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Wider neck circumference is related with severe asthma in children

Bulent Hacıhamdioglu¹, Mutluay Arslan², Ediz Yeşilkaya¹, Faysal Gok², Suleyman Tolga Yavuz³

GATA Military School of Medicine, Departments of ¹Pediatric Endocrinology, ²Pediatrics, ³Pediatric Allergy, 06010, Ankara, Turkey.

Running Title: Neck circumference in children with asthma

Corresponding Author:

Suleyman Tolga Yavuz, MD

Associate Professor of Pediatric Allergy

GATA Military School of Medicine

Department of Pediatric Allergy

06010, Ankara, Turkey

Phone: +90-312-304 15 91

e-mail: styavuz@yahoo.com

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List of Authors:

Bulent Hacıhamdioğlu, MD, Associate Professor of Pediatric Endocrinology

GATA Military School of Medicine, Department of Pediatric Endocrinology, Ankara, TURKEY

e-mail: hacihamdi@yahoo.com.tr

Mutluay Arslan, MD, Specialist of Pediatrics

GATA Military School of Medicine, Department of Pediatrics, Ankara, TURKEY

e-mail: mutluayarslan@yahoo.com

Ediz Yesilkaya, MD, Associate Professor of Pediatric Endocrinology

GATA Military School of Medicine, Department of Pediatric Endocrinology, Ankara, TURKEY

e-mail: eyesilkaya@gata.org.tr

Faysal Gök, MD, Professor of Pediatrics

GATA Military School of Medicine, Department of Pediatrics, Ankara, TURKEY

e-mail: faysalgok@yahoo.com

Süleyman Tolga Yavuz, MD, Associate Professor of Pediatric Allergy

GATA Military School of Medicine, Department of Pediatric Allergy, Ankara, TURKEY

e-mail: styavuz@yahoo.com

Authors Contributions

- ST Yavuz had primary responsibility for protocol development and analytic framework of the study, outcome assessment, and manuscript preparation.
- B Hacıhamdioğlu participated in the development of the protocol and analytic framework for the study, had primary responsibility for review of files, patient screening, enrollment, and data entry, and prepared the manuscript with ST Yavuz.

- M Arslan had contributed to data generation, patient screening, data analysis and prepared the manuscript with ST Yavuz.
- E Yesilkaya and F Gok had contributed to protocol development, data analysis and preparation and revision of the manuscript.

Hacihamdioglu B, Arslan M, Yesilkaya E, Gok F, Yavuz ST

Wider neck circumference is related with severe asthma in children

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Abstract

Background: Obesity is an established risk factor for asthma in children. Measures of central obesity are reported to be more associated with the severity of asthma in adults. The aim of the study is to investigate the association between fat distribution, which is determined by anthropometric measures including neck circumference (NC) and asthma severity in children.

Methods: Children with asthma who were followed in our pediatric allergy unit were consecutively recruited. Asthma severity was graded according to GINA guidelines. Children whose asthma were controlled with Step 1 or 2 treatment options formed Group 1 (mild asthma) whereas children who needed Step 3, 4 or 5 treatment options formed Group 2 (moderate-severe asthma). Anthropometric measures including height, weight, NC, waist circumference and hip circumference were obtained.

Results: A total of 127 children (82 male, 64.6%) with a median age of 8.3 (6.4-11.3) years were included. Atopy was present in 77 (60.6%) patients. 91 patients (71.6) were in the mild asthma group. NC of children with severe asthma was significantly wider than children with mild asthma (29.0 cm (27.0-32.0) vs. 28.0 (26.0-30.0), $p=0.019$). The prevalence of children with NC higher than 90th percentile was also more frequent in children with severe asthma (15 (41.7%) vs. 21 (23.1%)). Result of multivariable logistic regression analysis revealed that presence of NC > 90th percentile were associated with severe asthma in children (odds ratio; [95% confidence interval](2.52 [1.05–6.01]; $p=0.038$).

Conclusions: Neck circumference, which is a simple anthropometric tool, is associated with asthma severity in children.

Key words: asthma, children, fat distribution, neck circumference, obesity

Offprints should be sent to:

Suleyman Tolga Yavuz, MD

Associate Professor of Pediatric Allergy

GATA Military School of Medicine

Department of Pediatric Allergy

06010, Ankara, Turkey

Phone: +90-312-304 15 91

e-mail: styavuz@yahoo.com

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Introduction

Asthma and obesity are two important pediatric health problems especially in industrialized countries and their prevalence are increasing worldwide in recent years (1). Obesity has been established as a risk factor for higher prevalence of asthma and asthma-related symptoms in children (2-4). It was demonstrated that higher body mass index (BMI) values increased the risk for asthma exacerbations in children with persistent asthma (2). However, the distribution pattern of fat tissue rather than its total amount was reported to be crucial for the development of obesity-related complications (5).

Despite being a common anthropometric measure for assessing childhood obesity, BMI is limited in screening regional body fat distribution. Anthropometric indices such as waist circumference (WC) seemed to be superior to BMI in identifying central adiposity reflecting higher cardiovascular disease (CVD) risk and pointing out the importance of screening central obesity instead of total body mass (6).

Neck circumference (NC) has been proposed as a new marker to differentiate normal and abnormal fat distribution in children and adults (7, 8). Greater NC is associated with obstructive sleep apnea and metabolic syndrome in both adults and children (6, 9, 10).

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Recently it was showed that large NC was associated with some adverse respiratory events in children whose undergoing non-cardiac surgery (11). It was also demonstrated that NC might be an independent predictor of inflammatory status in adults (12). However, the relationship between asthma severity and NC has not been previously evaluated in children or adult populations.

The aim of this study was to investigate the association between body fat distribution that is determined by anthropometric measures including neck circumference and asthma severity in children.

Methods

Patients

The study was conducted in a single pediatric allergy-asthma outpatient clinic in Ankara, Turkey. One hundred and twenty-seven children with asthma, who were regularly followed up between 2011 and 2013 by the outpatient clinic were consecutively recruited and needed to fulfill the following inclusion criteria: (i) patients were aged > 6 years, (ii) patients who were regularly attending to outpatient clinic visits in the last year and (iii) patients whose asthma was controlled in the study visit. All children had a history of recurrent wheezing and dyspnea and had been diagnosed with asthma by pediatric allergy and asthma specialists. Children included in this study were followed up by our outpatient clinic for at least 1 year and were provided regular treatment according to the Global Initiative for Asthma (GINA) guidelines (13). Patients with recent exacerbation at the time of enrollment, additional or coexisting chronic lung diseases (e.g., bronchiectasis), and/or other chronic diseases were excluded. All patients and parents signed consent forms, and the institutional review board of GATA School of Medicine approved the study.

Diagnosis and classification of asthma

Asthma diagnosis was made in the presence of reversible airway obstruction as defined by at least a 12% improvement in FEV₁ following bronchodilator administration, or improvement in asthma symptoms after oral/inhaled steroid therapy. The severity of asthma was graded according to the GINA guidelines (13). Briefly, it was classified on the basis of the intensity of treatment step to achieve good asthma control and patients were categorized

into two groups; children whose asthma were well controlled with Step 1 or Step 2 treatment options formed Group 1 (mild asthma) whereas children who needed Step 3, Step 4 or Step 5 treatment options to gain asthma control formed Group 2 (moderate-severe asthma).

Study measurements

Anthropometric measures

Anthropometric measures including height, weight, NC, waist circumference (WC) and hip circumference (HC) were obtained. Height and weight were measured in post absorptive conditions and with an empty bladder. Height was measured to the nearest 0.5 cm on a standard height board, and weight was determined to the nearest 0.1 kg on a standard physician's beam scale with the subject dressed only in light underwear and no shoes. WC was measured three times at the end of gentle expiration using a flexible tape, midway between the lowest rib and the superior border of the iliac crest. HC was measured at the level of widest portion of trochanters. NC was measured at the level of the cricothyroid cartilage in the Frankfort horizontal plane. Obesity was defined as a BMI over the 95th percentile and overweight was defined as BMI over the 85th percentile for Turkish children; and BMI z scores were also calculated (14). Waist circumference and NC was defined high as the percentage above 90 centile for our population (15, 16).

Skin-prick tests

All subjects were skin-prick-tested for common aeroallergens for our region (17), including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), pollens (grass, weed, and tree), moulds (*Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*), animal dander (cat, dog, and horse) and histamine (10 mg/ml of histamine phosphate) as positive and 0.9% sterile saline as negative controls. The tests were applied on the volar surface of both forearms and recorded after 15 min, and considered as positive if the mean wheal diameter was ≥ 3 mm compared to the negative control. Atopy was defined as a positive skin prick to at least one allergen.

Blood eosinophil counts and serum total IgE levels

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leucocyte measurements. Serum total immune globulin E (IgE) levels were measured with the ImmunoCAP system (Phadia AB, Uppsala, Sweden) according to the manufacturer's instructions.

Statistical Analysis

The SPSS Statistics Version 21.0 (IBM, Chicago, IL, USA) was used for all calculations. Descriptive data for categorical variables were expressed as frequencies. The distributions of all numerical variables including age, total IgE levels, blood eosinophil counts and anthropometric measures were skewed; thus, results were summarized as medians and interquartile ranges. Group comparisons were established using Mann-Whitney tests for medians (and ranges) and the chi-square test for categorical variables.

OpenEpi Version 3.0, open source calculator was used for power analysis and the power of the study was calculated as 71.9%.

The association between demographic and anthropometric parameters and asthma severity was analyzed using logistic regression modeling. Variables with $p < 0.20$ in univariate analysis along with age, gender and birth weight were used for multivariate analysis. The strength of association between the severity of asthma and risk factors was measured using the odds ratios (ORs) and 95% confidence intervals (CIs).

A p level < 0.05 was considered significant.

Results

A total of 127 children (82 male, 64.6%) with a median age of 8.3 years (6.4-11.3) were included. The median follow-up duration of the study group was 20 months (15-22). Atopy was present in 77 (60.6%) patients. 17 (13.4%) patients were overweight and 25 (19.7%) of the study population were obese. The severity of asthma was classified as "mild" in 91 (71.6%) and moderate-severe in 36 (28.4%) patients.

There were no significant differences between two groups in terms of age, gender, age at asthma diagnosis, atopy, obesity prevalence, body mass index values, WC and HC (Table 3). However, the median NC of children with moderate-severe asthma (median, interquartile range) [29.0 cm (27.0–32.0)] was significantly higher than children with mild asthma [28.0 cm (26.0–30.0)] ($p=0.019$). The prevalence of children with NC higher than 90th percentile was also more frequent in children with moderate-severe asthma (15/36 (41.7%) vs. 21/91 (23.1%)) ($p = 0.036$) (Table 1).

The median NC of obese children [29.5 cm (28.0–32.0)] was significantly higher than non-obese children [27.5 cm (26.0–30.0)] ($p<0.001$) and the prevalence of children with NC higher than 90th percentile was more frequent in obese group (21/25 (84.0%) when compared to non-obese children (15/102 (14.7%)) ($p<0.001$).

Result of multivariable logistic regression analysis revealed that presence of NC > 90th percentile were associated with severe asthma in children (odds ratio; [95% confidence interval] (2.52 [1.05–6.01]; $p=0.038$) (Table 2).

Discussion

In this cross-sectional study, we found out that wider NC, which is a novel indicator of central obesity, may be associated with severe asthma in children and may serve better than conventional anthropometric measures such as WC and HC in determining the relationship between obesity and asthma severity in children.

Chronic inflammation, mechanical factors, comorbidities related to obesity, and common genetic etiology have been suggested as pathophysiologic mechanisms of asthma in obese subjects (18). Obesity might play a primary role on upper airway flows and fatty infiltration of muscles narrowing directly the upper airway may be a possible explanation (19). It also has a direct mechanical effect on airway smooth muscle that increases bronchial hyperresponsiveness (20). Structural abnormalities of airway remodeling are present in children with severe asthma (21). Tillie-Leblond et al. demonstrated that children with severe asthma with a persistent obstructive pattern had significantly more structural changes in airway and these parameters were correlated with the bronchial obstruction (22).

Body mass index has been widely used to investigate the association between asthma and obesity previously by several researchers (1, 23). However, BMI can neither distinguish muscle mass from fat mass, nor can it measure fat distribution. The evidence suggested that not only the amount but also the distribution of the fat tissue were important for the development of the obesity related morbidity (24). Regional deposition of fat, particularly in the upper body segment (central obesity), is reported to be associated with chronic diseases such as hypertension, diabetes, and obstructive sleep apnea (25). It was demonstrated that central fat distribution is associated with CVD risk in both adults and children (26, 27). Significant association between subcutaneous abdominal fat and airway hyperresponsiveness was also found in an adult study (28).

Neck circumference has been proposed as an additional and practical tool to evaluate upper body fat in children (7, 29) and several studies have demonstrated the association between upper body fat and various morbidities by using this anthropometric measure. Androutsos et al. showed that NC was associated with the CVD risk factors such as insulin and insulin resistance indexes and systolic blood pressure in children (6). Fadzil Abdullah et al. have determined that large NC was associated with sleep disordered breathing risk in children (30). It was also claimed that neck size plays a role in the pathophysiology of obstructive sleep apnea syndrome in adolescents, because increased NC was associated with increased upper airway collapsibility in adolescents in the hypotonic but not activated state (31).

In our study, we found that although there were not significant differences between two groups in terms of conventional anthropometric measures, NC of children with severe asthma was significantly wider and the prevalence of children with large NC was also more frequent in children with severe asthma. Neck region is anatomically related with respiratory airways, therefore NC may reflect the mechanical or inflammatory adverse effects of obesity on pulmonary functions better and earlier than conventional anthropometric measures such as HC or WC.

Several researchers who investigated the relationship between NC and co-morbidities have used NC > 90th percentile according to age and sex in a certain population as an anthropometric measure in their studies. Zen et al. have indicated that NC above the 90(th)

percentile doubled the chance of coronary artery disease in adults (32). Nafiu et al. reported that large NC (> 90th) was associated with a positive history of asthma, obstructive sleep apnea, loud snoring and perioperative adverse respiratory events in children (11). Our results have also indicated a relationship between NC> 90% and severe asthma in children. Therefore, NC > 90% might be a more sensitive and practical tool to assess body fat distribution and its harmful effects when compared to the widely used BMI in children and adults.

There were limitations of our study. First, this is a cross-sectional study and the severity of asthma may change by time. Second, we did not include any inflammatory biomarkers reflecting the effects of obesity. Studies with longer follow-up duration and concurrent measurement of obesity-related biomarkers may better help to identify the background of the relationship between NC and asthma severity. On the other hand, our study population is consisted of children with varying degrees of severity and it reflects the real-life distribution of children with asthma. Therefore, our results may directly guide physicians dealing with children with asthma.

To our knowledge, this is the first study investigating the association with NC and asthma severity in children. NC, which is a simple tool of anthropometric measures, is associated with asthma severity in children. As a novel measure, it may be potentially used in clinical fields along with future asthma research studies. Early detection and close monitoring of patients with wide NC may help to reduce asthma morbidity in children.

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Tables

Table 1. Comparison of study groups according to asthma severity

	Mild	Moderate-severe	<i>p</i>
	(n=91)	(n=36)	
Male gender	60 (65.9)	22 (61.1)	0.61
Age (yrs)	8.3 (6.3-11.1)	7.6 (6.4-11.6)	0.69
Age at symptoms start	4.0 (2.0-6.0)	4.0 (1.6-8.8)	0.64
Age at asthma diagnosis	6.0 (4.0-8.0)	5.8 (4.0-11.3)	0.86
Birth weight (gr)	3275 (2825-3600)	3300 (3000-3780)	0.27
Atopy	59 (64.8)	18 (50.0)	0.11
Total IgE (kU/L)	53 (17-136)	57 (16-122)	0.81
Eosinophil counts (/mm³)	254 (150-463)	210 (113-320)	0.22
Overweight	27 (29.7)	15 (41.7)	0.21
Obese	15 (16.5)	10 (27.8)	0.33
Body Height (cm)	132 (121-144)	130.5 (119-152)	0.49
Body Weight (kg)	30 (24-41)	32 (25-47)	0.17
BMI (kg/m²)	17.6 (15.5-20.1)	19.0 (16.1-21.2)	0.14
BMI z-score	0.35 (-0.42 - 1.29)	0.76 (-0.13 - 1.87)	0.22
NC (cm)	28.0 (26.0-30.0)	29.0 (27.0-32.0)	0.019
NC >90%	21 (23.1)	15 (41.7)	0.036
WC (cm)	58.0 (54.0-69.0)	62.0 (58.0-74.0)	0.08
WC >90%	26 (28.6)	17 (47.2)	0.05
HC (cm)	68.0 (61.0-80.0)	70.5 (66.0-85.0)	0.09
Waist/Hip ratio	0.87 (0.84-0.90)	0.87 (0.83-0.92)	0.65

Data are presented as frequency (percentage) or median (interquartile range)

BMI, body mass index; NC, neck circumference; WC, waist circumference;

HC, hip circumference

Table 2. Multivariable logistic regression analysis for severe asthma (n=127)

	OR	95% CI	<i>p</i>
Age	1.14	0.98-1.33	0.09
Female sex	1.43	0.60-3.42	0.42
Birth weight	1.00	1.00-1.01	0.23
NC > 90%	2.52	1.05-6.01	0.038
WC> 90%	1.58	0.60-4.24	0.36
HC	1.01	0.92-1.11	0.92
BMI	0.99	0.70-1.41	0.98
Atopy	0.42	0.18-1.02	0.06

OR, odds ratio; CI, confidence interval; NC, neck circumference;

WC, waist circumference; HC, hip circumference