Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease

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ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) is a multicomponent condition that is characterised by airflow obstruction that is not fully reversible and is a major global cause of morbidity and mortality. The most widely used marker of disease severity and progression is FEV_1. However, FEV_1 correlates poorly with both symptoms and other measures of disease progression and thus there is an urgent need for other biological markers to better characterise individuals with COPD. Fibrinogen is an acute phase plasma protein that has emerged as a promising biomarker in COPD. Here we review the current clinical evidence linking fibrinogen with COPD and its associated co-morbidities and discuss its potential utility as a biomarker.

Methods Searches for appropriate studies were undertaken on PubMed using search terms fibrinogen, COPD, emphysema, chronic bronchitis, FEV_1, cardiovascular disease, exacerbation and mortality.

Results There is strong evidence of an association between fibrinogen and the presence of COPD, the presence and frequency of exacerbations and with mortality. Fibrinogen is associated with disease severity but does not predict lung function decline, a measure used as a surrogate for disease activity. The role of fibrinogen in identifying inflammatory co morbidities, particularly cardiovascular disease, remains unclear. Fibrinogen is reduced by p38 mitogen-activated protein kinase inhibitors in individuals with stable disease and by oral corticosteroids during exacerbations.

Conclusions Fibrinogen is likely to be a useful biomarker to stratify individuals with COPD into those with a high or low risk of future exacerbations and may identify those with a higher risk of mortality.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a multicomponent disease that is characterised by airflow obstruction that is not fully reversible. It results from an aberrant inflammatory reaction to cigarette smoke, aerotoxins and biomass fumes. The airflow obstruction can result from either airways disease or alveolar destruction (emphysema) and is associated with mucus hypersecretion, loss of lean body mass and an increased risk of comorbidities such as cardiovascular disease and osteoporosis.[1] COPD is a major cause of morbidity and mortality worldwide and is estimated to become the third leading cause of death in 2020.[2] The most widely used marker of disease severity and progression is the forced expiratory volume in 1 s (FEV_1). However FEV_1 correlates poorly with both symptoms and other measures of disease

progression and may therefore not be a good surrogate marker of disease activity.[3] Therefore novel approaches are required to define the disease, monitor its progression and define clinically relevant endpoints. Biomarkers could become suitable surrogates in the early detection of disease, stratification of subjects and as endpoints for clinical trials.

The search for biomarkers has centred around proteins and other molecules, in breath condensate, sputum, urine, bronchoalveolar lavage and blood, that have been implicated in pathogenesis of COPD.[4] Profiling of blood biomarkers has identified a number of biomarkers that may distinguish individuals with COPD from control subjects, including lung-derived Clara cell protein-16 (CC-16), surfactant protein-D (SP-D) and CCL-18, markers of extracellular matrix breakdown including matrix metalloproteinases (MMPs) 8 and 9, and systemic inflammatory biomarkers: C-reactive protein (CRP), interleukin (IL)-6 and IL-8.[5 6] These associations are seen at a population level but none are sufficiently powerful for use in isolation as a biomarker for diagnosis or predictor of disease phenotypes. In addition, many of these biomarkers are variable in stable disease, which further limits their use.[5] The search therefore continues for single or composite biomarkers that are viable for use in individual patients.

Fibrinogen has emerged as a promising biomarker in COPD and is currently being considered for qualification as a drug development tool by the US Food and Drug Administration and the European Medicines Agency.[7] It is an acute phase soluble plasma glycoprotein, synthesised primarily in the liver and converted by thrombin into fibrin during blood coagulation. Normal fibrinogen levels in blood are between 1.5 and 3.5 g/litre but can increase threefold during acute phase stimulation[8] in response to increased IL-6 production.[9 10] We review here the potential of fibrinogen as a blood biomarker of COPD. We assess the evidence for an association between fibrinogen and risk of developing COPD, disease severity, progression and mortality. We also review whether fibrinogen is associated with the comorbidities of COPD or is affected by current or novel anti-inflammatory drugs (summarised in table 1).

METHODS

Searches were undertaken on PubMed using the search terms fibrinogen, COPD, emphysema, chronic bronchitis, FEV_1, cardiovascular disease, peripheral vascular disease, exacerbation and mortality, between March 2011 and May 2012.

Table 1 Summary of the literature assessing a relationship between fibrinogen and chronic obstructive pulmonary disease (COPD)

	Author, year	Ref	Patients	Findings
Risk of COPD	Dahl, 2001	11	8955 individuals from the general Danish population	Inverse relationship between baseline fibrinogen and FEV_1 % predicted. Higher fibrinogen associated with faster lung function decline
	Valvi, 2012	12	20 192 individuals from general US population; ARIC/CHS cohorts	Higher baseline fibrinogen associated with incident COPD, COPD hospitalisation and all-cause mortality
	Engstrom, 2009	13	5247 randomly selected men from Cardiovascular Screening Study	Baseline fibrinogen associated with COPD exacerbation hospital admissions during 25-year follow-up period
	Kalhan, 2010	14	2132 individuals from CARDIA study	Higher fibrinogen levels at year 7 associated with greater loss of FEV_1 and FVC, but not FEV_1:FVC ratio, between year 5 and year 20
	Jiang, 2008	15	5011 individuals >65 years old from CHS	Higher baseline fibrinogen associated with lower FEV_1 % predicted and FEV_1: FVC and faster decline in FEV_1
Diagnosis and disease severity	Alessandri, 1994	16	37 individuals with COPD, 30 controls	Fibrinogen higher in patients with COPD (p=0.0005) independent of smoking status
	Eickhoff, 2008	17	60 individuals with stable COPD, 20 healthy smokers, 20 healthy non-smokers	Higher fibrinogen in individuals with COPD compared with non-smoking controls. No association with disease severity
	Mannino, 2003	18	15 697 individuals from NHANES III study	Fibrinogen higher in patients with COPD. Association with disease severity in moderate and severe disease
	Gan, 2004	19	Meta-analysis comprising four studies and >9000 individuals	Fibrinogen higher in patients with COPD; standardised mean difference 0.37 g/litre between patients with COPD and controls
	Garcia-Rio, 2010	20	324 individuals with COPD and 110 controls from EPI-SCAN cohort	Fibrinogen associated with diagnosis of COPD in crude data; significance lost once adjustments made for covariates. In individuals with COPD, association between fibrinogen and MRC dyspnoea score, 6 min walk distance. No association with GOLD stage
Mortality	Danesh, 2005	21	Meta-analysis. 154 211 individuals from 31 studies	Association between fibrinogen and vascular and non-vascular mortality. Fibrinogen associated with death from COPD (HR 3.7 per 1 g/litre increase in fibrinogen)
	Mannino, 2012	22	8507 individuals from NHANES III study	Association between fibrinogen level and all-cause mortality. Individuals with GOLD stage 3 or 4 disease have higher fibrinogen than GOLD stage 1 or 2 disease
Disease Progression	Donaldson, 2005	23	148 individuals with COPD (median FEV_1 38%)	Fibrinogen increased over time. Higher baseline level associated with faster decline in FEV_1
	Higashimoto, 2009	24	73 Japanese individuals with COPD (median FEV_1 70% predicted)	Trend towards faster decline in lung function in those with higher fibrinogen (p=0.054)
	Vestbo, 2011	25	1793 individuals with COPD	Fibrinogen associated with FEV_1 at baseline but no association seen with annual decline in FEV_1
Components of COPD	Papaioannou, 2010	26	49 individuals with stable COPD	Fibrinogen higher in individuals with emphysema than those without
	Hurst, 2010	27	2138 individuals with COPD from the ECLIPSE cohort	Higher fibrinogen levels are associated with an increased rate of exacerbations in those with GOLD stage II disease
	Wedzicha, 2000	28	93 individuals with moderate to severe COPD	Fibrinogen increased during acute exacerbation and is significantly higher in the presence of purulent sputum, a symptomatic cold or increased cough
	Groenewegen, 2008	29	314 individuals with COPD from the COSMIC study	Higher fibrinogen associated with higher rate of moderate and severe exacerbations
	Mackay, 2012	30	161 individuals with COPD	CAT scores are higher at baseline in frequent exacerbators and are linked to fibrinogen levels
	Banerjee, 2004	31	67 individuals with stable moderate to severe COPD	Bacterial or viral airway colonisation associated with higher fibrinogen levels
	Seemungal, 2001	32	120 individuals with COPD	Higher fibrinogen in patients with RSV-positive stable COPD. Trend towards higher fibrinogen during exacerbation if RSV detectable vs undetectable
Exacerbations	Polalti, 2008	33	33 individuals with stable COPD, 26 individuals with acute exacerbations, 16 controls	Fibrinogen levels higher in COPD than controls and significantly higher during an exacerbation of COPD than in stable disease
	Saldias, 2011	34	85 individual with mild to moderate exacerbation of COPD	Fibrinogen levels are higher during exacerbations and return to baseline after 30 days
	Koutsokera, 2009	35	30 individuals with an acute exacerbation of COPD	Fibrinogen levels return to baseline 40 days after exacerbation but baseline levels do not predict recovery time
	Valipour, 2008	36	30 individuals with stable COPD, 30 individuals with acute exacerbations, 30 controls	Fibrinogen levels higher in individuals with COPD versus controls. No difference in fibrinogen between stable COPD and exacerbation but significant reduction in fibrinogen during 6-week recovery period following an exacerbation
Co-morbidities	Jousilahti, 1996	37	19444 Finish men from the general population	Symptoms of chronic bronchitis predict the risk of developing coronary heart disease
	Fowkes, 2006	38	89 individuals with AAA	Individuals with AAA more likely to have COPD and higher fibrinogen levels than those without. Association between lung function, COPD and AAA only marginally affected by smoking history and concurrent cardiovascular disease but substantially affected by composite markers of inflammatory disease
	Castagna, 2008	39	151 individuals with stable COPD, 31 smoker controls, 42 non-smoker controls	PVD is more prevalent in individuals with COPD than healthy controls
	Blum, 2011	40	27 individuals with COPD, 60 individuals with COPD and PVD	Individuals with COPD and PVD are more likely to have lower BMI and be older

Table 1 Continued

	Author, year	Ref	Patients	Findings
	Maksimovic, 2012	41	388 individuals with PVD	More severe PVD is associated with higher fibrinogen levels
	McDermott, 2005	42	107 individuals over 60 years with PVD, 848 controls over 60 years	PVD is associated with higher fibrinogen levels
	Watz, 2009	43	170 individuals with stable COPD, 30 individuals with chronic bronchitis	47.5% of individuals with chronic bronchitis/COPD have metabolic syndrome. Fibrinogen not associated with metabolic syndrome but does reflect level of physical activity
	Waschki, 2012	44	127 people with COPD, 44 healthy controls	Physical activity is associated with FEV_1 and is inversely associated with fibrinogen
	Watz, 2008	45	170 individuals with stable COPD	High fibrinogen levels and cardiac dysfunction are associated with reduced physical activity
	Waschki, 2011	46	170 individuals with stable COPD	Fibrinogen is increased in non-survivors but is not associated with the risk of death. Physical activity is correlated with FEV_1 and is inversely associated with fibrinogen level
Genetics	Yanbeava, 2009	47	355 individuals with stable moderate to severe COPD, 195 healthy smokers	No single nucleotide polymorphisms in fibrinogen associated with the presence of COPD
Treatments	Lomas, 2009	48	89 individuals with stable COPD	No change in fibrinogen level following a 6-week course of oral prednisolone
	Lomas, 2011	49	294 individuals with stable COPD	Treatment with inhaled steroid does not affect fibrinogen. The p38 MAPK inhibitor losmapimod reduces fibrinogen levels by 11% after a 12-week treatment (p=0.002)
	Kunter, 2008	50	30 individuals with acute exacerbations of COPD	Treatment of acute exacerbation with intravenous methylprednisolone results in a significant decrease in fibrinogen after 10 days; no effect in non-steroid treated group
	Barnes, 2009	51	71 individuals with stable COPD: 34 treated, 37 controls	The p38 MAPK inhibitor SB-681323 reduces fibrinogen levels by 11% after a 28-day treatment (p=0.02)
	Dentener, 2008	52	16 individuals with COPD: 8 treated, 8 controls	6 weeks' treatment with infliximab (anti-TNFα) does not alter fibrinogen levels
	Kaczmarek, 2010	53	56 individuals with stable COPD: 28 treated, 28 controls	No significant difference in fibrinogen levels after 3 months' treatment with simvastatin

AAA, abdominal aortic aneurysm; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CAT, COPD Assessment Test; CHS, Cardiovascular Health Study; COSMIC, COPD and Seretide: a Multi-Center Intervention and Characterization; EPI-SCAN, Epidemiologic Study of COPD in Spain; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative on Obstructive Lung Disease; MAPK, mitogen-activated protein kinase; MRC, Medical Research Council; NHANES III, Third National Health and Nutrition Examination Survey; PVD, peripheral vascular disease; RSV, respiratory syncytial virus; TNF, tumour necrosis factor.

FIBRINOGEN AND COPD IN GENERAL POPULATION COHORTS

Cohorts from the general population have been used to assess cross-sectional and longitudinal associations between fibrinogen and COPD. There was an inverse relationship at baseline between fibrinogen and % predicted FEV_1 in a cohort of 8955 people selected at random from the Copenhagen population; those with fibrinogen in the highest tertile had an excess annual decline in FEV_1 compared with those in the lowest tertile.[11] This difference was seen in current smokers and 'non-smokers'—defined as never-smokers and ex-smokers combined. Those with the highest baseline fibrinogen were also more likely to be admitted with an exacerbation of COPD during the 6-year follow-up period, with hospitalisation rates of 93 and 52 per 10 000 person-years in the highest and lowest fibrinogen tertiles, respectively. The differences between groups could not be explained by smoking alone. However, these data were not adjusted for lung function at baseline. By not excluding those with pre-existing lung disease, the number of individuals with COPD may have been over-represented in the highest fibrinogen group, accounting for a higher hospitalisation rate during follow-up.[11] However, two studies that did adjust for baseline lung function have shown an association between fibrinogen and COPD. Valvi and colleagues studied 20 192 individuals from the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS) cohort, showing that baseline fibrinogen levels predict future incident COPD and COPD-related hospitalisation.[12] An additional cohort of 5247 men randomly selected from a Malmö birth cohort also had

more hospital admissions with COPD if they had higher baseline fibrinogen after 25 years of follow-up, even after adjustment for smoking status and baseline FEV_1.[13] Fifteen-year follow-up data from the Coronary Artery Risk Development in Young Adults (CARDIA) study of 2132 individuals showed that higher fibrinogen resulted in greater loss of FEV_1 and forced vital capacity (FVC) and development of abnormal FEV_1 or FVC regardless of smoking status. However, they did not demonstrate an association with the development of obstructive spirometry consistent with a diagnosis of COPD.[14] In an older (>65 years) cohort from the CHS, where baseline fibrinogen was assessed in quintiles, there was an association between higher fibrinogen and lower % predicted FEV_1 and FEV_1:FVC ratio. Individuals had a faster decline in FEV_1 if they had higher baseline fibrinogen, although this effect was negated if current smokers were removed from the analysis.[15] The evidence provided by such studies on cohorts from the general population suggests that raised fibrinogen predicts faster decline in lung function at a population level, although there is no definitive proof of a predisposition to COPD. This effect appears to be independent of smoking status, suggesting an inherent predisposition to an exaggerated inflammatory response rather than occurring as a result of exposure to pro-inflammatory inhaled agents.

FIBRINOGEN AND COMPONENTS OF COPD
COPD diagnosis, severity and mortality

Many cross-sectional studies have shown that blood fibrinogen levels are higher in individuals with COPD compared with healthy controls.[16–18 33 36 50] A meta-analysis confirmed this

finding and noted that it is independent of current smoking status.[19] Mannino and colleagues showed in a cross-sectional cohort of 8342 individuals with COPD from the Third National Health and Nutrition Examination Survey (NHANES III) that plasma fibrinogen was associated with severity in moderate and severe disease.[18] Data from the 1793 individuals from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort confirmed an association between baseline fibrinogen and FEV_1.[25] Garcia-Rio and colleagues were unable to reproduce this finding in the smaller Epidemiologic Study of COPD in Spain (EPI-SCAN) cohort of 324 patients with COPD and 110 controls, additionally finding no association between fibrinogen and a diagnosis of COPD once they had adjusted for age, sex, body mass index (BMI) and smoking history.[20] Similarly Eickhoff and colleagues found no correlation between fibrinogen and disease severity (as defined by Global Initiative on Obstructive Lung Disease (GOLD) stage) in 60 patients with COPD recruited into a study of systemic vascular function in COPD.[17] This suggests a modest association between fibrinogen and disease severity that can only been seen in large cohorts.

Importantly a large meta-analysis of prospective studies of over 154 000 individuals demonstrated a clear correlation between plasma fibrinogen and death from COPD (HR 3.7 (95% CI 2.75–4.97) per 1 g/litre increase in fibrinogen).[21] Recent data from the ARIC/CHS and NHANES III general population cohorts also showed increased all-cause mortality in individuals with higher circulating fibrinogen.[12 22]

Disease progression
If plasma fibrinogen is able to predict decline in FEV_1 over time then it may act as a surrogate marker of disease activity in individuals with COPD. This would be of enormous value in the current clinical setting in which we are unable to predict those who will remain stable and those who are likely to deteriorate rapidly. Donaldson and colleagues followed a small cohort of 148 UK individuals with moderate COPD (median FEV_1 38% predicted) for a median of 3 years, finding that fibrinogen levels rose on average by 0.1 g/litre/year and that those with 'high' baseline fibrinogen (above the median) had a faster decline in FEV_1.[23] However, the data were not adjusted for smoking status, gender and baseline FEV_1. In another small cohort of 96 Japanese individuals with milder COPD (median FEV_1 70% predicted), Higashimoto and colleagues found that those with higher blood levels of fibrinogen had a non-significant trend towards faster decline in lung function (p=0.054) over a median 2-year follow-up.[24] Conversely fibrinogen was associated with baseline FEV_1 but not longitudinal decline in FEV_1, in a larger multinational cohort of 1793 individuals from the ECLIPSE study.[25] These data suggest that fibrinogen is not associated with longitudinal lung function decline despite the presence of an association with baseline lung function.

Components of COPD
Emphysema versus chronic bronchitis
In a small study (n=49) of men with stable COPD, blood fibrinogen was higher in those with CT evidence of emphysema than in those without emphysema (and presumably with small airways disease) when adjustments were made for differences in baseline FEV_1.[26]

Risk of exacerbations
Higher fibrinogen is associated with an increased rate of exacerbations in cohorts of individuals with COPD; individuals with

GOLD stage II disease in the ECLIPSE cohort had a higher risk of exacerbation if their plasma fibrinogen was >1 SD above the mean.[27] An earlier 1-year study of 111 individuals with moderate to severe disease did not find an association between fibrinogen and exacerbation frequency[28] but the numbers were likely to have been too small to detect any effect. There may also be an association between fibrinogen and the risk of severe exacerbations, that is, those necessitating hospital admission.[29] Large-scale longitudinal studies in cohorts from the general population also found that those with the highest fibrinogen had increased admission rates with COPD exacerbations during the follow-up period.[11 13] Recent evidence suggests that the COPD Assessment Test (CAT), an eight-item questionnaire, is increased at baseline in individuals with frequent exacerbations and that that this is significantly linked to fibrinogen levels. Furthermore, CAT scores are increased during exacerbations but not related to changes in fibrinogen.[30]

Airway colonisation
Even in stable disease, bacterial or viral airway colonisation (as measured by positive sputum culture and culture ± PCR respectively) is associated with higher blood fibrinogen than those with no detectable airway pathogens in two small studies.[31 32] Despite those with pathogenic organisms having a comparable % predicted FEV_1 to those without, they had a trend towards higher exacerbation frequency (p=0.09), which would itself predispose to higher fibrinogen.

Thus there is robust evidence for fibrinogen as a predictor of exacerbations but further evidence is required of associations with other components of the COPD phenotype.

Changes in fibrinogen during exacerbations of COPD
Plasma fibrinogen levels are reproducible in individuals with stable COPD.[5] However, in keeping with its role as an acute phase protein, levels increase at the time of an exacerbation[28 33 34] and reduce significantly during the following 4–6 weeks.[34–36] Small studies suggest that this rise is more marked in the presence of symptoms consistent with an infective aetiology, for example, purulent sputum, coryzal symptoms[28] and that there is a trend towards a more marked rise in fibrinogen with the identification of a viral pathogen.[32] However, fibrinogen levels early in the exacerbation did not correlate with improvement in symptoms during the recovery process in a small cohort of 30 individuals.[35]

Fibrinogen may prove useful in deciding whether to consider antimicrobial agents in the treatment of an exacerbation if larger scale studies can reproduce this association and define clinically relevant parameters for use on an individual basis. Larger studies are required to clarify the role of fibrinogen in predicting recovery from exacerbations of COPD.

FIBRINOGEN AND COMORBIDITIES OF COPD
Patients with COPD often also have comorbid diseases, including ischaemic heart disease, cardiac failure, diabetes, cachexia, lung cancer and osteoporosis. Though many of these conditions share common aetiological factors, some COPD comorbidities may be the consequence of a systemic inflammatory response in these individuals. Therefore as an inflammatory marker, fibrinogen may be an indicator of such comorbidities in COPD and, if raised, should prompt additional investigation.

Fibrinogen is raised in individuals with COPD and in cardiovascular disease.[54] Indeed circulating fibrinogen is an independent risk factor for the development of heart disease in a healthy cohort.[20] There is a high prevalence of cardiovascular disease in

COPD.[55] Moreover, symptoms of chronic bronchitis were linked to the risk of coronary heart disease in a population of 19 444 Finish men.[37] Fowkes and colleagues investigated the relationship between COPD and abdominal aortic aneurysm in a small cohort of 89 individuals, finding an association between abdominal aortic aneurysm and reduced lung function that was independent of smoking history and the presence of other cardiovascular disease. However, markers of systemic inflammation (including fibrinogen) were important confounding factors, suggesting a possible causal link.[38] Conversely Eickhoff and colleagues did not find an association between fibrinogen and flow-mediated arterial dilation (a measure of cardiovascular risk) in a cohort of 60 patients with COPD. However, there was a link with CRP, suggesting an association with systemic inflammation.[17]

Peripheral vascular disease (PVD) is more prevalent in individuals with COPD than in healthy controls.[39] Those with COPD and PVD are more likely to have a lower BMI and be older,[40] and more severe PVD is associated with higher levels of fibrinogen.[41 42] This association between low BMI and raised inflammatory markers could partially explain the 'obesity paradox' with lower BMI being linked to higher mortality.[56] The presence of PVD could also influence the relationship between fibrinogen and FEV_1.

Many of the studies described in this review, which investigated the relationship between fibrinogen and COPD, excluded individuals with significant cardiovascular disease on the basis that they may bias the results. Though understandable, it is possible that in doing so an important relationship between COPD, cardiovascular disease and fibrinogen is not being fully investigated. This component of the COPD phenotype is being evaluated in the recently initiated ERICA project (Evaluation of the Role of Inflammation In Non-pulmonary Disease Manifestations in Chronic Airways Disease).[57]

Metabolic syndrome, comprising hypertension, obesity, hypercholesterolaemia and insulin resistance, is a risk factor for the development of cardiovascular disease and is found more commonly in individuals with COPD.[43] Though fibrinogen is raised in metabolic syndrome[58] there was no direct association between fibrinogen and the presence/absence of metabolic syndrome in a cohort of 200 patients with COPD.[43]

In individuals with COPD, higher levels of fibrinogen are associated with a reduced level of physical activity.[44 45] Moreover, decreased levels of physical activity are linked to an increased risk of death. Fibrinogen was higher in non-survivors, although it was not associated with the risk of death in a study of 170 individuals with stable COPD,[46] leaving physical activity to be the strongest predictor of all-cause mortality in individuals with COPD.

Lack of physical activity is also related to the risk of developing COPD comorbidities. In his study of metabolic syndrome in COPD, Watz and colleagues found that fibrinogen was inversely associated with levels of physical activity, and lack of physical exertion is itself a risk factor for the development of metabolic syndrome.[43] Higher levels of physical activity also reduce the risk of cardiovascular disease. A study of 27 055 apparently healthy women showed that more physical activity was correlated with lower fibrinogen levels,[59] and that around a third of the apparent risk reduction in cardiovascular events due to physical activity can be explained by raised inflammatory markers, including fibrinogen.

There are to date no studies specifically investigating the importance of fibrinogen in determining the presence of other pro-inflammatory comorbidities in COPD. A large-scale observational study determining their association with fibrinogen and other biomarkers would be of enormous value in identifying markers reflecting the burden of systemic disease in COPD.

FIBRINOGEN AND GENETICS

Genetic polymorphisms should be considered when measuring a biomarker, as they may impact on the expression of the protein. Circulating levels of fibrinogen are heritable[60 61] with polymorphisms explaining some of the heritability of the acute-phase response.[62] Single nucleotide polymorphisms (SNPs) of the fibrinogen β chain-coding gene have been studied but no association between these SNPs and the risk of COPD or related phenotypes were found in a specific case–control association study.[47] This indicates that raised fibrinogen in individuals with COPD is a reflection of the disease rather than a causal factor.

THE EFFECT OF COPD TREATMENTS ON FIBRINOGEN

Valuable information may be gleaned by using fibrinogen as a surrogate marker of disease activity when assessing current and putative treatments for COPD. A treatment that affects plasma fibrinogen may modify important outcomes in COPD.

Corticosteroid treatment

Steroids form the mainstay of stable disease (in the form of inhalers) and exacerbations when short-course oral or intravenous corticosteroids are used. Higashimoto and colleagues found no difference in fibrinogen levels between those on inhaled or maintenance oral steroids.[24] Additionally we showed that treatment of individuals with stable disease with a 6-week course of oral prednisolone did not result in a change in fibrinogen levels[48]; nor did a 12-week course of inhaled steroids after a washout period prior to starting the treatment.[49] Conversely, in individuals with an exacerbation of COPD, intravenous steroid treatment (40 mg methylprednisolone for 10 days) resulted in a significantly larger reduction in fibrinogen than in patients treated with non-steroid drugs alone.[50]

Thus steroids affect plasma fibrinogen in patients with acute exacerbations, perhaps as part of a more general effect on the inflammatory response. However, no effect is seen in those with stable disease. This may provide insight into underlying disease mechanisms; in particular that the chronic inflammation driving disease progression is distinct from the acute inflammatory response of exacerbations and therefore that different treatments may be effective.

Other anti-inflammatory drugs

Mitogen-activated protein kinases (MAPKs) are signalling molecules that respond to stress stimuli such as osmotic stress, heat shock and pro-inflammatory cytokines. When activated, p38MAPK signalling leads to pro-inflammatory cytokine production. This pathway is upregulated in COPD[63] and has been implicated in the pathogenesis of this disease.[64] A p38 MAPK inhibitor, losmapimod, reduced plasma fibrinogen by 11% in individuals with stable COPD after a 3-month treatment period.[49] Similarly, SB-681323, another p38 MAPK inhibitor, reduced plasma fibrinogen by 11% in individuals with stable COPD after a 28-day treatment period.[51] This was not the case with inhaled steroids. Despite the small-scale nature of the studies, the effect of p38 MAPK inhibitors on fibrinogen in stable COPD is in stark contrast to the lack of effect seen with steroids. This suggests different mechanisms of action and highlights the potential utility of biomarkers in delineating pharmacological activity and response to treatment.

Other anti-inflammatory agents including the anti-tumour necrosis factor agent infliximab and statins have been studied in the context of COPD treatment; neither were shown to reduce plasma fibrinogen.[52 53]

DISCUSSION

Plasma fibrinogen may be an ideal blood biomarker for the existence of systemic inflammation. The levels are easily measured and are already integrated into clinical diagnostic practice. Furthermore, blood biomarkers can be readily measured in patients without the need for invasive procedures. These practical reasons have made it a candidate biomarker in a number of diseases including COPD.

Fibrinogen has joined a growing list of biomarkers that can distinguish individuals with COPD (defined by GOLD criteria) from controls at a population level. These include other markers of systemic inflammation (CRP, IL-6, IL-8) and lung-derived proteins (SP-D, CCL-18, CC-16) and markers of extracellular matrix breakdown (MMP-8 and MMP-9). The challenge now is to determine how, if at all, these biomarkers in isolation or as composite markers may be useful in clinical practice.

A clinically useful biomarker must be reproducible in stable disease. Indeed fibrinogen, SP-D and CC-16 were reproducible in stable disease over 3 months in a subset of the ECLIPSE cohort.[5 48 66] Lack of reproducibility is likely to limit the use of other candidate biomarkers, including CCL-18, CRP, IL-6 and IL-8.[5] Most of the studies described in this review measured only baseline fibrinogen but future studies must make serial measurements to confirm that in clinical practice a single sample gives a useful and representative result.

Biomarkers are required in COPD to aid diagnosis, define clinical phenotypes and monitor response to existing and new therapeutic strategies, particularly in the clinical trial setting. An individual or composite biomarker must therefore be useful at an individual level. To date, no single biomarker is powerful enough to be used as a diagnostic tool for COPD, but fibrinogen could foreseeably be used as part of a composite biomarker to aid diagnosis. Fibrinogen, along with CRP[65] and IL-8, correlates with disease severity as measured by GOLD stage. Using this FEV_1-based comparator may seem counterproductive as the aim is to develop biomarkers that better correlate with clinical phenotypes than FEV_1; however as the most widely used measure of disease severity it seems reasonable to use this as a crude assessment before profiling biomarkers of interest in more depth. Fibrinogen predicts risk of COPD-specific mortality and is associated with cardiovascular mortality[21]; CRP is also associated with COPD-specific and all-cause mortality[67] and cardiovascular mortality is increased in individuals with COPD with higher circulating levels of CCL-18.[68] Moreover, circulating fibrinogen is moderately associated with coronary heart disease, stroke and vascular and non-vascular mortality in a population with no history of cardiovascular disease.[21] Thus fibrinogen and other markers may be useful in identifying individuals at higher risk of mortality, whether due to respiratory complications or common co-morbidities such as cardiovascular disease, within the COPD population.

Fibrinogen is also higher in individuals with metabolic syndrome[58] and one of its components, low physical activity,[44 45] where inflammatory mediators account for much of the cardiovascular disease risk.[59] This indicates that fibrinogen may be a major contributor in the development of COPD comorbidities.

Defining those with more active disease will allow appropriate targeting of existing treatments and selecting suitable individuals for clinical trials of new therapeutic agents. Those with more active disease may have faster decline in lung function or be more prone to exacerbations. Fibrinogen has emerged as a useful tool in defining a subpopulation of individuals with COPD prone to more frequent exacerbations; CCL-18 and CRP were also associated with exacerbation frequency in the ECLIPSE cohort but both suffer from a lack of reproducibility.[5 27] Conversely, it is CC-16, and not fibrinogen, that is associated with the rate of lung function decline.[25]

The response of biomarkers to treatments may help identify those who will respond but also provide information on mechanisms of disease. Fibrinogen is reduced by steroids during exacerbations and p38 MAPK inhibitors in stable disease whereas SP-D and CCL-18 are reduced by steroids in stable disease.[48 68] This suggests that these biomarkers are indicators of two disparate inflammatory pathways and may be useful in monitoring responses to different treatments. The fact that p38 MAPK inhibitors affect fibrinogen will aid identification of appropriate individuals for enrolment in future trials of p38 MAPK inhibitors and adds weight to the argument that it is possible to use blood biomarker to 'phenotype' individuals with COPD and tailor treatments accordingly.

In summary, there is evolving evidence that fibrinogen is a useful biomarker in COPD, particularly in defining those more likely to exacerbate, linking to important clinical endpoints and in acting as a surrogate marker of treatment success.

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