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Blood Neutrophil Count is Associated with Body Mass Index in Adolescents with Asthma

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Abstract

Background—Sputum neutrophils are associated with severe asthma, poor pulmonary function and high body mass index (BMI) in adult patients. However, little is known about the relationships between blood neutrophils, BMI and asthma severity in pediatric patients. This brief report is to assess the predictive value of blood neutrophils for asthma severity, BMI and pulmonary function in adolescents with asthma

Methods—The study included 166 adolescents with physician diagnosed asthma for at least 1 year. Participants were recruited from three metropolitan cities in the U.S. BMI-for-age percentile (BMI %) was determined by standardized charts and absolute neutrophil counts (cells/μL) were obtained from the complete blood count. Asthma severity was measured based on the national guidelines. Spirometry was performed to obtain percent predicted values for Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and FEV1/FVC ratio as markers for pulmonary function.

Results—The average age of participants was 14.79 years (± 1.86) and 54% were female. The majority (84%) were black. Fifty-five percent of the sample were either overweight (21%) or obese (34%). Blood neutrophil count was significantly correlated with BMI% (r=0.25, p=.001), but not with symptom severity (r=0.087, p=.268), FEV1 (r=−0.00, p=.937), or FVC (r=−0.010, p=.897).After controlling for sex, age, and age at asthma diagnosis, blood neutrophil count was a significant predictor for overweightness or obesity (OR=1.38, 95% CI 1.11, 1.75, p=0.01).

Conclusions—Elevated blood neutrophils are associated with higher BMI, but not lung function or symptom severity in our adolescent sample with asthma. This study suggests blood neutrophils may be a potential inflammatory biomarker for overweightness and obesity in adolescents with asthma, but not for asthma morbidity.

Keywords

Blood neutrophils; Body mass index; asthma; adolescents; symptom severity; lung function

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INTRODUCTION

Over the past three decades, obesity and asthma are both on the rise in adolescents living the United States (U.S.), with the most recent prevalence at 20.5% [1] and 10% [2] respectively. Obesity is associated with increased risk of asthma-related morbidity [3]. Overweight or obese children with asthma tend to experience higher levels of symptoms or exacerbations [4,5], leading to greater use of urgent healthcare services [6]. Sputum neutrophils have been examined as an inflammatory biomarker of severe or acute asthma or poor pulmonary function in adult patients [7–9]. Obese adult patients with asthma showed a higher rate of neutrophilic asthma [10]. There have been inconsistent reports regarding neutrophils in sputum vs. blood in their relationships to BMI. Moore et al. [9], found that an asthma phenotype consisting of the highest BMI was characterized by higher neutrophil percentage than other phenotypes, and that the differences were more pronounced in sputum neutrophils than neutrophils in blood. On the other hand, a study by Telenga et al. [11], demonstrated significantly elevated blood neutrophil counts among obese adults with asthma, yet no significant differences in sputum neutrophil percentage between obese and lean patients. Despite these mixed findings, neutrophils appear to be an important consideration in defining a phenotype of asthma involving high BMI, and it remains to be investigated whether blood neutrophils are associated with body weight in pediatric patients with asthma. To date, the relationships between neutrophils and obesity or asthma severity have been primarily based on induced sputum specimens from adult patients using an exploratory approach (i.e., cluster analysis). Little is known about the relationships between blood neutrophils counts and obesity in pediatric patients with asthma. Because of differences in the patterns of inflammatory markers of asthma between adults and children [7], generalizing information learned from adult studies to pediatric patients is unwarranted. Literature is also limited in examining blood neutrophils in relation to asthma severity and pulmonary function in adolescents. The purpose of this brief report was to assess the predictive value of blood neutrophils for elevated BMI, asthma severity and decreased pulmonary function in adolescents with asthma.

MATERIALS AND METHODS

Sample and setting

This study was based on data collected for a multi-site randomized controlled trial evaluating the effectiveness of a peer-led asthma self-management program for adolescents with asthma (ClinicalTrials.gov Identifier: NCT02293499). Participants were recruited primarily through clinician referrals from three metropolitan cities in the U.S. Of 373 adolescents who participated in the original study, this study included 166 adolescents who provided a blood sample for a Complete Blood Count (CBC). Eligibility criteria include (1) age between 12 and 20 years, (2) having had physician diagnosed asthma for at least 1 year, (3) health care utilization related to asthma in the past 12 months, (4) primary residence in an urban community, and (5) English language proficiency. Those with other chronic health conditions requiring daily medication were excluded.

Data Collection and measures

The study protocol was approved by the Institutional Review Boards of participating institutions. Prior to data collection, informed consent was obtained from parents and adolescent participants if greater than 18 years old, and assent was obtained from those younger than 18 years old. Demographic data including age, gender, race and the age of asthma diagnosis were collected at baseline.

Body Mass Index (BMI)—Weight and height were measured by trained research assistants at each site. BMI was computed by dividing weight in kilograms by height in meters squared (kg/m^2), and the corresponding BMI-for-age percentile (BMI %) was determined based on gender specific BMI-for-age growth charts from the Center for Disease Control and Prevention [12]. According to the CDC classification, underweight was defined as BMI $<5^{th}$ percentile, normal or health weight as BMI $\geq 5^{th}$ percentile and$< 85^{th}$ percentile, overweight as BMI $\geq 85^{th}$ and$<95^{th}$ percentile, and obese as BMI $\geq 95^{th}$ percentile.

Absolute Neutrophil Counts (cells/μL)—Phlebotomists at each site collected whole blood specimens through venipuncture. Blood neutrophil counts were obtained from differential analysis of the white blood count of a CBC. A quantitative automated hematology analyzer, Sysmex® XN-9000, was used to perform a complete blood count. The coefficient of variation from the instrument at the normal levels for absolute neutrophil counts measurement is between 2.5 to 3%, indicating high precision or reproducibility. The within-assay and between-assay coefficients of variation at normal levels are less than 8.0%.

Asthma Severity—Asthma severity was assessed based on four impairment-based items (daytime symptoms, nocturnal awakening, activity limitation and rescue medication use in the past 4 weeks) from the National Asthma Education and Prevention Program Expert Panel Report-3 [13]. Each item was measured on a 4-point scale, and total scores were computed ranging from 4 to 16. In addition, based on the most severe impairment category, asthma severity was classified into four levels-intermittent asthma or mild, moderate, or severe persistent asthma.

Lung Function Test—Spirometry was performed by respiratory therapists at each site to obtain percent predicted values for Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC), and the FEV1/FVC ratio in accordance with the ATS/ERS standardization using a portable KoKo® spirometer.

RESULTS

The average age of participants was 14.79 years (±1.86) and 54% were female. The majority (84%) were black. A total of 55% of participants were either overweight (21%) or obese (34%). Forty-two percent of the sample had moderate to severe persistent asthma. There was no significant difference in the proportions of obese or overweight adolescents in intermittent/mild persistent asthma and moderate to severe persistent asthma, 56% vs. 44%, respectively (χ^2=0.08 p=0.78). Blood neutrophil count was significantly correlated with BMI% (r=0.25, p=.001), but not with symptom severity (r=0.087, p=.268), FEV1% (r=

−0.00, p=.937), or FVC% (r=−0.010, p=.897). We found no significant differences between under/normal weight adolescents and overweight/obese adolescents in terms of age, gender, race and age at diagnosis.

Table 1 summarizes logistic and linear regression results showing the extent to which blood neutrophil counts predict under/normal vs. overweight/obese weight BMI, lung function parameters, and symptom severity after controlling for gender, age, and age at diagnosis. The linear model predicting BMI% violated the regression assumptions of normality and linearity due to the large proportion (34%) of the subjects being over 95th %tile. Therefore, we opted for logistic regression in which adolescents were categorized into two groups (lean vs. overweight/obese) to assess BMI's relationship with neutrophils. Female gender predicted significantly higher spirometry values including FEV1, FVC, and FEV1/FVC ratio. Older age at diagnosis of asthma was significantly associated with a higher chance of overweight/obese BMI (9% higher odds per year, p=0.04). After controlling for covariates, blood neutrophil count was a significant predictor for BMI percentile indicating overweightness or obesity (38% higher odds per additional 1000 neutrophil count, OR=1.38 (95% CI 1.11, 1.75), p=0.01). The average neutrophil count in overweight or obese adolescents was 750 higher than that of their lean counterparts, 3740 (± 1820) vs. 2990 (± 1370), respectively (t=−3.01, p=.003).

DISCUSSION AND CONCLUSIONS

To our knowledge, this is the first study documenting the link between blood neutrophil counts and BMI in adolescents with asthma. In Moore et al.'s study [9] of adults, high sputum neutrophil counts were associated with high BMI and severe asthma, while such relationships were less pronounced with blood neutrophils. In contrast, our analysis demonstrated that elevated blood neutrophils predicted overweightness and obesity, but not lung function or symptom severity in our adolescent sample with asthma. The findings are consistent with an earlier study [14] of school-age children (6-12 years) that uncovered an asthma phenotype characterized by high BMI, pronounced blood neutrophil levels and older age (mean=10.3 years), but not by the levels of asthma severity. Given the positive relationships between blood neutrophils and BMI in individuals without asthma [15] and no relationships between blood neutrophils and asthma severity, the elevated neutrophils in the blood might simply be a reflection of the subjects' high BMI regardless of asthma conditions. This study suggests that blood neutrophils may be an important inflammatory biomarker for overweightness and obesity in adolescents with asthma, but its linkage to asthma severity remains uncertain. The main limitation of the study is a lack of data on sputum neutrophils with which to compare our findings. Additionally, in most cases, spirometry was conducted after administration of a bronchodilator, which may have contributed to the nonsignificant relationship between blood neutrophils and lung function parameters. Also, because the majority of our sample was African American or black, the generalizability of our findings may be limited.

Despite these limitations, this is one of very few studies examining the relationships between blood neutrophils and BMI, lung function and symptom severity in the pediatric population. Collecting sputum specimens through induction and analyzing them for accurate assessment

of inflammatory cells may not be practical in most primary care settings, particularly for children. Moreover, the sputum neutrophilic phenotype is uncommon (15%) and lacks stability (ICC=0.27) over time in childhood asthma [16]. Our observation cautiously suggests the assessment of blood neutrophils as an alternative to sputum neutrophil in identifying the neutrophilic asthma phenotype, specifically in adolescent patients who are either overweight or obese. Future studies are warranted to replicate the findings in pediatric samples with different demographics, controlling for potential confounding factors such as medication and smoking status that are thought to be associated with blood neutrophils. Furthermore, studies comparing blood neutrophils with sputum neutrophils and blood neutrophils' responsiveness to treatment are essential to establishing it as a potential biomarker for asthma. Such understanding of neutrophils has important implications not only for the phenotypic classification of asthma but also for the prediction of the disease prognosis and clinical decisions for efficacious treatments and management strategies (e.g., weight loss) tailored to the phenotype.

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ABBREVIATIONS

BMI	Body Mass Index
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity

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Table 1

Logistic regression results for overweight/obese classification and linear regression results for spirometry measures and asthma severity. For each outcome and predictor, the coefficient estimate (B) p-value and 95% confidence interval are shown.

Outcomes	Age	Gender	Age at Diagnosis	Neutrophil Count
Overweight/obese	−0.00, p= 1.00 (−0.18, 0.18)	0.09, p= 0.79 (−0.57, 0.75)	**0.09, p= 0.04 (0.01, 0.17)**	**0.32, p= 0.01 (0.10, 0.56)**
FEV1	−1.08, p= 0.13 (−2.49, 0.32)	**7.00, p= 0.01 (1.76, 12.24)**	0.50, p= 0.11 (−0.12, 1.11)	−0.34, p= 0.66 (−1.90, 1.21)
FVC	−0.55, p= 0.39 (−1.80, 0.70)	**4.68, p= 0.05 (0.01, 9.35)**	0.17, p= 0.54 (−0.38, 0.72)	−0.29, p= 0.68 (−1.68, 1.10)
FEV1/FVC	−0.09, p=0.86 (−1.01, 0.92)	**4.19, p=0.03 (0.42, 7.97)**	0.27, p=0.24 (−0.18, 0.71)	0.38, p=0.51 (−0.74, 1.50)
Asthma Severity	−0.13, p= 0.22 (−0.35, 0.08)	0.61, p= 0.14 (−0.19, 1.40)	−0.06, p= 0.20 (−0.15, 0.03)	0.10, p= 0.39 (−0.13, 0.34)