Association Between Pulmonary Function and Nonalcoholic Fatty Liver Disease in the NHANES III Study

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Abstract: Emerging evidence indicates that nonalcoholic fatty liver disease (NAFLD) is associated with a wide variety of extrahepatic complications. However, the potential association between impaired pulmonary function and NAFLD has been less investigated.

This study examined the relationship between pulmonary function and hepatic steatosis in 9976 adults participating in a cross-sectional analysis of the Third National Health and Nutrition Examination Survey (NHANES III). NAFLD was defined as hepatic steatosis presented on ultrasound examinations in the absence of other known liver diseases. The associations between predicted forced expiratory volume in 1 second (FEV1)% and predicted forced vital capacity (FVC)% and NAFLD were examined using multivariable linear regression while controlling for confounders. The association between obstructive or restrictive spirometry patterns and NAFLD was also evaluated using multivariable logistic regression analysis.

After adjustment for multiple covariates, predicted FEV1% and FVC% were significantly and inversely associated with the degree of hepatic steatosis (P for trend <0.001 for both). The restrictive lung pattern was significantly related to participants with moderate and severe hepatic steatosis as compared with those without steatosis (OR 1.65, 95% CI 1.14–2.39 and OR 1.85, 95% CI 1.13–2.82), whereas the obstructive lung pattern was not associated with the presence of hepatic steatosis.

Individuals with a greater degree of hepatic steatosis were at greater risk for poor pulmonary function, especially in restrictive pattern. These novel findings demonstrate that impaired pulmonary function is also an extrahepatic complication of NAFLD.

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Abbreviations: CRP = C-reactive protein, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HDL = high-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, NHANES III = Third National Health and Nutrition Examination Survey.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of hepatic steatosis without secondary causes for hepatic fat accumulation.1 NAFLD is the most common liver condition affecting 19% of the US population.2 The prevalence of NAFLD has increased over time. Increasing evidence suggests that NAFLD is associated with numerous extrahepatic complications such as metabolic syndrome,3,4 type 2 diabetes,5 cardiovascular diseases,6 chronic kidney disease,7 and sarcopenia.8 However, the potential association between NAFLD and impaired pulmonary function has been less investigated. Most previous studies focused on the fact that pulmonary dysfunction may be observed with hepatopulmonary syndrome, which is a distinctive disorder in cirrhotic patients characterized by impaired oxygenation and diffusion capacity. Although NAFLD may potentially progress to cirrhosis, the pathophysiology and clinical manifestations differ between these conditions. In addition, over recent years, a number of studies reported an association between decreased lung function and metabolic syndrome.9,10 Despite the fact that the mechanisms regulating these associations remain incompletely understood, the role of insulin resistance was a widely accepted hypothesis.11,12 However, evidence of the association between NAFLD, as an important cause or effect of insulin resistance, and decreased lung function rarely reported in the literature. To our knowledge, no nationally representative US studies on the relationship between NAFLD and lung function are available. Thus, we investigated the association between NAFLD and lung function using results from the Third National Health and Nutrition Examination Survey (NHANES III).

METHODS

Study Population

Data were obtained from the NHANES III, which was conducted in the United States between 1988 and 1994, using a stratified, multistage, clustered probability sample design, by the National Center for Health Statistics of the Centers for Disease Control and Prevention.13 A total of 14,797 participants aged 20 to 74 years received a hepatic steatosis assessment. Of this group, participants who were pregnant, positive for serum hepatitis B surface antigen, or positive for serum hepatitis C antibody were excluded from the analyses. In addition, patients with excessive alcohol consumption (average >21 drinks/week for men and >14 drinks/week for women), iron overload (transferrin saturation >50%), a self-reported history of asthma, a self-reported history of bronchitis, a self-reported history of emphysema, or missing hepatic steatosis data and lung function data were excluded from the analyses. In total, 9976 patients...
were included in this analysis (Figure 1). The survey was approved by the National Center for Health Statistics Institutional Review Board, and all participants provided written informed consent prior to the study.

Nonalcoholic Fatty Liver Disease
NAFLD was assessed by ultrasound. Using recorded Gallbladder Ultrasound Examination videotapes previously obtained as a part of the NHANES III (1988–1994), the Hepatic Steatosis Ultrasound Examination (HSUE) was implemented to grade the presence of fat within the hepatic parenchyma between 2009 and 2010.15 Hepatic steatosis was evaluated using the following parameters: liver to kidney contrast, parenchymal brightness, bright vessel walls, deep beam attenuation, and gallbladder wall definition. With regard to the interpretation of ultrasound images, readers were trained, observed, and approved by an experienced radiologist. The degree of hepatic steatosis was classified as normal, mild, moderate, or severe.

Pulmonary Function Data
Spirometry was performed using procedures based on the 1987 American Thoracic Society recommendations. Each participant performed at least 5 forced vital capacity (FVC) maneuvers to meet the American Thoracic Society acceptability and reproducibility criteria. Forced expiratory volume in 1 second (FEV₁) was measured using a dry rolling-seal spirometer. FEV₁ and FVC measurements are expressed in liters. We also used prediction equations to calculate predicted FEV₁ and FVC values. Predicted FEV₁ and FVC values differ according to the features (age, gender, height, and race/ethnicity) of different populations. For the United States population, predicted FEV₁ and FVC values were calculated using equations derived by Hankinson et al.14 Furthermore, participants with an FEV₁/FVC <70% were defined as having obstructive pulmonary function. Participants with an FEV₁/FVC ratio ≥70% and FVC <80% of the predicted value were defined as having restrictive pulmonary function.

Assessment of Covariates
The participants were interviewed to collect information on age, gender, race-ethnicity (including non-Hispanic white, non-Hispanic black, and Mexican-American), and physical activity. Hypertension was defined as doctor-diagnosed hypertension and/or the use of antihypertensive medication. Diabetes mellitus was defined as doctor-diagnosed diabetes and/or the use of hypoglycemic agent or insulin and/or fasting blood sugar ≥126 mg/dL and/or HbA1c ≥6.5%. Smoke status was categorized as “never smoker” in subjects who self-reported that they had not smoked at least 100 cigarettes during their lifetime, “ex-smoker” in subjects who self-reported smoked at least 100 cigarettes during their lifetime and did not smoke currently, and “current smoker” in subjects who self-reported smoked at least 100 cigarettes in life and smoke currently. Alcohol intake was determined through self-reports and was categorized as “never” and “low-moderate”. The “physically active” parameter was classified as ideal, intermediate, or poor. Waist circumference was measured from the right side of the body at the iliac crest. The C-reactive protein (CRP) level was measured by latex-enhanced nephelometry. The detection limit of CRP was 0.3 mg/dL, and a level of 0.21 mg/dL was assigned to those subjects with CRP concentrations below the detection limit. Serum high-density lipoprotein (HDL) cholesterol, serum cholesterol, and triglycerides levels were measured by chemical analysis (Hitachi 737 Analyzer; Boehringer-Mannheim Diagnostics, Indianapolis, IN). The serum uric acid level was measured by oxidation with the specific enzyme uricase to form allantoin and H₂O₂ (Hitachi 737 Analyzer; Boehringer-Mannheim Diagnostics, Indianapolis, IN). Details regarding the quality control procedures have been published elsewhere.15

Statistical Analysis
We classified participants according to the degree of hepatic steatosis. Baseline characteristics of participants were compared using chi-squared tests for categorical variables, ANOVA tests for continuous variables with normality, and Kruskal-Wallis tests for continuous variables without normality. The relationships between hepatic steatosis severity and lung function (predicted FEV₁ and FVC values) were assessed using multivariable linear regression. Models were adjusted for pertinent variables as follows: model 1 was adjusted for age, gender, and race/ethnicity; model 2 was additionally adjusted for waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum CRP, and serum uric acid; and model 3 was also adjusted for physical activity, alcohol consumption, smoking status, diabetes, and hypertension. Before the analysis, the continuous variables were checked for a linear relationship with the response variable. Variables that were nonlinearly related to the response variable (CRP and triglyceride) were natural log-transformed before analysis. Multivariable logistic regression analysis was also performed to identify the association between hepatic steatosis severity and spirometry patterns, which were defined as obstructive (FEV₁/FVC <70%) or restrictive (FEV₁/FVC ≥70% and FVC <80%). Tests for trends were used to assess the relationship between the degree of hepatic steatosis and the lung function. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Version 18.0 for Windows, SPSS, Inc., Chicago, IL), and the “Complex Samples” procedure was performed to account for the study design weights, clusters, and strata.

RESULTS
Baseline Characteristics and Demographic Data
The demographic and clinical characteristics of the 9976 participants are described in Table 1. Compared with the
participants who lacked hepatic steatosis, the patients with mild to severe hepatic steatosis were more likely to be older, male, Mexican American, and physically active. In addition, these patients were more likely to have a greater waist circumference; higher levels of serum cholesterol, serum triglycerides, CRP, and serum uric acid; restrictive pulmonary function; hypertension; and reduced serum HDL cholesterol. The predicted FEV1% and FVC% values gradually decreased as the degrees of hepatic steatosis increased (P < 0.001, both).

FEV1, FVC, and NAFLD

The results from individual comparisons of predicted FEV1% and FVC% based on the degree of hepatic steatosis are presented in Table 2. The variables were stepwise adjusted in model 3. In the unadjusted model, the β coefficients of the predicted FEV1% for individuals with mild, moderate, or severe hepatic steatosis were −0.014, −0.041, and −0.071, respectively (P for trend < 0.001), and the β coefficients of the predicted FVC% for those with mild, moderate, or severe hepatic steatosis were −0.017, −0.050, and −0.078, respectively (P for trend < 0.001). These significant associations persisted even after adjusting for potential confounding factors in models 1, 2, and 3.

 Spirometry Patterns and NAFLD

The results regarding the association between the severity of hepatic steatosis and the obstructive or restrictive spirometry patterns are presented in Table 3. Multiple logistic regression analysis with adjusted model 3 was performed using the degree of hepatic steatosis as an independent variable. The restrictive pattern was a dependent factor associated with moderate and severe hepatic steatosis (OR 1.65, 95% CI 1.14–2.39 and OR 1.85, 95% CI 1.13–2.82, respectively), but not with mild hepatic steatosis (adjusted OR 1.28, 95% CI 0.77–2.13). The obstructive pattern was not significantly associated with mild, moderate, or severe hepatic steatosis (OR 1.15, 95% CI 0.89–1.46; OR 0.95, 95% CI 0.71–1.26; and OR 0.91, 95% CI 0.56–1.47, respectively).

**DISCUSSION**

Our study revealed that the predicted FEV1% and FVC% substantially decreased as hepatic steatosis progressed. Notably, an increased risk of a restrictive pulmonary pattern, but not an obstructive pulmonary pattern, was also noted in the moderate and severe hepatic steatosis group. No clear definition is available regarding the grade of hepatic steatosis that can be
Spirometry parameters such as FEV₁ and FVC were identified as indicators of mortality. The link between poor lung function was also clearly evident in the cases of moderate and severe hepatic steatosis as the definition of NAFLD. In our study, the association between hepatic steatosis and reduced pulmonary function impaired. One possible explanation for this association involves abdominal obesity. Previous studies demonstrated that waist circumference and visceral fat were positively associated with NAFLD severity. As NAFLD worsens, the visceral adiposity gradually increases, which may mechanically decrease chest wall compliance. The inverse association between visceral adiposity and FEV₁ and FVC was demonstrated previously. In addition, the restrictive spirometry pattern was significantly correlated with NAFLD, whereas the obstructive pattern was not correlated in our study. This result provides further support for the explanation that abdominal obesity may limit lung expansion due to increased thoracic pressure, thereby impeding the descent of the diaphragm and causing restriction.

Recently, Hong et al demonstrated that decreased muscle mass was related to increased NAFLD risk. Reduced lean body mass as NAFLD, although previous studies used moderate and severe hepatic steatosis as the definition of NAFLD. In our study, the association between hepatic steatosis and reduced lung function was also clearly evident in the cases of moderate or severe hepatic steatosis.

| TABLE 3. Odds Ratio (95% CI) for Restrictive Impairment and Obstructive Impairment According to Hepatic Steatosis Status |
|---------------------------------------------------------------|
| **Hepatic Steatosis Status**                                  |
| Normal            | Mild          | P      | Moderate       | P      | Severe        | P      | **P for Trend** |
|-------------------|---------------|--------|----------------|--------|---------------|--------|----------------|
| Restrictive       |               |        |                |        |               |        |                |
| Unadjusted        | 1.46 (0.90–2.38) | 0.13   | 2.69 (1.95–3.70) | <0.01  | 3.76 (2.62–5.40) | <0.01  | <0.01          |
| Model 1           | 1.42 (0.87–2.34) | 0.16   | 2.26 (1.63–3.14) | <0.01  | 3.03 (2.09–4.41) | <0.01  | <0.01          |
| Model 2           | 1.26 (0.76–2.10) | 0.36   | 1.66 (1.20–2.31) | <0.01  | 2.01 (1.33–3.04) | <0.01  | <0.01          |
| Model 3           | 1.28 (0.77–2.13) | 0.34   | 1.65 (1.14, 2.39) | 0.01   | 1.85 (1.13–2.82) | 0.01   | <0.01          |
| Obstructive       |               |        |                |        |               |        |                |
| Unadjusted        | 1.21 (0.96–1.52) | 0.11   | 1.26 (0.95–1.67) | 0.10   | 1.37 (0.95–1.96) | 0.09   | 0.02           |
| Model 1           | 1.12 (0.88–1.43) | 0.35   | 0.86 (0.62–1.18) | 0.33   | 0.83 (0.56–1.23) | 0.35   | 0.26           |
| Model 2           | 1.10 (0.86–1.42) | 0.45   | 0.89 (0.66–1.19) | 0.41   | 0.88 (0.56–1.38) | 0.57   | 0.44           |
| Model 3           | 1.15 (0.89–1.46) | 0.30   | 0.95 (0.71–1.26) | 0.70   | 0.91 (0.56–1.47) | 0.69   | 0.69           |

CI = confidence interval.
Model 1: adjusted for age, gender, and race-ethnicity; Model 2: adjusted for age, gender, race-ethnicity, waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum C-reactive protein, and serum uric acid; Model 3: adjusted for age, gender, race-ethnicity, waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum C-reactive protein, serum uric acid, physical activity, alcohol consumption, smoking status, diabetes, and hypertension.
mass also leads to a decline in pulmonary function.24 The restrictive respiratory spirometry pattern, which may be caused by respiratory muscle weakness, was noted in our study. This result may also imply that reduced respiratory muscle mass partly contributes to the association between NAFLD and reduced pulmonary function. Furthermore, Hong et al also reported that the underlying mechanisms associated with both sarcopenia and NAFLD may involve inflammation and insulin resistance. The visceral adipose tissue may act as an important source of inflammation in NAFLD patients, because it correlated positively with circulating levels of hs-CRP, fibrinogen, interleukin-6 (IL-6), tumor necrosis factor-α, and leptin.25–27 Consistent with this observation, Mannino et al28 demonstrated the impact of inflammation on restrictive and obstructive lung disease, thereby providing a potential mechanism for the association between declined pulmonary function and NAFLD.

No consensus appears to exist regarding whether NAFLD is an initiating event, consequence of insulin resistance, or concurrent event. Nevertheless, insulin resistance plays a key role in NAFLD.29 Previous studies had examined the relationship between insulin resistance and impaired pulmonary function,11,12,19,30 but the exact causality is not well defined. In the British Women’s Health and Heart Study, FEV1 and FVC were negatively associated with insulin resistance.31 In a United States population study by Ford and Mannino,30 FEV1, FVC, predicted FEV1%, predicted FVC%, and the restrictive lung pattern were all inversely associated with the incidence of diabetes. In contrast, insulin resistance potentially precipitates pulmonary function impairment. In the Atherosclerosis Risk in Communities Study, FEV1, FVC, predicted FEV1%, and predicted FVC% were decreased by fasting glucose, A1c, and diabetes duration.19 Therefore, NAFLD, which shares an inseparable pathophysiology with insulin resistance, is potentially related to impaired pulmonary function, as demonstrated in our study.

A previous study by Jung et al31 demonstrated that NAFLD was associated with reduced pulmonary function in Korea. However, discrepancies in the prevalence of NAFLD, the degree of insulin resistance, and the distribution of adiposity were reported across genders and across racial and ethnic groups,25 and these factors may interfere with the association between NAFLD and lung function. In addition, only male participants were included in the analysis, and important confounders, such as alcohol consumption, physical activity, and CRP, were not analyzed. Therefore, the Korean result may not be generalized to the United States adult population.

Several limitations of this study should be mentioned. First, NHANES III is a cross-sectional study. Therefore, we were unable to establish a causal relationship between pulmonary function impairment and NAFLD. Second, a restrictive pulmonary pattern was defined as a normal FEV1/FVC ratio and a low FVC, rather than being determined from a confirmed measurement, such as the total lung capacity and residual volume. Third, no ideal diagnostic tool is available to distinguish nonalcoholic steatohepatitis from hepatic steatosis except for a liver biopsy. Therefore, we only evaluated the relationship between the degree of hepatic steatosis and lung function. Further studies on the association between lung function and nonalcoholic steatohepatitis are warranted.

In conclusion, individuals with a greater degree of hepatic steatosis exhibit increased risk of poor pulmonary function, particularly a restrictive pattern. These novel findings demonstrate that impaired pulmonary function is an extrahepatic complication of NAFLD. Further studies to elucidate the underlying pathophysiological pathways are necessary.

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