Association of C-Reactive Protein With Reduced Forced Vital Capacity in a Nonsmoking U.S. Population With Metabolic Syndrome and Diabetes

HWA MU LEE, MD[1,2]
TRUC VY LE[2]
VICTOR A. LOPEZ[2]
NATHAN D. WONG, PHD[2]

OBJECTIVE — A relationship between inflammation, measured by C-reactive protein (CRP), and forced vital capacity (FVC) in diabetes or metabolic syndrome (MetS) has not been established. We investigated whether high CRP is related to reduced FVC in MetS and diabetes.

RESEARCH DESIGN AND METHODS — We examined the association of MetS/diabetes and CRP (normal ≤3 mg/l, high >3 mg/l) with predicted FVC in 4,272 nonsmoking U.S. adults aged 18–79 years without lung disease in the Third National Health and Nutrition Examination Survey. Logistic regression examined odds of FVC <80% by CRP and MetS/diabetes.

RESULTS — Mean FVC in individuals with MetS and high CRP (95.7%) and those with diabetes and high CRP (93.7%) was lower than in those with no MetS/diabetes and normal CRP (101.7%) ($P < 0.01$) and was lower in those with MetS and high CRP (95.7%) than in those with MetS and normal CRP (98.5%) ($P < 0.01$). The odds ratio (95% CI) of FVC <80% was highest in individuals with MetS and high CRP (odds ratio 4.26 [95% CI 2.08–8.73], $P < 0.01$) compared with those with no MetS/diabetes and normal CRP.

CONCLUSIONS — Elevated CRP is associated with lower FVC in people with MetS.

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Cross-sectional (1,2) and prospective (3) studies have demonstrated impaired lung function in individuals with diabetes and metabolic syndrome (MetS). Recent studies show that reduced lung function may be a precursor of diabetes (4). People with reduced lung function have greater levels of inflammation (5), and people with diabetes or MetS (6,7), including those with elevated C-reactive protein (CRP) (8), are at increased risk of cardiovascular disease. Although the interplay among MetS, diabetes, and insulin resistance has been thoroughly investigated and extensively published, their role in systemic inflammation and lung function impairment has not been firmly established. We examined whether increased levels of CRP may help identify lung function impairment in individuals with MetS/diabetes.

RESEARCH DESIGN AND METHODS

— Using data from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 (9), we examined adults aged 18–79 years ($n = 4,272$ projected to 43.2 million, 59.7% female) with available forced vital capacity (FVC) data, who were nonsmokers, absent of pulmonary obstructions, and without known pulmonary disease. Spirometric data were obtained using a spirometry system following the modified 1987 procedures of the National Institute for Occupational Safety and Health (NIOSH) and American Thoracic Society (ATS). Predicted FVC was calculated using equations developed by Hankinson et al. (10). CRP was measured using a latex-enhanced nephelometry technique, providing a lowest detectable concentration of 2.1 mg/l. Additional details of the NHANES methodology have been published (9).

MetS was defined by the presence of at least three of the following: *1)* waist circumference >102 cm for men and >88 cm for women, *2)* triglyceride level ≥150 mg/dl if fasting, *3)* HDL cholesterol level <40 mg/dl for men or <50 mg/dl for women, *4)* blood pressure ≥130/85 mmHg or on antihypertensive medications, and *5)* fasting glucose level 100–125 mg/dl (7.0 mmol/l) according established criteria (11). Diabetes was defined by a fasting glucose ≥126 mg/dl (or ≥200 mg/dl if nonfasting), taking oral diabetes medication or insulin, or self-report. CRP cut points were defined as normal (≤3 mg/l) or high (>3 mg/l) based on established recommendations (12).

The χ^2 test of proportions or ANOVA was used to compare baseline characteristics among FVC groups. Multivariable logistic regression was used to examine the likelihood of decreased FVC (<80% of predicted) in those with MetS or diabetes by CRP group compared with those with neither of these conditions and low CRP, adjusted for age, sex, and ethnicity. SAS version 9.1.3 (SAS institute, Cary, NC) and SUDAAN version 9.0.1 (Research Triangle Institute, Research Triangle Park, NC) were used for analysis and computation of weighted estimates for projection to the U.S. population.

RESULTS

— Individuals in FVC quartile 1 (lowest FVC) exhibited the highest CRP levels ($P < 0.01$). Additionally, individuals in FVC quartile 1 had higher triglycerides, glucose, systolic blood pressure, and HDL cholesterol than those in FVC quartile 4 (highest FVC) ($P < 0.05$). Prevalence of MetS was highest among individuals in FVC quartile 1

From the [1]Division of Pulmonary Medicine, Department of Medicine, University of California, Irvine, California; and the [2]Heart Disease Prevention Program, Division of Cardiology, Department of Medicine, University of California, Irvine, California.
Corresponding author: Hwa Mu Lee, hwamuleemd@sbcglobal.net.
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Table 1—*Odds of FVC <80% by disease group and CRP level*

	OR (95% CI)	Subjects with FVC <80%/*n*
No MetS or diabetes		
Normal CRP	1.00 (1.00–1.00)	73/2,176
High CRP	1.55 (0.79–3.02)	23/444
MetS		
Normal CRP	1.32 (0.55–3.15)	17/340
High CRP	4.26 (2.08–8.73)†	24/256
Diabetes		
Normal CRP	3.57 (1.31–9.72)*	13/111
High CRP	2.85 (1.18–6.88)*	15/101

*$P < 0.05$, †$P < 0.01$ compared with no MetS or diabetes with normal (≤3 mg/l) CRP; estimates adjusted for age, sex, and ethnicity.

(24.7%) compared with those in FVC quartile 4 (11.5%) ($P < 0.01$). There were no significant differences in waist circumference, BMI, and sex across quartiles of FVC.

Predicted mean FVC values, adjusted for age, sex, and ethnicity, were significantly lower in those with high versus normal CRP levels among individuals with MetS ($P < 0.01$). FVC in those with MetS and high CRP (95.7%) was notably lower than in those with MetS and normal CRP (98.5%) ($P < 0.01$) and those with no MetS/diabetes and normal CRP (101.7%) ($P < 0.01$). Individuals with diabetes and high CRP had the lowest FVC (93.7%), significantly lower compared with those with no MetS/diabetes and normal CRP (101.7%) ($P < 0.01$).

When examining the odds of FVC <80%, adjusted for age, sex, and ethnicity, individuals with MetS and high CRP had the greatest odds of FVC <80% (odds ratio 4.26 [95% CI 2.08–8.73]) followed by individuals with diabetes and high CRP (2.85 [1.18–6.88]) as compared with those with no MetS/diabetes and normal CRP ($P < 0.01$ and $P < 0.05$, respectively) (Table 1). Those with diabetes, regardless of CRP level, had higher odds of FVC <80% than those with no MetS/diabetes and normal CRP (3.57 [1.31–9.72] and 2.85 [1.18–6.88], respectively) ($P < 0.05$).

CONCLUSIONS — We demonstrate that elevated CRP is associated with reduced FVC in individuals with MetS. Those with elevated CRP have an approximate threefold greater likelihood of low FVC than those with normal CRP. Individuals with diabetes appear to have reduced FVC regardless of CRP level. However, individuals with MetS and elevated CRP appear to have odds of reduced FVC similar to those of individuals with diabetes, suggesting that CRP measurement may aid in stratification of risk for low FVC in individuals with MetS.

Recent prospective studies suggest reduced FVC to be a precursor of diabetes and MetS (5). It is not clear why reduced FVC occurs in people with diabetes and MetS, although several possible explanations have been suggested. First, in studies involving the alteration in alveolar wall and capillaries, with subsequent lung elastic recoil and carbon monoxide diffusion tests, there were no significant differences between insulin-dependent subjects with diabetes and healthy nonsmokers (13); however, other studies show a relationship (14). Second, while hypoxemia could reduce FVC in diabetes and MetS, mildly reduced FVC is unlikely to be associated with significant hypoxemia (5). Third, inflammation has been shown to promote impaired lung function. CRP is an acute-phase protein that is produced by the liver under the influence of cytokines. These cytokines are produced at several extrahepatic sites, including the heart, vessel wall, and adipose tissues. Increased CRP levels have been described in people with diabetes, MetS, obesity, and inflammation (15).

Limitations of this study include its cross-sectional design; it is uncertain whether the inflammatory process actually led to reduced FVC in those with MetS and diabetes. An important strength is the large sample and weighting, allowing findings to be generalized to the U.S. adult population. Moreover, the standardized measurement of lung function and other laboratory measurements, including CRP, lipids, and blood pressure, enabled accurate classification of individuals with MetS and diabetes.

Our study demonstrates that individuals with MetS and elevated CRP levels, in particular, may have a further increased likelihood of low FVC, which may further contribute to increased cardiovascular disease risk beyond what MetS and CRP may individually confer. This suggests that CRP may be useful in risk stratification for pulmonary disease in people with MetS. Longitudinal studies are needed to confirm the prognostic significance of our findings.

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