CHEST

Original Research

COPD

Daily Step Count Is Associated With Plasma C-Reactive Protein and IL-6 in a US Cohort With COPD

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Background: **Physical activity is an important clinical marker of disease status in COPD. COPD is also characterized by low-grade systemic inflammation. However, the relationship between physical activity and systemic inflammation in COPD is unclear.**

Methods: **We monitored daily step count, a directly measured physical activity, using the StepWatch Activity Monitor, an ankle-worn accelerometer, in 171 people with stable COPD. Exercise capacity was assessed with the 6-min walk test (6MWT). We measured plasma C-reactive protein (CRP) and IL-6 levels. Linear regression models examined the cross-sectional associations of daily step count and 6MWT distance with CRP and IL-6 levels.**

Results: **Subjects had a mean age 72 ± 8 years and mean FEV_1 1.5 ± 0.57 L (54 ± 20% predicted). Median daily step count was 5,203 (interquartile range [IQR], 3,627-7,024], CRP level was 2.4 mg/L (IQR, 1.2-5.0), and IL-6 level was 2.9 pg/mL (IQR, 2.0-5.1). Each 1,000-step increase in daily step count was associated with a 0.94 mg/L and 0.96 pg/mL decrease in CRP (*P* = .020) and IL-6 (*P* = .044) levels, respectively, adjusting for age, FEV_1 % predicted, pack-years smoked, cardiac disease, current statin use, history of acute exacerbations, and season. There was a significant linear trend of increasing daily step count by quartiles and decreasing CRP (*P* = .0007) and IL-6 (*P* = .023) levels. Higher 6MWT distance was also significantly associated with lower CRP and IL-6 values.**

Conclusion: **People with COPD who walked the most had the lowest plasma CRP and IL-6 levels. These results provide the conceptual basis to study whether an intervention to promote walking will reduce systemic inflammation in people with COPD.** ***CHEST 2014; 145(3):542–550***

Abbreviations: 6MWT = 6-min walk test; AE = acute exacerbation; CRP = C-reactive protein; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IQR = interquartile range; NSAID = nonsteroidal antiinflammatory drug; PA = physical activity; SAM = StepWatch Activity Monitor; SGRQ = St. George's Respiratory Questionnaire

COPD, a major cause of global morbidity, is projected to become the third leading cause of death in the world by 2020.[1,2] Level of physical activity (PA) is an important clinical marker of disease status in COPD. Higher levels of PA are associated with better functional status, fewer hospital admissions, and lower mortality.[3-7] Daily step count is a direct measure of PA that is easy to understand, can be accurately monitored, and can be potentially targeted for intervention.[8-10] A higher daily step count in COPD is associated with a lower risk of future acute exacerbations (AEs) and COPD-related hospitalizations[11] and with lower mortality,[12] independent of % predicted FEV_1.

COPD is characterized by low-grade systemic inflammation.[13-16] People with COPD have elevated levels of C-reactive protein (CRP) and IL-6 in the stable clinical state[13,14]; these become even higher during AEs.[14,17] Elevated CRP level is associated with reduced lung function,[13] lower exercise capacity,[18] higher risk of future AEs,[15] and higher risk of COPD-related hospitalizations.[19] Elevated CRP level is also positively associated with all-cause[15,20] and COPD-related mortality.[19]

The few studies that have examined the relationship between PA and inflammation in COPD have had conflicting results.[21-26] One previous study reported that a higher plasma fibrinogen level was associated with a lower daily step count in COPD.[21] However, that study did not account for season of PA monitoring,[27] prior exacerbations, or statin use. Garcia-Rio et al[22] found no significant relationship between daily PA (vector magnitude units) and IL-6 and tumor necrosis factor-α

receptor 1 in exhaled breath condensate, rather than plasma. A separate study showed significant associations between lower CRP and tumor necrosis factor-α levels with higher PA assessed by questionnaire, which tends to overestimate PA and assesses activities not typically performed by patients with COPD.[23,28,29] Small studies assessing the effects of exercise intervention on systemic inflammation have shown equivocal results.[24-26] These studies enrolled participants who completed a pulmonary rehabilitation program, limiting the generalizability of results.[24,25]

In the current cross-sectional study, our primary aim was to examine the independent relationship between PA, directly measured with an accelerometer, and plasma markers of systemic inflammation in a well-characterized cohort of people with COPD. Specifically, we hypothesized that higher daily step count would be associated with lower plasma CRP and IL-6 levels, independent of exacerbation history, statin use, and season. As a secondary aim, we assessed results of the 6-min walk test (6MWT), a commonly used, clinic-based test of exercise capacity, and examined its relationship with plasma CRP and IL-6 values.

Materials and Methods

Study Design and Participants

Between January 2009 and November 2011, 176 participants with COPD were enrolled from the general pulmonary clinics. All 176 subjects had one assessment; in addition, 98 of the 176 subjects had a second assessment a median of 3.9 months after the first assessment as part of a previously published observational study characterizing daily step count in COPD.[8,11] Clinical variables, inflammatory biomarkers, and PA were measured at each assessment.

Eligible participants were aged > 40 years and had COPD defined as a smoking history of at least 10 pack-years and a ratio of FEV_1 to FVC < 0.70. Exclusion criteria were inability to ambulate or collect daily step-count data. All subjects were in stable clinical state at the time of assessments. We defined a patient with stable COPD as one who had not had an AE in the 4 weeks prior to assessment and who reported being at baseline clinical status at the time of assessment.[30] The protocol (#1961) was approved by the VA Boston Healthcare System Committee on Human Research, and written informed consent was obtained from each participant.

Clinical Variables

We measured weight and height to calculate BMI. We obtained a medical history of cigarette use; coronary artery disease; congestive heart failure; medication use, including statins, inhaled corticosteroids, and nonsteroidal antiinflammatory drugs (NSAIDs); prior participation in pulmonary rehabilitation; and occurrence of AE in the year prior to enrollment.[11,30] At each assessment, participants underwent measurement of FEV_1 using an Eaglet spirometer (nSpire Health, Inc).[31] The 6MWT was performed following American Thoracic Society guidelines.[32] Health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ),[33] with lower scores indicating better health-related quality of life (range, 0-100). Dyspnea was assessed using the modified Medical Research Council dyspnea scale.[34]

Inflammatory Biomarkers

Peripheral blood was collected by venipuncture into vacutainer tubes with ethylenediaminetetraacetic acid anticoagulant. Blood was collected between 9:30 AM and 3:00 PM at each in-clinic assessment. Plasma was obtained by centrifugation of tubes at 1,459 × *g* for 15 min. The samples were stored at −80°C until analyzed. Plasma CRP and IL-6 levels were measured by the Clinical & Epidemiologic Research Laboratory, Children's Hospital, Boston, Massachusetts. CRP and IL-6 levels were determined using a high-sensitivity immunoturbidimetric assay with a sensitivity of 0.03 mg/L and 0.094 pg/mL, respectively.

Physical Activity Assessment

The StepWatch Activity Monitor (SAM) (Orthocare Innovations LLC), an ankle-worn accelerometer, accurately measures step counts in people with COPD.[8] After each in-clinic assessment, participants were sent home to wear the SAM for 14 consecutive days and were instructed to perform their usual PAs. Subjects were blinded to step-count data, since the instrument does not provide feedback. Subjects returned the SAM by mail and staff downloaded date- and time-stamped step-count data via a docking station. No-wear days, defined as days with < 200 steps recorded and < 8 h of wear time, were excluded from the analysis.[8,11,35] Five of the 176 subjects, who were unable to complete daily step count monitoring and had ≥ 8 no-wear days, were excluded from the final analysis.

Statistical Analysis

Descriptive results at study entry for 171 subjects are reported as median (interquartile range [IQR]), mean ± SD, or percentage, as appropriate. Levels of CRP and IL-6 were converted to the natural logarithmic values to best approximate a normal distribution. To analyze all collected data and maximize power, the final linear regression models included 269 assessments (171 assessments in all subjects plus 98 assessments in those who had a second

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