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ABSTRACT

Background: Fibrinogen is a marker of systemic inflammation and may represent an important biomarker for the progression of chronic obstructive pulmonary disease (COPD).

Methods: We used baseline data from the Third National Health and Nutrition Examination Survey (NHANES III) and follow-up mortality data to determine the relation between fibrinogen levels and COPD and to examine how fibrinogen levels at baseline affected long term outcomes in subjects. The elevated fibrinogen level was defined as the upper 10% of the fibrinogen level distribution (top decile).

Results: Our study sample included 8,507 subjects, of whom 3,290 died during the follow-up period. The mean fibrinogen level was 303.6 g/dL and 10% of the sample had levels higher than 403.0 mg/dL. Subjects with Stage 3 or 4 COPD were more likely to have a fibrinogen level > 403.0 mg/dL (odds ratio 3.4, 95% confidence interval [CI], 2.1, 5.6) than were people with normal lung function, after adjusting for covariates. An elevated fibrinogen level increased the risk of mortality (hazards ratio 1.36, 95% CI 1.13, 1.63).

Conclusion: In the nationally representative NHANES III data, impaired lung function is a correlate of fibrinogen levels and the presence of higher fibrinogen levels increases the risk of mortality.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality worldwide(1). In the United States, COPD is now the third leading cause of death, surpassing stroke (2). Understanding the natural history of COPD has been important in the field of pulmonary medicine, dating back to the work of Burrows (3), and Fletcher and Peto (4;5). Over subsequent years, researchers have championed different hypotheses about COPD development, including the “British” hypothesis stating that the presence of cough and sputum was the key factor (6) and the “Dutch” hypothesis stating that the presence of increased airways responsiveness was the major factor(7).

The relation between COPD and other diseases and the effect that these other diseases have on COPD has become increasingly important in recent years(8;9) . Epidemiological data indicates that many COPD deaths result from cardiovascular complications(10) and cardiovascular events are increased in COPD patients(11) . While this relation has been, traditionally, thought to be related to the shared risk factor of smoking, recent work has suggested that systemic inflammatory processes may be important in both of these processes.

Fibrinogen is an acute phase reactant protein predominantly derived from the liver that is a marker of systemic inflammation(12). Fibrinogen levels are increased in both cardiovascular disease (CVD) and COPD(13;14). Fibrinogen may be a tool for stratifying COPD patients in clinical trials by identifying populations at higher risk for poor outcome such as frequent exacerbations(13) or hospitalization(15).

Literature exists linking fibrinogen and CVD,(16) fibrinogen and COPD,(17) and fibrinogen and COPD outcomes(15). Few studies, however, have longitudinal follow-up, general population samples and excellent ascertainment of CVD. This paper examines

correlates of fibrinogen levels in a nationally representative cohort of U.S. adults and determines the effect of elevated fibrinogen levels on long term mortality in this population controlling for multiple concurring risks, including CVD.

METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention, Atlanta, Ga. In this study a stratified multistage clustered probability design was used to select a sample of the U.S. population. Study participants completed extensive questionnaires in the household and a comprehensive physical examination, including pulmonary function testing, either in the household or at a specially equipped mobile examination center. A total of 81 sites were included in the final sample. The study was approved by the National Center for Health Statistics' Institutional Review Board (No approval number provided). A follow-up of the original NHANES III cohort, linking study subjects to the National Death Index, determined vital status in December 2006.

This analysis was limited to subjects aged 40 years and older (fibrinogen levels were not obtained on subjects younger than 40 years old) who completed the baseline survey and had their vital status determined at the end of follow-up.

Fibrinogen levels

Fibrinogen levels in the NHANES III survey were measured using thrombin clotting times of dilute plasma, as has been described previously(18).

Baseline lung function

Predicted values from NHANES III (developed using only asymptomatic, lifelong nonsmoking subjects with at least two acceptable maneuvers) were used in the analysis(19). We used age, sex, height and race/ethnicity to determine the predicted values. We used the values for “white” subjects to classify those of “other race”. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed criteria to aid both the diagnosis and epidemiologic study of COPD. (20) The study participants were classified into a modified “GOLD Stage”, using the pre-bronchodilator lung function (post-bronchodilator values were not obtained in this survey), into categories based on a modification of COPD classification criteria: Stage 3 or 4 ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted), Stage 2 ($FEV_1/FVC < 0.70$ and $FEV_1 > 50$ to $< 80\%$ predicted), Stage 1 ($FEV_1/FVC < 0.70$ and $FEV_1 > 80\%$ predicted), Restricted ($FEV_1/FVC > 70\%$ and $FVC < 80\%$ predicted, Symptoms only (presence of chronic respiratory symptoms in the absence of any lung function abnormality), and no lung disease.

Definitions

Data included in this analysis are age, sex, race/ethnicity, body mass index (BMI), smoking status, modified GOLD Stage (defined above), diabetes mellitus, cardiovascular disease, educational level, and poverty income ratio. Age was classified at baseline and was categorized for use in tables (40-49, 50-59, 60-69, 70-79, and 80 and older), and was used as a continuous variable in the regression analyses. Race/ethnicity was classified as white, black, Mexican-American, or other. BMI was classified at baseline and was categorized into 5 categories (missing, < 18.5 , $18.5-24$, $25-29$, and $\geq 30 \text{ kg/m}^2$). We defined subjects as being current smokers, former smokers, or never smokers based on

their responses to series of questions. One had to have smoked more than 100 cigarettes to qualify as a former or current smoker. A person was considered as having diabetes mellitus either if they reported physician diagnosed diabetes or reported treatment for diabetes or had a fasting blood glucose of higher than 126 g/L. A person was considered as having cardiovascular disease if they reported a physician diagnosis of a heart attack, coronary artery disease, congestive heart failure, or stroke. Education status was stratified into three levels (< 12 years, 12 years, and > 12 years). Poverty income ratio was extracted from the database and stratified into four categories, < 1 (very poor), 1 to < 2 (poor), 2 or higher (not poor), and “unknown” for those not reporting income.

Mortality

Death from any cause was ascertained by the end of 2006 and the date was used to determine months of follow-up from the baseline examination.

Statistical Analysis

Data analysis was completed using statistical software (Statistical Analysis Software, version 9.2; SAS Institute; Cary, NC and SUDAAN version 10.1; RTI, Research Triangle Park, NC, and SPSS 17, Somers, NY). NHANES III weights were used in all of the analyses.

We determined the correlates of fibrinogen levels in linear models using the SUDAAN procedure REGRESS in models controlling for age, sex, race/ethnicity, BMI, smoking status, modified GOLD stage, diabetes mellitus, cardiovascular disease, educational level, and poverty income ratio. These were replicated examining fibrinogen levels in the top decile (> 403.0 mg/dL) using the SUDAAN procedure RLOGIST, controlling for the same factors. Our primary outcome of interest in the survival models

was mortality by 2006. Cox proportional hazard regression models were developed using the SUDAAN procedure SURVIVAL to account for differential follow up in cohort participants. Time of follow up was used as the underlying time metric. Censoring occurred at the date of death certificate or date the participant was last known to be alive. Plots of the log-log survival curves for each covariate were produced to evaluate the proportional hazards assumptions. We determined the interaction between modified GOLD Stage and elevated fibrinogen levels as predictors of mortality in models adjusted for covariates as noted above.

RESULTS

The NHANES III adult cohort consisted of 20,050 individuals. We excluded 8,602 who were under the age of 40, 2,098 who did not have fibrinogen levels obtained, 839 who did not have pulmonary function testing done, and 4 who did not have mortality data. The studied cohort consisted of 8,507 subjects representing an estimated 83.8 million U.S. adults aged 40 and older during 1988-1994. By the end of 2006, 3,209 subjects, representing an estimated 23.4 million (27.9 %, weighted percentage) of the original cohort, had died.

The distribution of age, sex, race/ethnicity, BMI, smoking status, modified GOLD stage, diabetes mellitus, cardiovascular disease, educational level, and poverty income ratio is displayed in Table 1, including the actual numbers of studied subjects and the weighted percentage. This Table also reports the mean fibrinogen levels, the proportion of subjects with fibrinogen levels > 403.0 mg/dL, and the proportion of subjects who had died by the end of the follow-up period.

Tables 2 and 3 report the correlates of fibrinogen levels (Table 2) and the correlates of elevated fibrinogen levels (Table 3). There was considerable overlap

between these two analyses; for example, in both age, current smoking, and the presence of diabetes or cardiovascular disease were significant correlates of fibrinogen. The presence of severe or very severe COPD was one of the strongest predictors of fibrinogen levels, with a mean increase of 43.7 mg/dL (standard error 9.70 mg/dL) in the linear regression models and an odds ratio (OR) for elevated fibrinogen of 3.10 (95% confidence interval [CI] 1.99, 4.81).

In Cox proportional hazard models adjusted for all covariates, fibrinogen predicted a higher risk of death both as a categorical variable (Level $\geq$ 403 mg/dL, Table 4 Model A) or a continuous one (Table 4, Model B). An elevated fibrinogen level increased the risk of mortality in all modified GOLD subgroups (Figure 1), although this comparison only reached statistical significance in those with normal lung function.

DISCUSSION

In this nationally representative dataset of a U.S. population we found that fibrinogen levels were related to the presence of spirometrically determined obstructive lung disease and that these levels predicted long term mortality in this cohort. Higher fibrinogen levels predicted mortality when evaluated as both a continuous and categorical variable.

Fibrinogen is a major plasma protein coagulation factor that is linked to adverse health events when levels are either low or high. Low levels have been linked to an increased risk of bleed due to impaired hemostasis whereas high levels have been linked to an increased risk of cardiovascular events(21). Variability in fibrinogen levels are thought to be related to both inherited and acquired factors(22), and the presence of COPD is a well-established predictor of elevated fibrinogen levels (23;24). In addition,

patients with COPD are at increased risk for thrombotic events, such as venous thromboembolism (25) and acute cardiac events (11).

This analysis demonstrated that fibrinogen levels in this cohort were significantly related to a number of factors, including age, sex, smoking status, race/ethnicity, and the presence of chronic diseases such as cardiovascular disease, diabetes mellitus, and COPD. As fibrinogen levels were only determined at baseline we are unable to infer whether the elevated fibrinogen levels preceded or followed the development of these chronic diseases.

Our analysis demonstrated a dose-response effect for COPD, with more advanced GOLD stages 3 or 4 of the disease exhibiting a greater elevation in fibrinogen (43.71 mg/dL, $p < 0.0001$) than GOLD stage 2 or GOLD stage 1 disease (19.79 mg/dL, $p < 0.0001$ and 3.04 mg/dL, $p = 0.4731$ respectively), relative to people with normal lung function. We also demonstrated that people with a restrictive spirometric impairment also had elevated fibrinogen levels (17.19 mg/dL, $p = 0.0011$), suggesting this group may be a subtype of COPD or have other characteristics that precludes their inclusion as “normal” subjects in epidemiologic and clinical studies (17;26).

While we demonstrated an effect of elevated fibrinogen on mortality in the overall cohort (Table 4), this effect was diminished in the analysis that examined the interaction between lung function impairment and elevated fibrinogen levels (Figure 1). The finding of elevated fibrinogen and higher mortality, however, raises the intriguing possibility that fibrinogen might serve as both a biomarker of disease activity in COPD and a potential target for therapeutic intervention(27).

This analysis has certain limitations. As noted above, fibrinogen was assessed at a single point in time, so one cannot determine the temporal association between fibrinogen levels and any of our markers of disease. The strict classification of COPD

using GOLD criteria requires the use of a post-bronchodilator FEV₁, which was not available in this study (20). In addition, not all subjects were able to complete pulmonary function testing, potentially biasing our sample towards a healthier population. We did not have other indicators of disease activity for COPD, such as validated measures of exacerbations or imaging data.

In summary, we have demonstrated in this nationally representative cohort that fibrinogen levels are increased in subjects with COPD and other chronic diseases and that elevated fibrinogen levels predict a higher risk of mortality. Fibrinogen is a marker for the systemic component of COPD and may provide an opportunity for improved targeting of interventions to patients with evidence of systemic inflammation.

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Table 1. Demographic characteristics, fibrinogen levels, and mortality of subjects included in analysis.

	N	Weighted Percent	Mean Fibrinogen Level in mg/dL (Standard Error)	Weighted Proportion with Fibrinogen > 403.0 mg/dL	Weighted Proportion Dead by December 2006
Age					
40-49	2,303	36.1	285.6 (3.4)	5.7	7.5
50-59	1,673	24.2	300.0 (3.8)	9.7	15.4
60-69	2,017	21.0	316.5 (3.6)	13.0	36.4
70-79	1,496	13.6	326.1 (4.3)	14.5	66.1
80 and Older	1,018	5.1	333.9 (4.8)	17.7	93.2
Sex					
Male	4,059	46.6	297.4 (3.2)	8.8	29.7
Female	4,448	53.4	309.0 (2.8)	11.1	26.3
Race-ethnicity					
White	4,385	81.5	302.3 (3.2)	9.8	28.8
Black	1,925	8.7	317.5 (2.8)	13.7	30.2
Mexican-American	1,885	3.5	303.2 (4.2)	9.2	21.3
Other	312	6.3	301.4 (6.7)	8.2	16.7
Body Mass Index					
< 18.5	136	1.7	288.7 (9.0)	10.3	45.9
18.5 – 24	2,690	35.3	294.8 (3.1)	8.7	27.3
25 – 29	3,259	36.6	300.9 (3.6)	9.0	27.8
>= 30	2,422	26.4	319.9 (2.9)	13.3	27.6
Smoking Status					
Current Smoker	1,868	23.0	315.7 (3.5)	13.0	30.9
Former Smoker	2,824	35.1	301.4 (3.7)	9.8	30.4
Never Smoker	3,815	41.9	298.8 (3.1)	8.5	24.0
Modified GOLD Stage					
Stage 3 or 4	245	2.9	351.2 (8.4)	24.4	70.2
Stage 2	826	9.1	327.5 (4.0)	16.9	52.4
Stage 1	1,081	11.7	303.6 (5.0)	11.2	38.8
Symptoms Only	1,823	22.1	306.8 (4.0)	10.3	25.8
Restrictive	1,233	10.2	324.3 (5.3)	14.1	40.0

None	3,299	44.0	289.0 (2.7)	6.3	15.3
Diabetes Mellitus					
Yes	1,216	9.8	333.1 (4.9)	18.5	49.8
No	7,291	90.2	300.4 (2.8)	9.1	25.5
Cardiovascular Disease					
Yes	1,178	10.1	334.0 (4.7)	17.9	63.8
No	7,329	89.9	300.2 (2.7)	9.1	23.8
Education Level					
< 12	3,955	29.8	318.9 (4.1)	14.4	40.2
12 Years	2,197	29.0	303.5 (3.2)	9.5	29.1
>= 13 Years	2,355	41.2	292.5 (2.6)	7.2	18.1
Poverty Income Ratio					
< 1	1,463	8.7	320.2 (5.3)	13.7	41.5
1 to 2	2,081	17.7	316.3 (3.7)	13.6	41.9
>= 2	4,125	66.6	297.2 (2.9)	8.3	21.4
unknown	838	7.1	311.6 (3.9)	12.6	36.9
Total	8,507	100.0	303.6 (2.8)	10.0	27.9

Table 2 – Correlates of fibrinogen levels from linear regression models.

Covariate	Beta estimate	Standard Error	p Value
Age (per 1 year)	1.15	0.15	< 0.0001
Sex			
Male	-12.46	2.56	< 0.0001
Female	0	0	
Race-ethnicity			
White	0	0	
Black	11.14	3.38	0.0018
Mexican-American	-1.17	4.74	0.8069
Other	0.86	6.04	0.8873
Body Mass Index			
< 18.5	-22.5	7.73	0.0054
18.5 - 24	0	0	
25 - 29	7.15	2.81	0.0143
>= 30	22.44	3.40	< 0.0001
Smoking Status			
Current Smoker	21.54	4.60	< 0.0001
Former Smoker	2.90	2.75	0.2962
Never Smoker	0	0	
GOLD Stage			
Stage 3 or 4	43.71	9.70	< 0.0001
Stage 2	19.79	4.29	< 0.0001
Stage 1	3.04	4.20	0.4731
Symptoms Only	6.08	3.32	0.0730
Restrictive	17.19	4.95	0.0011
None	0	0	
Diabetes Mellitus			
Yes	16.78	4.54	0.0005
No	0	0	
Cardiovascular Disease			
Yes	11.96	4.33	0.0081
No	0	0	
Education Level			
< 12	5.95	4.21	0.1645
12 Years	-0.54	3.26	0.8683
>= 13 Years	0	0	
Poverty Income Ratio			
< 1	3.18	5.07	0.5325
1 to 2	2.38	3.20	0.4606
>= 2	0	0	
unknown	-0.76	3.53	0.8304

Table 3 – Correlates of Fibrinogen levels > 403 mg/dL (top decile) from logistic regression models.

Covariate	Odds Ratio	95% Confidence Interval
Age (per 1 year)	1.03	(1.01, 1.04)
Sex		
Male	0.73	(0.59, 0.91)
Female	1	1
Race-ethnicity		
White	1	1
Black	1.35	(1.08, 1.70)
Mexican-American	0.89	(0.64, 1.24)
Other	0.87	(0.52, 1.47)
Body Mass Index		
< 18.5	0.76	(0.38, 1.49)
18.5 - 24	1	1
25 - 29	1.06	(0.79, 1.42)
>= 30	1.54	(1.19, 2.01)
Smoking Status		
Current Smoker	1.76	(1.25, 2.48)
Former Smoker	1.15	(0.91, 1.45)
Never Smoker	1	1
GOLD Stage		
Stage 3 or 4	3.10	(1.99, 4.81)
Stage 2	1.95	(1.41, 2.71)
Stage 1	1.43	(0.96, 2.14)
Symptoms Only	1.29	(0.95, 1.75)
Restrictive	1.57	(1.15, 2.15)
None	1	1
Diabetes Mellitus		
Yes	1.65	(1.27, 2.15)
No	1	1
Cardiovascular Disease		
Yes	1.29	(1.01, 1.65)
No	1	1
Education Level		
< 12	1.37	(0.99, 1.90)
12 Years	1.03	(0.75, 1.40)
>= 13 Years	1	1
Poverty Income Ratio		
< 1	1.02	(0.77, 1.35)
1 to 2	1.11	(0.84, 1.48)
>= 2	1	1
unknown	1.09	(0.77, 1.54)

Table 4: Results of Cox Proportional Hazards Models for mortality at up to 18 years of follow-up. Model A includes fibrinogen as either elevated (> 403.0 mg/dL) or not elevated, Whereas Model B includes fibrinogen as a continuous variable.

Covariate	Model A Hazard Ratio	95% Confidence Interval	Model B Hazard Ratio	95% Confidence Interval
Age (per 1 year)	1.10	(1.09, 1.11)	1.10	(1.09, 1.11)
Sex				
Male	1.45	(1.31, 1.61)	1.46	(1.32, 1.62)
Female	1			
Race-ethnicity				
White	1			
Black	1.16	(1.03, 1.32)	1.15	(1.02, 1.30)
Mexican-American	0.85	(0.72, 1.00)	0.84	(0.72, 0.99)
Other	0.62	(0.46, 0.83)	0.62	(0.45, 0.84)
Body Mass Index				
< 18.5	1.88	(1.29, 2.74)	1.93	(1.31, 2.84)
18.5 - 24	1			
25 - 29	0.89	(0.77, 1.03)	0.88	(0.77, 1.02)
>= 30	0.95	(0.84, 1.07)	0.93	(0.82, 1.05)
Smoking Status				
Current Smoker	1.82	(1.58, 2.09)	1.79	(1.55, 2.05)
Former Smoker	1.20	(1.04, 1.38)	1.20	(1.04, 1.38)
Never Smoker	1			
GOLD Stage				
Stage 3 or 4	3.34	(2.53, 4.41)	3.29	(2.50, 4.33)
Stage 2	1.82	(1.54, 2.15)	1.78	(1.51, 2.10)
Stage 1	1.15	(0.98, 1.36)	1.15	(0.98, 1.35)
Symptoms Only	1.32	(1.16, 1.51)	1.32	(1.16, 1.50)
Restrictive	1.81	(1.51, 2.18)	1.79	(1.48, 2.15)
None	1			
Diabetes Mellitus				
Yes	1.51	(1.33, 1.71)	1.49	(1.31, 1.70)
No	1			
Cardiovascular Disease				
Yes	1.55	(1.37, 1.75)	1.54	(1.37, 1.74)
No	1			
Education Level				
< 12	1.10	(0.93, 1.30)	1.09	(0.92, 1.29)
12 Years	1.22	(1.03, 1.44)	1.22	(1.03, 1.44)
>= 13 Years	1			
Poverty Income Ratio				
< 1	1.42	(1.19, 1.70)	1.42	(1.19, 1.70)
1 to 2	1.28	(1.13, 1.46)	1.29	(1.13, 1.46)
>= 2	1			
unknown	1.08	(0.90, 1.31)	1.08	(0.89, 1.31)
Fibrinogen > 403.0 g/L				
Yes	1.36	(1.13, 1.63)		
No	1			
Fibrinogen level (per 100 g/L)			1.17	(1.09, 1.26)

Figure 1. Interaction between elevated fibrinogen levels and modified GOLD stage , in Cox proportional hazard models predicting mortality and adjusted for age, sex, race-ethnicity, body mass index, smoking, diabetes, cardiovascular disease, education level, and poverty income ratio. The box represents the point estimate and the vertical line represents the 5% and 95% confidence interval.

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