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WALKING ABNORMALITIES ARE ASSOCIATED WITH COPD: AN INVESTIGATION OF THE NHANES III DATASET

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Summary:

Research on the peripheral effects of COPD has focused on physiological and structural changes. However, different from muscular weakness or decreased physical activity, mechanical abnormalities of the muscular system, e.g. walking, have yet to be investigated. Our purpose was to utilize the National Health and Nutritional Examination Survey (NHANES) dataset to determine whether walking abnormalities are associated with COPD severity. To determine if walking abnormalities were independently associated with COPD severity, our analysis aimed to investigate the association of physical activity levels with COPD severity and with walking abnormalities. The NHANES III dataset that contains data for 31,000 persons that were collected from 1988-1994, was used to explore the association of COPD severity on gross walking abnormalities, i.e. limp, shuffle, etc. Logistic regression models were created using FEV_1/FVC ratio, age, gender, BMI, and smoking status as predictors of walking abnormalities and physical activity in persons aged 40 to 90 years old. Results demonstrated a significant correlation between the presence of walking abnormalities and severe COPD (odds ratio: 1.97; 95% CI: 1.1 to 3.5). This suggests that disease severity can contribute to mechanical outcomes of patients with COPD. In addition, decreased physical activity levels were significantly associated with all COPD severity levels with the exception of mild COPD. The association between altered gait and COPD status may be due to the presence of physical inactivity that is present in patients with COPD. Future research directions should include investigating more closely the mechanical outcomes of persons with COPD.

Keywords:

Locomotion, Gait, Lung Disease, Physical Activity

Conflict of Interest Statement:

SR has participated as a speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline and Pfizer. He has consulted with several pharmaceutical companies with relevance to the topics noted in the present manuscript (Almiral, Altana Amersham, Array Biopharma, AstraZeneca, Aventis, Boehringer Ingelheim, Critical Therapeutics, GlaxoSmithKline, Globomax, Intermune, Merck, Novartis, Ono, Otsuka, Roche, Sanofi, Scios, Wyeth). He serves on advisory boards for Altana and Pfizer. He has been sponsored by GlaxoSmithKline for several clinical trials and has received laboratory support. He has also conducted clinical trials for Roche, Pfizer, Sanofi and Novartis. He has conducted both clinical trials and basic studies under the sponsorship of Centocor. He has conducted basic studies under the sponsorship of AstraZeneca. A patent is pending on the use of miR-146a in lung disease; SR is a co-inventor of the patent owned by the University of Nebraska Medical Center.

The other authors have no conflicts of interest to disclose.

Introduction:

The effects of COPD are not limited to the lungs; rather the effects typically include "systemic and complex abnormalities" affecting the peripheral systems [1]. At the forefront of these are the effects of COPD on the cardiovascular and muscular systems. Much of the research into the effects of COPD on the muscular system has focused on skeletal muscle changes, including muscle atrophy, mitochondrial changes and shifting of muscle fiber types [2-5]. It is possible then that changes in muscular structure could affect mechanical outcomes, such as gait (walking). However, this has not been explored in the COPD population.

COPD patients are less active than the average population [6-9]. Using accelerometers to objectively quantify physical activity [10-13], it is reported that one third of severe COPD patients walk less than 15 min/day [8]. Patients with the most severe levels of COPD spend less time walking and when they do, they walk at slower speeds [14]. The decreased physical activity seen in COPD patients is not directly associated with disease severity. Mild COPD patients, that have relatively normal lung function, walk approximately 50% less than healthy controls [7]. Watz et al. (2009) have further demonstrated that patients with moderate COPD have significantly decreased physical activity levels and that these decremented physical activity levels are not reflective of clinical tests of disease severity [15]. Physical inactivity in COPD patients is the result of many abnormalities, including the ventilatory, musculoskeletal, neurosensory, and cardiovascular systems. Respiratory limits to physical activity are well established [16-18]. Including dynamic hyperinflation that worsens with activity, can impact activity levels by constraining tidal volume, contributing to inspiratory muscle weakness, greater neuromechanical dissociation, and increased perception of dyspnea regardless of the level of severity of COPD [16-18]. In addition,

it has been noted that dynamic hyperinflation contributes to a circle of increased weakness and fatigue of respiratory musculature; hence, causing a further impact physical activity levels [17]. Additional extrapulmonary effects of COPD include an association of physical inactivity with systemic inflammation and impaired left cardiac function, as well as an increased prevalence of peripheral arterial disease and depression [19].

There is evidence that lack of physical activity contributes to peripheral muscle abnormalities and dysfunction. Disuse of the muscular system can result in muscular atrophy, decreased muscle strength, increased muscle fatigability, reduced oxidative capacity, and capillary loss [20-23]. It has also been reported that activity may be limited in COPD patients due to leg fatigue [24]. Muscle fatigue is present in mild to moderate COPD patients irrespective to lung function, anthropometric data, or quadriceps strength [25]. A contributing factor to leg fatigue could be abnormal skeletal muscle structure, including abnormal body cell mass alterations, muscular protein degradation leading to muscle wasting/atrophy, impaired energy production and metabolic performance, and increased susceptibility to muscle weakness [2, 26-33]. These muscular impairments may also lead to abnormal walking patterns; however this has not previously been tested in COPD patients. In support of such a concept, however, Butcher et al. (2004) investigated balance, coordination and mobility in COPD patients and determined that decrements in these measures were found when compared to controls [34]. These differences were attributed to severity of disease and lower levels of physical activity [34]. Whatever the cause, mechanical abnormalities are present in COPD patients. Using biomechanical measures to quantify static balance control in COPD, it has been found that COPD patients demonstrate greater medio-lateral center of pressure displacement and increased hip angular displacement of

the hip [35]. Whether these are reflected in walking abnormalities remains to be determined. Interestingly, patients with COPD also demonstrate an increase risk of falls as compared to healthy controls, with a reported odds ratio of 4 to 5 times higher [36, 37]. Roig et al. (2009) propose a theoretical framework to identify fall risk factors in COPD patients which includes walking abnormalities leading to poor mobility [38]. Hence, there is a demonstrated need to investigate mechanical outcomes in COPD, including but not limited to, walking abnormalities and balance measures.

The purpose of this study was to investigate whether or not walking abnormalities are associated with the presence of COPD using data from the NHANES III dataset. The National Health and Nutritional Examination Survey (NHANES) III dataset is a public use data set that provides interview and physical examination information on over 31,000 American patients from 1988 to 1994. NHANES is a major program of the United States National Center for Health Statistics that is regulated by Centers for Disease Control and Prevention. This dataset provides information regarding mechanical outcomes of patients as well as history, physical examination and laboratory measures, including information on the prevalence of chronic diseases.
Using this dataset, we hypothesized that walking abnormalities would be significantly associated with COPD severity, due to the prevalence of peripheral muscle abnormalities and dysfunction noted in COPD. It is thought that these peripheral muscle changes are due to the severe physical inactivity commonly present in patients with COPD. Therefore, a secondary analysis conducted investigating the association of subjective physical activity levels with COPD severity. It was hypothesized that all levels of COPD severity would be significantly associated with decreased physical activity levels, providing further support that physical inactivity associated with COPD

is related to walking abnormalities. The relationship between COPD severity and activity level is neither novel nor unexpected; however the goal was to determine if activity level was related to walking abnormality and which variables are independently associated with abnormal walking patterns.

Methods and Materials:

Data from the NHANES III dataset were used for analysis. Extensive details of the sampling and data collection methodologies are available at www.cdc.gov/nchs/about/major/nhanes/nh3data.htm. In order to account for the sampling design that produced the NHANES dataset, all modeling analyses and descriptive analyses where weights are taken into account were performed using SAS SURVEY procedures with appropriate stratification, clustering, and weighting variables (SAS Institute Inc., Cary, NC). These analyses utilized data from the full six year sample as recommended by the study documentation. These analyses were approved as exempt by the University's Institutional Review Board.

Selection Criteria: The original NHANES III dataset contains data on 31,311 Americans examined and surveyed from 1988-1994. Patients that had completed the adult examination and were 40 to 90 years old were selected for analysis (n = 10,049). From this selected group, subjects were eliminated from analyses if they reported being unable to walk without help (n = 240). This variable is included in the physical function evaluation given to anyone over the age of 60 years. Persons who were coded as "no" they could not walk without help were removed from the analyses. Finally, potential subjects were removed if they were missing data from one of the key variables for analyses (FEV_1, FVC, walking abnormalities, age, gender, body mass

index (BMI) (n = 1,404)). In total, 8,405 patient records were utilized as a sample for this analysis.

Selection of Variables: The independent variable chosen for this analysis was classification of COPD status. Spirometric function was used for the definition of COPD. The key parameters were the patient's forced expiratory volume in one second (FEV_1) and the ratio of the FEV_1 to the forced vital capacity (FVC) [39]. Patients with an FEV_1 to FVC ratio less than 0.7 were classified as having COPD with severity stages determined by classification based on their measured FEV_1 values as a percent of their predicted FEV_1 values. The percent predicted FEV_1 values were calculated using equations derived by Harkinson et al. [40] for the NHANES III dataset which calculate predicted values for each subject based on the subject's age, height, race, and gender. Utilizing standards from The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), subjects were classified into three COPD levels [41] as well as symptoms, restrictive, and normal classification groups (Table 1) [42].

Two separate models were developed. The first model was developed to investigate the presence of walking abnormalities in persons with COPD, using the presence of gait abnormality as a dependent variable. Three variables in the NHANES III dataset address walking abnormalities. The protocol for NHANES states that the physician should evaluate the patient for a limp or shuffle (variable PEP1A1). According to the NHANES instructions this must be a chronic limp on either leg that is a current condition. If a limp or shuffle were not present, the physician could additionally evaluate the patient for any other walking abnormality (variable PEP1A2). If the physician marked "yes" to either of these conditions, the overall finding for walking

abnormalities was marked as "yes" (variable PEP1). Only the overall finding for the locomotion variable was used for analysis. This variable was coded as "yes, findings" if either one or both of the other two variables (limp or shuffle and/or other walking abnormalities) were coded as "yes". The second model was developed to investigate the association of physical activity levels with COPD status. The dependent variable for this model was a subjective measure of physical activity. In the NHANES III Adult Household Survey, physical activity was assessed using the following variable, "How active are you compared with men/women your age?" (variable HAT28) In the NHANES data set, the data was coded as: more active, less active, about the same, blank but applicable, and don't know.

Age, gender, and BMI were chosen as covariates. Descriptive statistics for all analysis variables are presented in Table 2. In addition to the covariates, smoking status was added to the analysis. Data from the NHANES III Adult Household Survey was used to create the smoking status variable. A person was classified as "never" smoking if he/she reported smoking fewer than all of 100 cigarettes, 20 cigars, or 20 pipefuls of tobacco in his/her lifetime. Among persons who had smoked at least 100 cigarettes, 20 cigars, or 20 pipefuls of tobacco, those who reported they were not currently smoking any of cigarettes, pipes, or cigars were classified as "former" smokers, while those who indicated they were currently using at least one of these three options were classified as "current" smokers.

Model Development: The SAS SURVEYLOGISTIC procedure was used to generate logistic regression models with gait abnormality and physical activity as dependent variables and COPD classification as the independent variable. Age, BMI, gender, and smoking status were added to

the model to control for their effects on the outcome variable. Significance was set at an alpha level of 0.05. For the physical activity model, responses of "More active" and "About the same" were combined into a single category and used as a reference for comparison against responses of "Less active".

Results:

Using COPD status as a predictor of the walking abnormalities without covariates, it was found that each COPD classification compared against normal were significantly ($p < 0.05$) associated to walking abnormalities. Upon adding the covariates into the model, SEVERE COPD (odds ratio: 2.53, 95% CI: 1.2 to 5.3) remained significantly ($p = 0.01$) associated to walking abnormalities. The covariates of age (odds ratio: 1.10, 95% CI: 1.1 to 1.1) and BMI (odds ratio: 1.06, 95% CI: 1.0 to 1.1) were also significantly ($p < 0.0001$) associated to walking abnormalities. These results are presented in Table 3 and 4.

Furthermore, we found that SEVERE (odds ratio: 4.57, 95% CI: 2.6 to 7.9), MODERATE (odds ratio: 1.83, 95% CI: 1.3 to 2.5), SYMPTOMS (odds ratio: 1.84, 95% CI: 1.5 to 2.3), RESTRICTIVE (odds ratio: 2.43, 95% CI: 1.9 to 3.1), BMI (odds ratio: 1.0, 95% CI: 1.0 to 1.1), and current smoker (odds ratio: 1.4, 95% CI: 1.2 to 1.8) were significantly ($p < 0.05$) associated with less activity than other men/women their age. Age (odds ratio: 0.97, 95% CI: 0.96 to 0.98) was significantly ($p < 0.0001$) associated with the response of more active or about the same compared to other men/women their age. These results are presented in Table 5.

Discussion:

The purpose of this study was to investigate whether or not walking abnormalities are associated with the presence of COPD using data from the NHANES III dataset. It was hypothesized that walking abnormalities would be significantly associated with COPD severity, due to the prevalence of peripheral dysfunction due to decrease physical activity levels noted in COPD. The novel finding is that COPD is related to walking abnormalities. When using a comprehensive classification scheme for COPD status, a significant association between severe COPD status and walking abnormalities was observed. From clinical point of view, reduced physical activity in daily life and impaired muscle strength are the mostly likely causes. This was confirmed as demonstrated by decreased physical activity being significantly associated will all levels of COPD severity. These results strengthen the novel findings by demonstrating the importance of physical activity and the effect of inactivity on walking abnormalities. Thus, questions are raised as to why persons with severe COPD would suffer from walking abnormalities and how is this clinically relevant?

One potential explanation for the association between walking abnormalities and COPD severity could be the result of decreased physical activity. It has been shown that decreased levels of physical activity result in decreased muscle fiber cross-sectional area, reduction in mitochondrial density, capillary density, and amount of contractile proteins, and increased susceptibility to assuming properties of type II fibers [43]. Skeletal muscle dysfunction present in COPD includes loss of body cell mass and protein degradation, impaired energy production and metabolic performance, increased susceptibility to leg fatigue, and leg weakness leading to reduced activity [2, 6-8, 14, 15, 26-32]. These dysfunctions in the muscular system may impact walking patterns, causing an irregular walking pattern, and further causing decreased levels of physical activity. Mechanisms

leading to reduced physical activity levels of COPD patients have been debated, though it has been demonstrated that activity may be limited in COPD patients due to peripheral muscle fatigue [24]. Recently, using surface electromyography COPD patients demonstrated muscle contractile fatigue in the rectus femoris and vastus lateralis during a 6 minute walk test of COPD patients [44]. There is a growing body of evidence that peripheral muscle fatigue is associated to structural and mechanical abnormalities of skeletal muscle in COPD patients. For instance, it has been documented that skeletal muscle contractile fatigue is affected by metabolic changes in the skeletal muscle, redox status, systemic inflammation, and lactic acid accumulation [45-48]. It is possible that fatigue is the result of mitochondrial changes in COPD skeletal muscle that are related to a greater presence of type II muscle fibers [4, 49]. It has been demonstrated that sedentary controls also demonstrate a profile of increased number of type II muscle fibers [50]; therefore, it is possible disuse may be the mechanism for mitochondrial changes in COPD patients leading to further decrements in activity levels. This is further strengthened by studies that have demonstrated that limitation in mechanical efficiency and submaximal exercise is related to an increased percentage of type II fibers and muscle disuse as opposed to peripheral muscle oxygenation, respectively [51, 52]. Further, studies have demonstrated positive effects of exercise training on COPD patients [53-57]. These positive effects include increased muscular size, strength, power, endurance, mitochondrial capacity, and restoration of protein levels [58-61].

Alternatively, systemic inflammation in organ systems outside of the lungs, distinct from local pulmonary inflammation may potentially be another mechanism to walking abnormalities in COPD. This inflammation, characterized by oxidative stress, increased levels of cytokines and leukocytes, has been speculated as an underlying mechanism of abnormal skeletal muscle

structure and function in COPD [2, 3, 5, 45-47]. Whether the abnormalities in gait in COPD patients demonstrated in the present study result from inactivity or from other processes remains to be determined.

There are limitations associated with this study. NHANES III dataset allows for limited investigations into the association of COPD and walking abnormalities. Walking abnormalities in this dataset are poorly defined and include overall observations of walking patterns, such as the presence of a limp or shuffle. Future studies should investigate mechanical abnormalities using a biomechanical analysis in order to thoroughly understand the muscular joint responses and contributions to walking patterns. In addition, the variable used to define physical activity levels was subjectively provided. Subjects were asked their opinion on their activity level as compared to other adults their same age. Use of accelerometers and pedometers provide objective measures of physical activity [10-13].

This analysis of the NHANES III dataset is the first study that investigated whether or not walking abnormalities are associated with COPD status. The novel finding of this study is that COPD is related to gait abnormalities. From clinical point of view, reduced physical activity in daily life and impaired muscle strength are the mostly likely causes. There has been much debate in the literature as to the peripheral effects of COPD and whether or not mechanical outcomes are associated with severity of the disease. Further studies should employ objective analyses to investigate mechanical outcomes of COPD patients to determine these associations. The biomechanical analysis of walking abnormalities would provide procedures and measures that can clearly examine the locomotion of COPD patients by identifying physical deficiencies and

316 determining the severity of their mechanical limitations. In conclusion, this study provides
317 preliminary evidence that a decline in mechanical outcomes (e.g. walking abnormalities) is
318 associated with persons that have severe COPD.
319
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325

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Table Captions.

Table 1. Classification of subjects based upon GOLD standards.[42]

Table 2. Descriptive Statistics for Continuous and Categorical Variables.

Table 3. Logistic Regression of Walking Abnormalities by COPD Status. N=8,405 (84,234,791)

1. Reference category is Normal.

Table 4. Logistic Regression of Walking Abnormalities by COPD Status, Age, BMI, Sex, and Smoking Status. N=8,389 (84,146,857) (Note: * indicates $p < 0.05$)

1. Reference category is Normal.
2. Reference category is Never Smoked.

Table 5. Logistic Regression of Physical Activity compared to men/women of comparable age by COPD Status, Age, BMI, Sex, and Smoking Status. N=8,193 (82,225,630) (Note: * indicates $p < 0.05$)

1. Reference category is Normal.
2. Reference category is Never Smoked.