The Association of C-Reactive Protein to Reduced Forced Vital Capacity in a Non-Smoking U.S. Population with Metabolic Syndrome and Diabetes

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Objective: The relationship of inflammation, measured by C-reactive protein (CRP), to forced vital capacity (FVC) in diabetes (DM) or metabolic syndrome (MetS) is not established. We investigated whether high CRP is related to reduced FVC in MetS and DM.

Research Design and Methods: We examined the association of MetS/DM and CRP (normal<3mg/l, high>3mg/l) with predicted FVC in 4,272 non-smoking US adults aged 18-79 without lung disease in the Third National Health and Nutrition Examination Survey. Logistic regression examined odds of FVC<80% by CRP and MetS/DM.

Results: Mean FVC in persons with MetS/high CRP (95.7%) and DM/high CRP (93.7%) were lower than those with no MetS/DM/normal CRP (101.7%)(p<.01) and lower in MetS/high CRP (95.7%) compared to MetS/normal CRP (98.5%)(p<.01). Odds (95% confidence interval) of FVC<80% was highest in MetS/high CRP (4.26 [2.08-8.73], p<.01) when compared to no MetS/DM/normal CRP.

Conclusions: Elevated CRP is associated with lower FVC in persons with MetS.
Cross-sectional\(^1\)\(^,\)\(^2\) and prospective\(^3\) studies have demonstrated impaired lung function in persons with diabetes (DM) and metabolic syndrome (MetS). Recent studies show reduced lung function may be a precursor of DM\(^4\). Persons with reduced lung function have greater levels of inflammation\(^5\) and persons with DM or MetS\(^6\)\(^,\)\(^7\) including those with elevated CRP\(^8\) are at increased risk of cardiovascular disease (CVD). Even though the interplay between MetS, DM, 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 examine whether increased levels of CRP may help identify lung function impairment in individuals with MetS/DM.

**METHODS**

In the Third National Health and Nutrition Examination Survey 1988-1994 (NHANES III),\(^9\) we examined adults aged 18 to 79 (n=4,272 projected to 43.2 million, 59.7% female) with forced vital capacity data, non-smokers, absent of pulmonary obstructions, and without known pulmonary disease. Spirometric data were obtained using a spirometry system following the procedures of the modified 1987 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 \(\geq 3\) of the following: (1) waist circumference \(>102\) cm for men and \(>88\) cm for women, (2) triglyceride level \(\geq 150\) mg/dl if fasting, (3) high-density lipoprotein cholesterol level \(<40\) mg/dl if male or \(<50\) mg/dl if female, (4) blood pressure \(\geq 130/85\) mmHg or on antihypertensive medications, and (5) fasting glucose level 100-125 mg/dL (7.0 mmol/L) according established criteria.\(^11\) DM was defined by a fasting glucose \(\geq 126\) mg/dL (or \(\geq 200\) mg/dL if nonfasting), taking oral medication or insulin, or self-reported diabetes. CRP cut points were defined as normal (\(< 3\) mg/l) or high (\(>3\) mg/l) based on established recommendations.\(^12\)

The Chi-square test of proportions or analysis of variance was used to compare baseline characteristics between FVC groups. Multivariable logistic regression was used to examine the likelihood of decreased FVC (<80% of predicted) in those with MetS or DM by CRP group compared to those with neither of these conditions and low CRP, adjusted for age, gender, 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**

FVC Q1 (lowest FVC) exhibited the highest CRP levels (\(p<0.01\)). Additionally, individuals in FVC Q1 had higher levels of triglycerides, glucose, systolic blood pressure, and HDL-C when compared to FVC Q4 (highest FVC) (\(p<0.05\)). Prevalence of MetS was highest among persons with FVC Q1 (24.7%) when compared to those with FVC Q4 (11.5%) (\(p<0.01\)). There were no significant differences in waist circumference, BMI, and gender across quartiles of FVC. Predicted mean FVC values, adjusted for age, sex, and ethnicity, were significantly lower in those with high vs. normal CRP levels in those with MetS (\(p<0.01\)). FVC in those with MetS/high CRP (95.7%) was notably lower when compared to those with MetS/normal.
CRP (98.5%)(p<0.01) and no MetS/DM/normal CRP (101.7%)(p<0.01). Persons with DM/high CRP had the lowest FVC (93.7%), significantly lower compared to those with no MetS/DM/normal CRP (101.7%) (p<0.01).

When examining odds of FVC <80%, adjusted for age, sex, and ethnicity, individuals with MetS/high CRP had the greatest odds of FVC <80% (OR=4.26 [CI: 2.08-8.73]) followed by individuals with DM/high CRP (OR=2.85 [CI:1.18-6.88]) when compared to persons with no MetS/DM/normal CRP (p<0.01 and p<0.05 respectively) (Table 1). Those with DM, regardless of CRP level had a higher odds of FVC <80% when compared to those with no MetS/DM/normal CRP (OR=3.57 [CI: 1.31-9.72] and OR=2.85 [CI:1.18-6.88], respectively) (p<0.05).

DISCUSSION

We demonstrate that elevated CRP is associated with reduced FVC in persons with MetS. Those with elevated CRP have an approximately three-fold greater likelihood of low FVC compared to those with normal CRP. Persons with DM appear to have reduced FVC regardless of CRP levels. However, persons with MetS and elevated CRP appear to have similar odds of reduced FVC as persons with DM, suggesting that CRP measurement may aid in stratification of risk for low FVC in persons with MetS.

Recent prospective studies suggest reduced FVC to be a precursor of DM and MetS. It is not clear why reduced FVC occurs in persons with DM 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, however; other studies show a relationship. Secondly, while hypoxemia could reduce FVC in DM and MetS, mildly reduced FVC is unlikely to be associated with significant hypoxemia. Lastly, 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 DM, MetS, obesity, and inflammation.

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 DM. 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 DM.

Our study demonstrates that persons with MetS and elevated CRP levels, in particular, may have a further increased likelihood of low FVC, which may further contribute to increased CVD risk beyond what MetS and CRP may individually confer. This suggests that CRP may be useful in risk stratification for pulmonary disease in persons with MetS. Longitudinal studies are needed to confirm the prognostic significance of our findings.
REFERENCES
1. Lawlor DA, Ebrahim S, Smith GD. Associations of measures of lung function with insulin resistance and Type 2 diabetes: findings from the British Women's Heart and Health Study. Diabetologia 2004; 47: 195-203
### Table 1. Odds of FVC < 80% by Disease Group and CRP Level

<table>
<thead>
<tr>
<th></th>
<th>No MetS or DM</th>
<th>MetS</th>
<th>DM</th>
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<tr>
<td></td>
<td>Normal CRP</td>
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<td>1.00 (1.00-1.00), [73/2,176]</td>
<td>1.32 (0.55-3.15), [17/340]</td>
<td>3.57 (1.31-9.72)*, [13/111]</td>
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<td>1.55 (0.79-3.02), [23/444]</td>
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<td>4.26 (2.08-8.73)**, [24/256]</td>
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*\textit{p<0.05, **p<0.01 when compared to No MetS or DM with Normal (≤3 mg/L) CRP; estimates adjusted for age, gender, and ethnicity.}
[\textit{number of subjects with FVC<80%/number of subjects}]

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<th>Odds Ratio (95% Confidence Interval)</th>
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<tr>
<td>Normal CRP</td>
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<tr>
<td>High CRP</td>
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