC-16 were associated with accelerated decline in FEV₁ over 9 years [65].

Repeated measurements of CC-16 in a sub-population from the ECLIPSE cohort found that serum CC-16 is a stable marker over time [66]. In a study including 357 twins with respiratory symptoms, a positive association

with FEV₁ and an inverse association with residual volume/total lung capacity were found. However, analysis of a sub-cohort of 100 COPD patients within this twin population found no significant association to these measures [33].

Hard clinical outcomes

Serum CC-16 did not associate independently with mortality in the ECLIPSE cohort [37].

Modification by interventions and correlations between changes in clinical outcomes and biomarker changes

A pilot randomized clinical trial (RCT) with 16 cachectic COPD patients and 25 controls treated with TNF- α antibody reported a rise in plasma CC-16 in COPD patients after 8 weeks of treatment; treatment effects on other end-points were not considered in this study [67]. In an RCT with approximately 100 subjects in three treatment arms (a p38 mitogen-activated protein kinase (p38 MAPK) inhibitor, salmeterol/fluticasone propionate and placebo), a reduction in CC-16 levels was seen in the salmeterol/fluticasone group after 2 weeks treatment [68].

In summary, results from animal studies suggest a causal role of CC-16 in COPD. However, the lack of a strong association between genotype variations, circulating CC-16 levels and risk of COPD indicates that CC-16 associates with pulmonary inflammation in general rather than with COPD pathogenesis explicitly. Furthermore, the inconsistent association to severity in COPD, the lack of association to mortality, the confounding effects in basal variation and the close association between CC-16 and asthma, all make the use of CC-16 as a biomarker in COPD problematic. However, additional studies validating the association between CC-16 and FEV₁ decline are warranted.

PARC/CCL-18

PARC/CCL-18 is a chemokine highly expressed in the lungs [69] with a chemotactic effect on primarily lymphocytes [70]. PARC/CCL-18 is synthesized mainly in dendritic and monocytic cells [71], but has also been shown to stimulate fibrinogenic activity and collagen production in lung fibroblasts [72,73]. Due to its predominant production in the lungs, PARC/CCL-18 has been evaluated in multiple pulmonary pathologies. In pulmonary fibrosis, an up-regulation in lung tissue [74] and an association to mortality has been reported [75].

Biological plausibility

No studies have directly addressed a mechanistic role for PARC/CCL-18 in COPD.

Independent association to disease

LPS-inhalation challenge in smokers increased levels of PARC/CCL-18 in serum after 24 h [76]. Few studies have evaluated PARC/CCL-18 as a biomarker for COPD. One small study has shown an association between PARC/CCL-18 and FEV₁, Body Mass Index, Obstruction, Dyspnea score and Exercise capacity (BODE) index, and exacerbation rate [77]; another study reported elevated PARC/CCL-18 during COPD exacerbation [78]. The largest study to date of PARC/CCL-18 in COPD, included different COPD populations: 4,800 subjects from lung health study (LHS) with mild or moderate COPD, 1,800 COPD subjects from the ECLIPSE study representing all GOLD stages, 312 smoking and 226 non-smoking controls, and 89 COPD subjects from a prednisolone intervention study [79]. The results were somewhat contradictory. In LHS, higher PARC/CCL-18 levels associated with lower baseline FEV₁ and increasing cardiovascular mortality. In the ECLIPSE subjects, PARC/CCL-18 levels were higher in COPD subjects than in controls, but the association with FEV₁ could not be replicated.

Hard clinical outcomes

PARC/CCL-18 was associated with all-cause mortality in the ECLIPSE cohort [79].

Modification by interventions and correlations between changes in clinical outcomes and biomarker changes

Two weeks treatment with prednisolone was associated with a significant reduction in PARC/CCL-18 levels compared to placebo in the ECLIPSE cohort [79].

In summary, although some evidence of association between PARC/CCL-18 and severity and mortality in COPD exists, additional validation and data regarding intervention effects on PARC/CCL-18 are warranted.

CRP

CRP is an acute phase protein, mainly induced by interleukin 6 (IL-6) and is a component of the innate immune response [80]. Increased systemic levels of CRP are seen in a variety of inflammatory conditions, particularly in infections.

Biological plausibility

The direct link between systemic inflammation and the development and progression of COPD is debated; however, the effect of CRP on activation of the complement system [80] can serve as a factor in maintaining an inflammatory state in stable COPD and thereby contribute to the negative systemic effects associated with COPD.

Although CRP levels are genetically determined [81], SNPs or haplotypes known to effect CRP levels have not been associated COPD risk [18,81-83].

Independent association to disease

In large population based case-control studies [84], as in large COPD cohorts [84-86] levels of CRP are demonstrably higher in stable COPD patients than in controls after adjusting for the confounding factors: sex, age, tobacco consumption and ischemic heart disease. Reported associations between CRP and airflow limitation have been inconsistent, with reports of weak to moderate unadjusted correlations between FEV₁ and CRP [87-90]. Analysis of CRP association with COPD severity, after adjustment for age, gender, pack-year history, presence of cardiovascular risk factors or disease and treatment with inhaled corticosteroids, showed an inverse association with 6-minute walking distance (6MWD) [88,91], diffusing capacity (adjusted for age, gender, height, smoking and BMI) [33], and hypoxemia (adjusted for sex, age, body composition and smoking) [87]. However, in one additional study (n = 222) no association with 6MWD or BODE index was found [92].

A link between systemic inflammation and comorbidity in COPD has been suggested, and elevated CRP levels in COPD patients with cardiovascular disease (CVD) [93,94], type II diabetes [94], and lung cancer [94] have been reported. CRP furthermore associated with cardiovascular and cancer mortality [95]. In a recent study, higher levels of CRP were found in a "metabolic" comorbidity cluster with the characteristics of obesity, hyperglycemia, dyslipidemia, hypertension, and atherosclerosis when compared with the cluster of CVD without the metabolic features [96], indicating that the link between COPD, systemic inflammation and CVD could be metabolic impairment. CRP levels are higher during exacerbations than during stable COPD (AUC: 0.73) [78] and can be used to distinguish between exacerbation with or without bacterial infection (AUC: 0.8) [97,98]. In addition, CRP levels were higher in patients with frequent exacerbations compared to stable state patients [85], although CRP levels were not predictive of an exacerbation [99].

CRP has been shown to exhibit high variability over time. For example, in 201 COPD patients with CRP measured at baseline and 3 months later, only 21% had values within 25% of each other [66].

Hard clinical outcomes

CRP levels have been shown to predict all-cause mortality in a group with mild to moderate disease in a population-based cohort (n = 5000) [95], but not in a smaller (n = 218) cohort with moderate to severe COPD [90]. In the ECLIPSE cohort, higher CRP

associated with all-cause mortality but did not alone contribute to better prediction of mortality than a multivariate model [88]. Another large COPD population study found that CRP levels predicted mortality and hospitalization [84].

Modification by interventions and correlations between changes in clinical outcomes and biomarker changes

In a RCT with 41 COPD subjects, randomized to oral prednisolone, inhaled glucocorticoid or placebo, there was a significant fall in oral prednisolone and inhaled glucocorticoid compared to placebo [100].

In summary, evidence that CRP plays a causal role in COPD is controversial. There have been conflicting reports regarding the value of CRP to predict mortality and hospitalizations. Although associations with COPD have been reported, CRP may not be a suitable biomarker in COPD, due to its low specificity and high variability.

Fibrinogen

Fibrinogen is primarily synthesized in the liver [101], is involved in clotting formation [102] and systemic levels are elevated in an IL-6-stimulated acute phase response [103,104].

Biological plausibility

The genes coding for three peptide chains in fibrinogen are located on chromosome 4 [105]. Circulating fibrinogen levels are genetically determined [106] and SNPs have been associated with risk of cardiovascular disease [106]. A candidate gene study with selected SNPs in the *FBG* gene encoding fibrinogen did not find an association with circulating fibrinogen levels [107]. A direct role in COPD is not found.

Independent association to disease

After adjusting for cardiovascular risk factors, several large population based cohorts have found an association between smoking and elevated systemic fibrinogen levels in healthy subjects [108-110]. A meta-analysis from "Fibrinogen Studies Collaboration" consisting of 154,211 apparently healthy subjects from 31 cohorts reported a positive association between fibrinogen and age, female gender, and alcohol abstinence [111].

Fibrinogen is shown to associate with the risk of COPD [112-114]. Higher fibrinogen levels were associated with the rate of decline in FEV₁/FVC in a population of elderly subjects [115], and in cohorts with stable COPD patients, fibrinogen was shown to associate with FEV₁ [2], dyspnea, exercise capacity [87] and the composite BODE index [116]. However, a study of 102 COPD patients did not report a significant association of fibrinogen with FEV₁, but with diffusing capacity of

the lung for carbon monoxide (DLCO) [117]. There have further been conflicting reports about the association between fibrinogen and decline in FEV₁. In a COPD cohort, comprising 148 patients [118] an association between increasing fibrinogen levels and decline in FEV₁ was found. However, this was not replicated in a small Japanese study (n = 73) [119], nor in the ECLIPSE investigation [2].

Fibrinogen has moreover been evaluated as a tool for distinguishing subgroups of COPD. In a small study of male COPD patients, a group with emphysematous lesions involving more than 15% of the lung parenchyma (n = 24) had higher fibrinogen levels than controls (n = 25) [120]. Elevated levels of fibrinogen in stable COPD patients have been shown to be predictive of risk of exacerbation [99,121,122], and elevated fibrinogen levels have been reported during an exacerbation [121]. Lastly, there has been a trend towards higher fibrinogen levels in patients suffering from exacerbations with accompanying purulent sputum [121], or virus infection [123].

Increased circulating fibrinogen levels have been suggested as a risk factor for cardiovascular disease and associated mortality [124]. In the meta-analysis from "Fibrinogen Studies Collaboration", a moderately strong association between fibrinogen and risk of coronary heart disease was reported [111]. However, a recent study from same group reported that cardiovascular event risk prediction when adding fibrinogen to a model with established risk factors gave little improvement [125]. In a Danish cohort of 8,656 COPD patients, fibrinogen alone was not a strong predictor for ischemic heart disease or myocardial infarction; however, together with CRP and leukocyte count, and hazard ratios for ischemic heart disease, myocardial infarction and heart failure were approximately two-fold higher in the group with high levels of the biomarkers compared to those with low-levels [94]. On the other hand, a small study of 60 COPD patients along with 20 smoking and 20 non-smoking controls showed no independent association between fibrinogen and flow-mediated vasodilatation (an independent predictor of cardiovascular morbidity and mortality) [38].

Hard clinical outcomes

Fibrinogen has been shown to associate with both the risk of COPD and of hospitalizations in a Swedish population cohort (n = 5,247) [112], in a Danish population cohort (n = 8,955), which also showed an inverse association to decline in FEV₁ [113], and in a US population cohort (n = 20,192), that also found associations with GOLD group and mortality [114]. Fibrinogen has further been shown to predict all-cause mortality in COPD [37,126], although in a later investigation, when comparing c-statistics, fibrinogen alone did not contribute to a better prediction of mortality

than a basic model (including age, BODE index and hospitalizations).

Modification by interventions and correlations between changes in clinical outcomes and biomarker changes

In a small study of patients with exacerbation (n = 30), fibrinogen was suppressed by systemic corticosteroid treatment [127]. However, in a study of stable COPD, plasma fibrinogen was not affected by oral prednisolone [25]. In an RCT with approximately 100 subjects in three treatment arms (p38 mitogen-activated protein kinase (p38-MAPK) inhibitor, salmeterol/fluticasone propionate and placebo), treatment with a p38-MAPK inhibitor resulted in an 11% reduction in plasma fibrinogen levels [68].

In summary, there has been no emerging evidence of direct causality between circulating fibrinogen levels and COPD. Fibrinogen levels have nevertheless been shown to be independently associated with COPD, prediction of all-cause mortality, and risk of exacerbation. In addition, fibrinogen levels are modifiable by treatment interventions. As a systemic inflammatory marker with less variability over time than CRP, fibrinogen is an interesting candidate biomarker with putative value in distinguishing subtypes

and comorbidity clusters in COPD and is currently being taken forward by the collaborative COPD Biomarker Qualification Consortium [128]. However, further investigations of fibrinogen in the assessment of treatment response are still needed.

Summary and conclusion

A summary of conclusions is provided in Table 1.

Biological plausibility

Findings from animal studies and gene-association studies point at a plausible role of the pulmonary proteins SP-D and CC-16 in COPD.

Independent association to disease and hard clinical outcomes

There is evidence that SP-D, CC-16 and PARC/CCL-18 reflect disease severity. Findings indicate association between pulmonary inflammatory proteins and risk of exacerbations, hospitalizations and death. However, results do not show the same consistency as with systemic inflammatory proteins. Fibrinogen appears to be a more specific biomarker for COPD than CRP, and is demonstrated to predict exacerbation risk and all-cause

Table 1 Summary of evidence of reviewed biomarkers in relation to questions raised by Sin & Vestbo [4]

	SP-D	CC-16	PARC/ CCL-18	CRP	Fibrinogen
Is there a strong biological plausibility in terms of its role in pathogenesis of disease?	Evidence from animal studies and gene-association studies [10-19]	Suggested from <i>in vitro</i> , animal study and gene-association studies [18,52,53]	N.A.	Experimental data suggest role in systemic effects and comorbidity [81]	Experimental data suggest role in systemic effects and comorbidity [108,109]
Is there a strong, consistent and independent association between the biomarker and COPD?	Level IIb [16,20-35]	Level IIb [33,45,63-66]	Level III [77-79]	Conflicting results from large population studies [78,85-99]	Level IIb [32,87,112-122,125]
Is there a strong, independent association between the biomarker and hard clinical outcomes such as mortality and hospitalisations?	Level IIa [36,37]	No evidence [37]	Level IIb [79]	Level IIa; on all cause mortality [84,86,99]	Level IIa [37,112-114,126]
Is there evidence from randomised controlled trials that the biomarker is modifiable by interventions?	Evidence from 3 cohort studies of prednisolone treatment [25,38,39]	Evidence from one RCT of TNF-R antibody treatment [67] and one RCT in salmeterol/fluticasone propionate-arm [68]	Evidence from one RCT with prednisolone treatment [79]	Evidence from one RCT with inhaled glucocorticoid, prednisolone or placebo [100]	Evidence from one RCT with p38 MAPK inhibitor [68,127]
Is there evidence from randomised controlled trials that changes in the biomarker status results in changes in an important (and accepted) clinical outcome (e.g. mortality, exacerbations, rate of decline in FEV ₁ and health status)?	N.A.	N.A.	N.A.	N.A.	N.A.

la - Evidence from Meta-analysis of Randomized Controlled Trial, lb - Evidence from at least one Randomized Controlled Trial, IIa - Evidence from at least one well designed controlled trial which is not randomized, IIb - Evidence from at least one well designed experimental trial, III - Evidence from case, correlation, and comparative studies, IV - Evidence from a panel of experts. SP-D: Surfactant protein D, CC-16: club cell protein 16, PARC/CCL-18: pulmonary and activation-regulated chemokine 18, CRP: C-reactive protein. N.A.: no available studies.

mortality. However, systemic inflammatory proteins are influenced by additional pathologies such as heart disease and metabolic disturbances, which are both common comorbidities in COPD. As the only one of the above reviewed biomarkers CC-16 has showed to associate with decline in lung function, which indicates a utility in evaluation of disease activity.

Modification by interventions and correlations between changes in clinical outcomes and biomarker changes

All of the reviewed biomarkers have showed to be modifiable by either oral prednisolone or inhaled glucocorticoid to different extents. However, only few randomized clinical trials have been evaluating this matter. Though biomarkers in COPD are extensively investigated, most of the studies comprise cohort and experimental studies. Randomized clinical trials evaluating changes in biomarkers in relation to interventions and clinical outcome are lacking.

In conclusion, none of the biomarkers in this review fulfill all of the criteria presented by Sin & Vestbo [4] and an additive approach, with different biomarkers combined, may contribute to increased specificity and sensitivity for prognosis of COPD.

Competing interests

Sofie Lock Johansson and Grith Lykke Sorensen have no declared competing interests. Jørgen Vestbo has not received any financial support in relation to the current manuscript. Outside this work he has received honoraria for advising and presenting from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, and Novartis. He co-chaired the ECLIPSE study, funded by GSK.

Authors' contributions

SLJ, JV and GLS have made substantial contributions to conception and design. SLJ have drafted the manuscript. JV and GLS have revised the manuscript critically. All authors have given final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Acknowledgements

Funding was obtained from the Region of Southern Denmark, Odense University Hospital Research Council, the Danish Strategic Research Council, Centre of COPD research (www.cekol.dk) (09-066945), the Danish Lung Association.

Author details

¹Institute of Molecular Medicine, University of Southern Denmark, JB Winsloews Vej 25.3, Odense 5000, Denmark. ²Department of Respiratory Medicine, Gentofte Hospital, Hellerup, Denmark. ³Respiratory Research Group, Manchester Academic Science Centre University Hospital South Manchester NHS Foundation Trust Manchester, Manchester, UK.

Received: 24 August 2014 Accepted: 7 November 2014

Published online: 25 November 2014

References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M: **Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.** *Lancet* 2012, **380**:2095–2128.
- Chronic obstructive pulmonary disease (COPD) <http://www.who.int/respiratory/copd/en/>
- Bucher HC, Guyatt GH, Cook DJ, Holbrook A, McAlister FA: **Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points.** *Evidence-Based Medicine Working Group. JAMA* 1999, **282**:771–778.
- Sin DD, Vestbo J: **Biomarkers in chronic obstructive pulmonary disease.** *Proc Am Thorac Soc* 2009, **6**:543–545.
- Christensen AF, Hoegh SV, Lottenburger T, Holmskov U, Tornøe I, Horslev-Petersen K, Sorensen GL, Junker P: **Circadian rhythm and the influence of physical activity on circulating surfactant protein D in early and long-standing rheumatoid arthritis.** *Rheumatol Int* 2011, **31**:1617–1623.
- Day AJ: **The C-type carbohydrate recognition domain (CRD) superfamily.** *Biochem Soc Trans* 1994, **22**:83–88.
- Persson A, Rust K, Chang D, Moxley M, Longmore W, Crouch E: **CP4: a pneumocyte-derived collagenous surfactant-associated protein. Evidence for heterogeneity of collagenous surfactant proteins.** *Biochemistry* 1988, **27**:8576–8584.
- Voorhout WF, Veenendaal T, Kuroki Y, Ogasawara Y, van Golde LM, Geuze HJ: **Immunocytochemical localization of surfactant protein D (SP-D) in type II cells, Clara cells, and alveolar macrophages of rat lung.** *J Histochem Cytochem* 1992, **40**:1589–1597.
- Madsen J, Kliem A, Tornøe I, Skjodt K, Koch C, Holmskov U: **Localization of lung surfactant protein D on mucosal surfaces in human tissues.** *J Immunol* 2000, **164**:5866–5870.
- Crouch E, Wright JR: **Surfactant proteins a and d and pulmonary host defense.** *Annu Rev Physiol* 2001, **63**:521–554.
- Wert SE, Yoshida M, LeVine AM, Ikegami M, Jones T, Ross GF, Fisher JH, Korfhagen TR, Whitsett JA: **Increased metalloproteinase activity, oxidant production, and emphysema in surfactant protein D gene-inactivated mice.** *Proc Natl Acad Sci U S A* 2000, **97**:5972–5977.
- Fisher JH, Larson J, Cool C, Dow SW: **Lymphocyte activation in the lungs of SP-D null mice.** *Am J Respir Cell Mol Biol* 2002, **27**:24–33.
- Botas C, Poulain F, Akiyama J, Brown C, Allen L, Goerke J, Clements J, Carlson E, Gillespie AM, Epstein C, Hawgood S: **Altered surfactant homeostasis and alveolar type II cell morphology in mice lacking surfactant protein D.** *Proc Natl Acad Sci U S A* 1998, **95**:11869–11874.
- Yoshida M, Whitsett JA: **Alveolar macrophages and emphysema in surfactant protein-D-deficient mice.** *Respirology* 2006, **11**(Suppl):S37–S40.
- Collins RA, Ikegami M, Korfhagen TR, Whitsett JA, Sly PD: **In vivo measurements of changes in respiratory mechanics with age in mice deficient in surfactant protein D.** *Pediatr Res* 2003, **53**:463–467.
- Sorensen GL, Hjelmberg J, Kyvik KO, Fenger M, Hoj A, Bendixen C, Sorensen TI, Holmskov U: **Genetic and environmental influences of surfactant protein D serum levels.** *Am J Physiol Lung Cell Mol Physiol* 2006, **290**:L1010–L1017.
- Foreman MG, Kong X, DeMeo DL, Pillai SG, Hersh CP, Bakke P, Gulsvik A, Lomas DA, Litonjua AA, Shapiro SD, Tal-Singer R, Silverman EK: **Polymorphisms in surfactant protein-D are associated with chronic obstructive pulmonary disease.** *Am J Respir Cell Mol Biol* 2011, **44**:316–322.
- Kim DK, Cho MH, Hersh CP, Lomas DA, Miller BE, Kong X, Bakke P, Gulsvik A, Agusti A, Wouters E, Celli B, Coxson H, Vestbo J, MacNee W, Yates JC, Rennard S, Litonjua A, Qiu W, Beaty TH, Crapo JD, Riley JH, Tal-Singer R, Silverman EK, ECLIPSE, ICGN, and COPD Gene Investigators: **Genome-wide association analysis of blood biomarkers in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2012, **186**:1238–1247.
- Ishii T, Hagiwara K, Kamio K, Ikeda S, Arai T, Mieno MN, Kumasaka T, Muramatsu M, Sawabe M, Gemma A, Kida K: **Involvement of surfactant protein D in emphysema revealed by genetic association study.** *Eur J Hum Genet* 2012, **20**:230–235.
- More JM, Voelker DR, Silveira LJ, Edwards MG, Chan ED, Bowler RP: **Smoking reduces surfactant protein D and phospholipids in patients with and without chronic obstructive pulmonary disease.** *BMC Pulm Med* 2010, **10**:53.
- Betsuyaku T, Kuroki Y, Nagai K, Nasuhara Y, Nishimura M: **Effects of ageing and smoking on SP-A and SP-D levels in bronchoalveolar lavage fluid.** *Eur Respir J* 2004, **24**:964–970.
- Winkler C, Atochina-Vasserman EN, Holz O, Beers MF, Erpenbeck VJ, Krug N, Roepcke S, Lauer G, Elmlinger M, Hohlfeld JM: **Comprehensive characterisation of pulmonary and serum surfactant protein D in COPD.** *Respir Res* 2011, **12**:29.

23. Honda Y, Takahashi H, Kuroki Y, Akino T, Abe S: **Decreased contents of surfactant proteins A and D in BAL fluids of healthy smokers.** *Chest* 1996, **109**:1006–1009.
24. Mutti A, Corradi M, Goldoni M, Vettori MV, Bernard A, Apostoli P: **Exhaled metallic elements and serum pneumoproteins in asymptomatic smokers and patients with COPD or asthma.** *Chest* 2006, **129**:1288–1297.
25. Lomas DA, Silverman EK, Edwards LD, Locantore NW, Miller BE, Horstman DH, Tal-Singer R: **Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD.** *Eur Respir J* 2009, **34**:95–102.
26. Duvoix A, Miranda E, Perez J, Sorensen GL, Holmskov U, Trapnell BC, Madsen J, Clark HW, Edwards LD, Miller BE, Tal-Singer RM, Lomas DA: **Evaluation of full-length, cleaved and nitrosylated serum surfactant protein D as biomarkers for COPD.** *COPD* 2011, **8**:79–95.
27. Sorensen GL, Hjelmborg JV, Leth-Larsen R, Schmidt V, Fenger M, Poulain F, Hawgood S, Sorensen TI, Kyvik KO, Holmskov U: **Surfactant protein D of the innate immune defence is inversely associated with human obesity and SP-D deficiency infers increased body weight in mice.** *Scand J Immunol* 2006, **64**:633–638.
28. Zhao XM, Wu YP, Wei R, Cai HX, Tornoe I, Han JJ, Wang Y, de Groot PG, Holmskov U, Xia ZL, Sorensen GL: **Plasma surfactant protein D levels and the relation to body mass index in a chinese population.** *Scand J Immunol* 2007, **66**:71–76.
29. Sorensen GL, Husby S, Holmskov U: **Surfactant protein A and surfactant protein D variation in pulmonary disease.** *Immunobiology* 2007, **212**:381–416.
30. Kobayashi H, Kanoh S, Motoyoshi K: **Serum surfactant protein-A, but not surfactant protein-D or KL-6, can predict preclinical lung damage induced by smoking.** *Biomarkers* 2008, **13**:385–392.
31. Colin Mathers TBaDMF: *The Global Burden of Disease: 2004 Update, 2008.* WHO Press: WHO Library Cataloguing-in-Publication Data: World Health Organization; 2008.
32. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Coxson HO, Crim C, Lomas DA, MacNee W, Miller BE, Silverman EK, Tal-Singer R, Wouters E, Rennard SI, ECLIPSE Investigators: **Changes in forced expiratory volume in 1 second over time in COPD.** *N Engl J Med* 2011, **365**:1184–1192.
33. Engstrom G, Lindberg C, Gerhardsson De Verdier M, Nihlen U, Anderson M, Svartengren M, Forsman Semb K: **Blood biomarkers and measures of pulmonary function—a study from the Swedish twin registry.** *Respir Med* 2012, **106**:1250–1257.
34. Ju CR, Liu W, Chen RC: **Serum surfactant protein D: biomarker of chronic obstructive pulmonary disease.** *Dis Markers* 2012, **32**:281–287.
35. Shakoobi TA, Sin DD, Ghafoor F, Bashir S, Bokhari SN: **Serum surfactant protein D during acute exacerbations of chronic obstructive pulmonary disease.** *Dis Markers* 2009, **27**:287–294.
36. Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Crim C, Duvoix A, Fauerbach PN, Lomas DA, Macnee W, Mayer RJ, Miller BE, Müller NL, Rennard SI, Silverman EK, Tal-Singer R, Wouters EF, Vestbo J, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators: **The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study.** *Lancet Respir Med* 2013, **1**:129–136.
37. Celli BR, Locantore N, Yates J, Tal-Singer R, Miller BE, Bakke P, Calverley P, Coxson H, Crim C, Edwards LD, Lomas DA, Duvoix A, MacNee W, Rennard S, Silverman E, Vestbo J, Wouters E, Agustí A, ECLIPSE Investigators: **Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2012, **185**:1065–1072.
38. Eickhoff P, Valipour A, Kiss D, Schreder M, Cekici L, Geyer K, Kohansal R, Burghuber OC: **Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2008, **178**:1211–1218.
39. Liu W, Ju CR, Chen RC, Liu ZG: **Role of serum and induced sputum surfactant protein D in predicting the response to treatment in chronic obstructive pulmonary disease.** *Exp Ther Med* 2014, **8**:1313–1317.
40. Singh G, Singh J, Katyal SL, Brown WE, Kramps JA, Paradis IL, Dauber JH, Macpherson TA, Squeglia N: **Identification, cellular localization, isolation, and characterization of human Clara cell-specific 10 KD protein.** *J Histochem Cytochem* 1988, **36**:73–80.
41. Broers JL, Jensen SM, Travis WD, Pass H, Whitsett JA, Singh G, Katyal SL, Gazdar AF, Minna JD, Linnoila RI: **Expression of surfactant associated protein-A and Clara cell 10 kilodalton mRNA in neoplastic and non-neoplastic human lung tissue as detected by in situ hybridization.** *Lab Invest* 1992, **66**:337–346.
42. Boers JE, Ambergen AW, Thunnissen FB: **Number and proliferation of clara cells in normal human airway epithelium.** *Am J Respir Crit Care Med* 1999, **159**:1585–1591.
43. Bernard A, Roels H, Lauwerys R, Witters R, Gielens C, Soumillion A, Van Damme J, De Ley M: **Human urinary protein 1: evidence for identity with the Clara cell protein and occurrence in respiratory tract and urogenital secretions.** *Clin Chim Acta* 1992, **207**:239–249.
44. Shijubo N, Itoh Y, Yamaguchi T, Shibuya Y, Morita Y, Hirasawa M, Okutani R, Kawai T, Abe S: **Serum and BAL Clara cell 10 kDa protein (CC10) levels and CC10-positive bronchiolar cells are decreased in smokers.** *Eur Respir J* 1997, **10**:1108–1114.
45. Bernard A, Marchandise FX, Depelchin S, Lauwerys R, Sibille Y: **Clara cell protein in serum and bronchoalveolar lavage.** *Eur Respir J* 1992, **5**:1231–1238.
46. Shijubo N, Itoh Y, Shigehara K, Yamaguchi T, Itoh K, Shibuya Y, Takahashi R, Ohchi T, Ohmichi M, Hiraga Y, Abe S: **Association of Clara cell 10-kDa protein, spontaneous regression and sarcoidosis.** *Eur Respir J* 2000, **16**:414–419.
47. Hermans C, Petrek M, Kolek V, Weynand B, Pieters T, Lambert M, Bernard A: **Serum Clara cell protein (CC16), a marker of the integrity of the air-blood barrier in sarcoidosis.** *Eur Respir J* 2001, **18**:507–514.
48. Janssen R, Sato H, Grutters JC, Bernard A, van Velzen-Blad H, du Bois RM, van den Bosch JM: **Study of Clara cell 16, KL-6, and surfactant protein-D in serum as disease markers in pulmonary sarcoidosis.** *Chest* 2003, **124**:2119–2125.
49. Lesur O, Bernard AM, Begin RO: **Clara cell protein (CC-16) and surfactant-associated protein A (SP-A) in asbestos-exposed workers.** *Chest* 1996, **109**:467–474.
50. Shijubo N, Itoh Y, Yamaguchi T, Sugaya F, Hirasawa M, Yamada T, Kawai T, Abe S: **Serum levels of Clara cell 10-kDa protein are decreased in patients with asthma.** *Lung* 1999, **177**:45–52.
51. Starosta V, Ratjen F, Rietschel E, Paul K, Griese M: **Anti-inflammatory cytokines in cystic fibrosis lung disease.** *Eur Respir J* 2006, **28**:581–587.
52. Johnston CJ, Mango GW, Finkelstein JN, Stripp BR: **Altered pulmonary response to hyperoxia in Clara cell secretory protein deficient mice.** *Am J Respir Cell Mol Biol* 1997, **17**:147–155.
53. Lesur O, Bernard A, Arsalane K, Lauwerys R, Begin R, Cantin A, Lane D: **Clara cell protein (CC-16) induces a phospholipase A2-mediated inhibition of fibroblast migration in vitro.** *Am J Respir Crit Care Med* 1995, **152**:290–297.
54. Laing IA, Hermans C, Bernard A, Burton PR, Goldblatt J, Le Souef PN: **Association between plasma CC16 levels, the A38G polymorphism, and asthma.** *Am J Respir Crit Care Med* 2000, **161**:124–127.
55. Candelaria PV, Backer V, Laing IA, Porsbjerg C, Nepper-Christensen S, de Klerk N, Goldblatt J, Le Souef PN: **Association between asthma-related phenotypes and the CC16 A38G polymorphism in an unselected population of young adult Danes.** *Immunogenetics* 2005, **57**:25–32.
56. Liu S, Li B, Zhou Y, Zhong N, Ran P: **Genetic analysis of CC16, OGG1 and GCLC polymorphisms and susceptibility to COPD.** *Respirology* 2007, **12**:29–33.
57. Nomori H, Horio H, Fuyuno G, Kobayashi R, Morinaga S, Hirabayashi Y: **Protein 1 (Clara cell protein) serum levels in healthy subjects and patients with bacterial pneumonia.** *Am J Respir Crit Care Med* 1995, **152**:746–750.
58. Bernard AM, Roels HA, Buchet JP, Lauwerys RR: **Serum Clara cell protein: an indicator of bronchial cell dysfunction caused by tobacco smoking.** *Environ Res* 1994, **66**:96–104.
59. Nomori H, Horio H, Takagi M, Kobayashi R, Hirabayashi Y: **Clara cell protein correlation with hyperlipidemia.** *Chest* 1996, **110**:680–684.
60. Hermans C, Dong P, Robin M, Jadoul M, Bernard A, Bersten AD, Doyle IR: **Determinants of serum levels of surfactant proteins A and B and Clara cell protein CC16.** *Biomarkers* 2003, **8**:461–471.
61. Ekberg-Jansson A, Andersson B, Bake B, Boijesen M, Enander I, Rosengren A, Skoogh BE, Tølen U, Venge P, Lofdahl CG: **Neutrophil-associated activation markers in healthy smokers relates to a fall in DL(CO) and to emphysematous changes on high resolution CT.** *Respir Med* 2001, **95**:363–373.
62. Van Miert E, Sardella A, Bernard A: **Biomarkers of early respiratory effects in smoking adolescents.** *Eur Respir J* 2011, **38**:1287–1293.
63. Lomas DA, Silverman EK, Edwards LD, Miller BE, Coxson HO, Tal-Singer R: **Evaluation of serum CC-16 as a biomarker for COPD in the ECLIPSE cohort.** *Thorax* 2008, **63**:1058–1063.

64. Sin DD, Leung R, Gan WQ, Man SP: **Circulating surfactant protein D as a potential lung-specific biomarker of health outcomes in COPD: a pilot study.** *BMC Pulm Med* 2007, **7**:13.
65. Park HY, Chung A, Wright JL, Li Y, Tam S, Man SP, Tashkin D, Wise RA, Connett JE, Sin DD: **Club Cell Protein 16 and Disease Progression in Chronic Obstructive Pulmonary Disease (COPD).** *Am J Respir Crit Care Med* 2013, **188**:1413–1419.
66. Dickens JA, Miller BE, Edwards LD, Silverman EK, Lomas DA, Tal-Singer R: **COPD association and repeatability of blood biomarkers in the ECLIPSE cohort.** *Respir Res* 2011, **12**:146.
67. Dentener MA, Creutzberg EC, Pennings HJ, Rijkers GT, Mercken E, Wouters EF: **Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study.** *Respiration* 2008, **76**:275–282.
68. Lomas DA, Lipson DA, Miller BE, Willits L, Keene O, Barnacle H, Barnes NC, Tal-Singer R: **An oral inhibitor of p38 MAP kinase reduces plasma fibrinogen in patients with chronic obstructive pulmonary disease.** *J Clin Pharmacol* 2012, **52**:416–424.
69. Hieshima K, Imai T, Baba M, Shoudai K, Ishizuka K, Nakagawa T, Tsuruta J, Takeya M, Sakaki Y, Takatsuki K, Miura R, Opendakker G, Van Damme J, Yoshie O, Nomiyama H: **A novel human CC chemokine PARC that is most homologous to macrophage-inflammatory protein-1 alpha/LD78 alpha and chemotactic for T lymphocytes, but not for monocytes.** *J Immunol* 1997, **159**:1140–1149.
70. Adema GJ, Hartgers F, Verstraten R, de Vries E, Marland G, Menon S, Foster J, Xu Y, Nooyen P, McClanahan T, Bacon KB, Figdor CG: **A dendritic-cell-derived C-C chemokine that preferentially attracts naive T cells.** *Nature* 1997, **387**:713–717.
71. Schraufstatter I, Takamori H, Sikora L, Sriramarao P, DiScipio RG: **Eosinophils and monocytes produce pulmonary and activation-regulated chemokine, which activates cultured monocytes/macrophages.** *Am J Physiol Lung Cell Mol Physiol* 2004, **286**:L494–L501.
72. Atamas SP, Luzina IG, Choi J, Tsymbalyuk N, Carbonetti NH, Singh IS, Trojanowska M, Jimenez SA, White B: **Pulmonary and activation-regulated chemokine stimulates collagen production in lung fibroblasts.** *Am J Respir Cell Mol Biol* 2003, **29**:743–749.
73. Song E, Ouyang N, Horbelt M, Antus B, Wang M, Exton MS: **Influence of alternatively and classically activated macrophages on fibrogenic activities of human fibroblasts.** *Cell Immunol* 2000, **204**:19–28.
74. Pardo A, Smith KM, Abrams J, Coffman R, Bustos M, McClanahan TK, Grein J, Murphy EE, Zlotnik A, Selman M: **CCL18/DC-CK-1/PARC up-regulation in hypersensitivity pneumonitis.** *J Leukoc Biol* 2001, **70**:610–616.
75. Prasse A, Probst C, Bargagli E, Zissel G, Toews GB, Flaherty KR, Olschewski M, Rottoli P, Muller-Quernheim J: **Serum CC-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis.** *Am J Respir Crit Care Med* 2009, **179**:717–723.
76. Aul R, Armstrong J, Duvoix A, Lomas D, Hayes B, Miller BE, Jagger C, Singh D: **Inhaled LPS challenges in smokers: a study of pulmonary and systemic effects.** *Br J Clin Pharmacol* 2012, **74**:1023–1032.
77. Pinto-Plata V, Toso J, Lee K, Park D, Bilello J, Mullerova H, De Souza MM, Vessey R, Celli B: **Profiling serum biomarkers in patients with COPD: associations with clinical parameters.** *Thorax* 2007, **62**:595–601.
78. Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, Vessey RS, Wedzicha JA: **Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2006, **174**:867–874.
79. Sin DD, Miller BE, Duvoix A, Man SF, Zhang X, Silverman EK, Connett JE, Anthonisen NA, Wise RA, Tashkin D, Celli BR, Edwards LD, Locantore N, Macnee W, Tal-Singer R, Lomas DA, ECLIPSE Investigators: **Serum PARC/CCL-18 concentrations and health outcomes in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2011, **183**:1187–1192.
80. Volanakis JE: **Human C-reactive protein: expression, structure, and function.** *Mol Immunol* 2001, **38**:189–197.
81. Hersh CP, Miller DT, Kwiatkowski DJ, Silverman EK: **Genetic determinants of C-reactive protein in COPD.** *Eur Respir J* 2006, **28**:1156–1162.
82. Dahl M, Vestbo J, Zacho J, Lange P, Tybjaerg-Hansen A, Nordestgaard BG: **C reactive protein and chronic obstructive pulmonary disease: a Mendelian randomisation approach.** *Thorax* 2011, **66**:197–204.
83. van Durme YM, Verhamme KM, Aarnoudse AJ, Van Pottelberge GR, Hofman A, Witteman JC, Joos GF, Brusselle GG, Stricker BH: **C-reactive protein levels, haplotypes, and the risk of incident chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2009, **179**:375–382.
84. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG: **C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2007, **175**:250–255.
85. Eagan TM, Ueland T, Wagner PD, Hardie JA, Mollnes TE, Damas JK, Aukrust P, Bakke PS: **Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study.** *Eur Respir J* 2010, **35**:540–548.
86. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E, Crim C, Yates JC, Silverman EK, Coxson HO, Bakke P, Mayer RJ, Celli B, valuation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators: **Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype.** *PLoS One* 2012, **7**:e37483.
87. Garcia-Rio F, Miravittles M, Soriano JB, Munoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J: **Systemic inflammation in chronic obstructive pulmonary disease: a population-based study.** *Respir Res* 2010, **11**:63.
88. de Torres JP, Pinto-Plata V, Casanova C, Mullerova H, Cordoba-Lanus E, Muros De Fuentes M, Aguirre Jaime A, Celli BR: **C-reactive protein levels and survival in patients with moderate to very severe COPD.** *Chest* 2008, **133**:1336–1343.
89. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM: **Raised CRP levels mark metabolic and functional impairment in advanced COPD.** *Thorax* 2006, **61**:17–22.
90. Thorleifsson SJ, Margretardottir OB, Gudmundsson G, Olafsson I, Benediktssdottir B, Janson C, Buist AS, Gislason T: **Chronic airflow obstruction and markers of systemic inflammation: results from the BOLD study in Iceland.** *Respir Med* 2009, **103**:1548–1553.
91. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR: **C-reactive protein in patients with COPD, control smokers and non-smokers.** *Thorax* 2006, **61**:23–28.
92. Gaki E, Kontogianni K, Papaioannou AI, Bakakos P, Gourgoulis KI, Kostikas K, Alchanatis M, Papiris S, Loukides S: **Associations between BODE index and systemic inflammatory biomarkers in COPD.** *COPD* 2011, **8**:408–413.
93. Sin DD, Man SF: **Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease.** *Circulation* 2003, **107**:1514–1519.
94. Thomsen M, Dahl M, Lange P, Vestbo J, Nordestgaard BG: **Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2012, **186**:982–988.
95. Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD: **C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease.** *Thorax* 2006, **61**:849–853.
96. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, Van Empel VP, Bruijnzeel PL, Rutten EP, Op T, Roodt J, Wouters EF, Franssen FM: **Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with Chronic Obstructive Pulmonary disease.** *Am J Respir Crit Care Med* 2013, **187**:728–735.
97. Peng C, Tian C, Zhang Y, Yang X, Feng Y, Fan H: **C-reactive protein levels predict bacterial exacerbation in patients with chronic obstructive pulmonary disease.** *Am J Med Sci* 2013, **345**:190–194.
98. Weis N, Almdal T: **C-reactive protein—can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease?** *Eur J Intern Med* 2006, **17**:88–91.
99. Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlosser NJ, Wouters EF: **Increased systemic inflammation is a risk factor for COPD exacerbations.** *Chest* 2008, **133**:350–357.
100. Sin DD, Lacy P, York E, Man SF: **Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2004, **170**:760–765.
101. Takeda Y: **Studies of the metabolism and distribution of fibrinogen in healthy men with autologous 125-I-labeled fibrinogen.** *J Clin Invest* 1966, **45**:103–111.
102. Standeven KF, Ariens RA, Grant PJ: **The molecular physiology and pathology of fibrin structure/function.** *Blood Rev* 2005, **19**:275–288.
103. Gabay C, Kushner I: **Acute-phase proteins and other systemic responses to inflammation.** *N Engl J Med* 1999, **340**:448–454.
104. Huber P, Laurent M, Dalmon J: **Human beta-fibrinogen gene expression. Upstream sequences involved in its tissue specific expression and its dexamethasone and interleukin 6 stimulation.** *J Biol Chem* 1990, **265**:5695–5701.

105. Fish RJ, Neerman-Arbez M: **Fibrinogen gene regulation.** *Thromb Haemost* 2012, **108**:419–426.
106. Yang Q, Tofter GH, Cupples LA, Larson MG, Feng D, Lindpaintner K, Levy D, D'Agostino RB, O'Donnell CJ: **A genome-wide search for genes affecting circulating fibrinogen levels in the Framingham Heart Study.** *Thromb Res* 2003, **110**:57–64.
107. Sunyer J, Pistelli R, Plana E, Andreani M, Baldari F, Kolz M, Koenig W, Pekkanen J, Peters A, Forastiere F: **Systemic inflammation, genetic susceptibility and lung function.** *Eur Respir J* 2008, **32**:92–97.
108. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK: **Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States.** *Ann Intern Med* 2003, **138**:891–897.
109. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH: **Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease.** *Eur Heart J* 2005, **26**:1765–1773.
110. Lind P, Hedblad B, Hultberg B, Stavenow L, Janzon L, Lindgarde F: **Risk of myocardial infarction in relation to plasma levels of homocysteine and inflammation-sensitive proteins: a long-term nested case-control study.** *Angiology* 2003, **54**:401–410.
111. Kaptoge S, White IR, Thompson SG, Wood AM, Lewington S, Lowe GD, Danesh J: **Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration.** *Am J Epidemiol* 2007, **166**:867–879.
112. Engstrom G, Segelstrom N, Ekberg-Aronsson M, Nilsson PM, Lindgarde F, Lofdahl CG: **Plasma markers of inflammation and incidence of hospitalisations for COPD: results from a population-based cohort study.** *Thorax* 2009, **64**:211–215.
113. Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG: **Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2001, **164**:1008–1011.
114. Mannino DM, Valvi D, Mullerova H, Tal Singer R: **Fibrinogen, COPD and mortality in a nationally representative U.S. cohort.** *COPD* 2012, **9**:359–366.
115. Jiang R, Burke GL, Enright PL, Newman AB, Margolis HG, Cushman M, Tracy RP, Wang Y, Kronmal RA, Barr RG: **Inflammatory markers and longitudinal lung function decline in the elderly.** *Am J Epidemiol* 2008, **168**:602–610.
116. Duvoix A, Dickens J, Haq I, Mannino D, Miller B, Tal Singer R, Lomas DA: **Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease.** *Thorax* 2012, **68**:670–676.
117. Cockayne DA, Cheng DT, Waschki B, Sridhar S, Ravindran P, Hilton H, Kourteva G, Bitter H, Pillai SG, Visvanathan S, Müller KC, Holz O, Magnusson H, Watz H, Fine JS: **Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity.** *PLoS One* 2012, **7**:e38629.
118. Donaldson GC, Seemungal TA, Patel IS, Bhowmik A, Wilkinson TM, Hurst JR, MacCallum PK, Wedzicha JA: **Airway and systemic inflammation and decline in lung function in patients with COPD.** 2005. *Chest* 2009, **136**:e30.
119. Higashimoto Y, Iwata T, Okada M, Satoh H, Fukuda K, Tohda Y: **Serum biomarkers as predictors of lung function decline in chronic obstructive pulmonary disease.** *Respir Med* 2009, **103**:1231–1238.
120. Papaioannou AI, Mazioti A, Kiropoulos T, Tsilioni I, Koutsokera A, Tanou K, Nikoulis DJ, Georgoulas P, Zakyntinos E, Gourgoulis KJ, Kostikas K: **Systemic and airway inflammation and the presence of emphysema in patients with COPD.** *Respir Med* 2010, **104**:275–282.
121. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, Jeffries DJ, Meade TW: **Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels.** *Thromb Haemost* 2000, **84**:210–215.
122. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG: **Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease.** *JAMA* 2013, **309**:2353–2361.
123. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, Message S, MacCallum P, Meade TW, Jeffries DJ, Johnston SL, Wedzicha JA: **Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2001, **164**:1618–1623.
124. Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ: **Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study.** *Lancet* 1993, **342**:1076–1079.
125. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, Walker M, Thompson A, Sarwar N, Caslake M, Butterworth AS, Amouyel P, Assmann G, Bakker SJ, Barr EL, Barrett-Connor E, Benjamin EJ, Björkelund C, Brenner H, Brunner E, Clarke R, Cooper JA, Cremer P, Cushman M, Dagenais GR, D'Agostino RB Sr, Dankner R, Davey-Smith G, Deeg D, et al: **C-reactive protein, fibrinogen, and cardiovascular disease prediction.** *N Engl J Med* 2012, **367**:1310–1320.
126. Valvi D, Mannino DM, Mullerova H, Tal-Singer R: **Fibrinogen, chronic obstructive pulmonary disease (COPD) and outcomes in two United States cohorts.** *Int J Chron Obstruct Pulmon Dis* 2012, **7**:173–182.
127. Kunter E, Ilvan A, Ozmen N, Demirel E, Ozturk A, Avsar K, Sayan O, Kartaloglu Z: **Effect of corticosteroids on hemostasis and pulmonary arterial pressure during chronic obstructive pulmonary disease exacerbation.** *Respiration* 2008, **75**:145–154.
128. Casaburi R, Celli B, Crapo J, Criner G, Croxton T, Gaw A, Jones P, Kline-Leidy N, Lomas DA, Merrill D, Polkey M, Rennard S, Sciruba F, Tal-Singer R, Stockley R, Turino G, Vestbo J, Walsh J: **The COPD Biomarker Qualification Consortium (CBQC).** *COPD* 2013, **10**:367–377.

doi:10.1186/s12931-014-0147-5

Cite this article as: Lock-Johansson et al.: Surfactant protein D, Club cell protein 16, Pulmonary and activation-regulated chemokine, C-reactive protein, and Fibrinogen biomarker variation in chronic obstructive lung disease. *Respiratory Research* 2014 **15**:147.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

