Sex differences in body composition affect total airway resistance during puberty

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Abstract

Background: During puberty, changes in body composition due to sex hormones are associated with lung mechanics. However, little is known about the mediation effect of sex differences in body composition during puberty with total airway resistance.

Methods: We prospectively recruited 620 children (10–12 years old) from the general population and conducted a cross-sectional study. This study assessed pubertal status according to the five Tanner stages using a questionnaire, line drawings, and each subject’s blood sex hormone profile. Both the impulse oscillation system for total lung mechanics and multifrequency bioelectrical impedance for body composition analyses were conducted. The effects of puberty on body composition and subsequent total lung resistance were evaluated using mediation analysis.

Results: Among the 503 children enrolled, there were 261 males (51.9%) and 242 females (48.1%). In males, higher testosterone levels corresponded with reduced total lung resistance ($\beta = -0.13$, 95% CI = $-0.21$ to $-0.05$, $p < 0.001$), and the proportion of the mediating effect through the muscle-fat ratio was 19% (95% CI = 4 to 59, $p = 0.02$). In contrast, in females, pubertal status reduced total lung resistance ($\beta = -0.27$, 95% CI = $-0.58$ to $-0.05$, $p = 0.04$), however, the proportion of the mediating effect through the body mass index was $-51\%$ (95% CI = $-244$ to $-4\%$, $p = 0.04$).

Conclusion: The muscle-fat ratio in adolescent males had a synergistic effect with testosterone on improving total airway resistance, whereas improvements in lung resistance by pubertal status were partially masked by body mass index in adolescent females. In conclusion, body composition changes during puberty between males and females have differing effects on total airway resistance.

Introduction

Although males have a larger lung size than females, the lungs of females tend to have lower airway resistance and higher airway conductance in young childhood [1]. In addition, females have higher threshold responses to inhaled methacholine and a decreased prevalence of airway hyper-responsiveness throughout childhood. However, these findings were reversed in males and females after puberty [1, 2]. Several studies attributed these sex differences to the immunologic functions of sex hormones or changes in lung physiology related to sex and age, but the underlying mechanisms remain elusive [3].

Sex differences in body composition become striking with the increased release of sex hormones during puberty, such as increased fat gain by adolescent females compared to increased fat-free skeletal mass gain by adolescent males during this period [4]. Moreover, body composition, including body mass index (BMI), fat mass, and muscle mass, was significantly associated with pulmonary function in males and females [5–8]. Despite these previous findings, little is known about the different mediating effects of body composition changes between males and females on the association between puberty.
and total airway resistance. Therefore, we aimed to investigate the different mediating effects of sex-dependent changes in body composition on total airway resistance during puberty.

**Methods**

**Study population**

This general population-based cross-sectional study examined children (aged 10–12 years) from 11 elementary schools as part of the Seongnam Atopy Project in Korea [9]. Questionnaires were administered to the parents of 2,382 children, and 745 completed questionnaires were collected. A total of 125 children were excluded due to the absence of written consent or incorrect questionnaires; thus, 620 children were eligible. Questionnaires were used to obtain the demographic and clinical variables of all participants. Of the 620 children, 503 children who underwent impulse oscillometry (IOS), their blood and body composition tests were included. The study protocol was approved by the Institutional Review Board of CHA University, and written informed consent was obtained from the parents or caregivers (2017–04-049).

**Impulse oscillometry (IOS)**

IOS was performed based on current guidelines [10]. Airway resistance at 5 Hz (Rrs5) was measured using a Jaeger MasterScreen IOS system (Jaeger Company, Wurzburg, Germany). The signal duration was 30 s or longer, and measurements of three acceptable maneuvers were acquired at each time while monitoring the flow curves. Rrs5 is the total airway resistance [11].

**Laboratory tests**

Venous serum was obtained from participants at their elementary schools. All serum samples were safely transported to the Department of Laboratory Medicine at Bundang CHA hospital by putting them in a dedicated transport box that is kept refrigerated at 2 to 4°C. Thereafter, all serum sample were centrifuged within 2 h and stored at −80°C until the day of the study. Blood testosterone levels were determined using a Cobas 8000 c702 Chemistry Autoanalyzer (Roche, Basel, Switzerland). Levels of 25-OH vitamin D were measured using a fluorescent enzyme-linked immunosorbent assay kit (ImmunoDiagnostic Systems, COBAS 6000 Roche, Mannheim, Germany). Six types of serum inhalant allergen-specific IgE (Alternaria, birch, cat dander, dog dander, Dermatophagoides farina, Japanese hop) and total IgE levels were measured using the ImmunoCAP system (Phadia AB, Uppsala, Sweden). Allergen-specific serum IgE levels ≥ 0.35 kU/L were defined as positive for each allergen.

**Pubertal development**

Assessments of pubertal status in females were based on the development of breasts using the Tanner stages and a detailed questionnaire with line drawings [12]. Breast development is divided into five stages: 1 (preadolescent), 2 (breast buds), 3 (areola darkens and breast tissue enlarges), 4 (areola and nipple ridge), and 5 (nipple protrusion and fully developed breast) [13]. Female pubertal status was dichotomized into early (1 and 2) and late (3, 4, and 5) puberty stages [14]. Pubertal status in males was assessed using log-substituted testosterone levels [15].

**Body composition**

Multifrequency bioelectrical impedance (InBody 720; Biospace, Tokyo, Japan) was used to measure body composition. Children participating in the bioelectrical impedance analysis adhered to the following protocol: fasting for at least three hours, empty bladder just before bioelectrical impedance analysis, and avoidance of vigorous physical activity. Parameters including height, weight, BMI, and muscle-fat ratio were automatically measured within 2 min. BMI is used as an indirect indicator of body fat mass in children due to its high correlation with body fat mass [16, 17]. The muscle-fat ratio has been used to assess the association between muscle and fat mass [18].

**Statistical analysis**

The relationship between pubertal status (testosterone level and Tanner stage) and body composition (muscle-fat ratio and BMI), body composition and Rrs5, and pubertal status and Rrs5 were determined using generalized linear regression with a gamma function, with adjustment for confounding factors (prematurity [<37 weeks’ gestation], low birth weight [<2500 g], passive smoking, aeroallergen sensitization, history of wheezing episode, and 25-OH vitamin D levels). Analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA). The “Mediation” package from R (version 3.1.0) was used to quantitatively estimate the mediating and direct effects of body composition factors on the association between pubertal status and pulmonary function, with adjustment for confounding factors. This package estimated confidence intervals (CIs) using bootstrapping with 1000 resamples. Statistical significance was defined as a two-sided p value < 0.05.

**Results**

**Population characteristics**

The demographic and clinical characteristics of participants are presented in Table 1. There were 261 males (51.9%) and 242 females (48.1%). The mean values of height and weight...
Table 1  Demographic and clinical characteristics of study subjects (n = 503)

|                      | Male (n = 261, 51.9%) | Female (n = 242, 48.1%) |
|----------------------|-----------------------|-------------------------|
| **Anthropometrics**   |                       |                         |
| Age, years, mean (SD)| 11.03 (0.70)          | 11.05 (1.03)            |
| Height, cm, mean (SD)| 149.61 (7.99)         | 149.53 (7.48)           |
| Weight, kg, mean (SD)| 43.11 (9.57)          | 42.47 (8.77)            |
| **Birth characteristics** |                   |                         |
| Gestational age, weeks (SD) | 38.77 (2.15) | 38.98 (2.06) |
| Birth weight, kg, mean (SD) | 3.30 (0.43)  | 3.16 (0.43)   |
| Passive smoking, n (%) | 100 (43.5)          | 103 (45.4)             |
| Aeroallergen sensitizationa, n (%) | 168 (73.0) | 131 (57.7)   |
| Wheeze episodes, n (%) |                       |                         |
| None                  | 225 (86.2)            | 219 (90.9)             |
| 1 or over             | 36 (13.8)             | 22 (9.1)               |
| BMI z score, mean (SD) | −0.08 (1.04)         | 0.04 (1.05)            |
| Muscle fat ratio, median (IQR) | 3.54 (2.44 to 5.53) | 2.93 (2.16 to 3.91)   |
| **Pubertal status, n (%)** |                   |                         |
| Early pubertal stageb | 200 (87.3)            | 91 (38.9)              |
| Late pubertal stageb  | 29 (12.7)             | 143 (61.1)             |
| Testosterone, ng/mL, median (IQR) | 0.70 (0.12 to 2.49) | 0.19 (0.12 to 0.27)   |

Abbreviations: n number, SD Standard deviation, GM Geometric mean, GSD Geometric standard deviation, IQR Inter quartile range, IgE Immunoglobulin E, Rrs5 Resistance at 5 Hz, BMI Body mass index

a Aeroallergen sensitization was defined as an IgE value of 0.35 kU/L or more in response to at least 1 of 6 allergens (Dermatophagoides farina, Alternaria, birch, Japanese hop, cat dander, and dog dander)

b Early and late pubertal status were determined by the breast development in females and the genital development in males of Tanner stage

Missing data, Birth characteristics, n = 8; Passive smoking, n = 3; Aeroallergen sensitization, Total IgE, and 25-OH vitamin D, n = 33; Wheeze episodes, n = 1; Pubertal status, n = 40

Numbers in bold indicate significant differences (P < 0.05)

were 149.61 cm (standard deviation [SD], 7.99 cm) and 43.11 kg (SD, 7.97 kg) in males and 149.53 cm (SD, 7.48 cm) and 42.47 kg (SD, 8.77 kg) in females, respectively, and there were no significant differences between sexes. Birth weight was higher in males (mean [SD], 3.30 kg [0.43 kg]) than in females (mean [SD], 3.16 kg [0.43 kg]). Allergen sensitization was more prevalent in males (168, 73.0%) than in females (131, 57.7%). Furthermore, Rrs5 was higher in males (median [interquartile range [IQR]], 4.99 hPa/L/s [4.42 to 5.77 hPa/L/s]) than in females (4.79 hPa/L/s [4.21 to 5.46 hPa/L/s]). There was a greater number of females in late pubertal stage (143, 61.1%) than males (29, 12.7%).

Association between pubertal status, body composition, and lung function

Figure 1 shows all associations between pubertal status and Rrs5, pubertal status and body composition, and body composition and Rrs5 in males and females. First, pubertal status was negatively associated with the numerical value of Rrs5 in males and females (β [95% CI], −0.06 [−0.10 to −0.02] and −0.03 [−0.15 to −0.01], respectively). Second, pubertal status was positively associated with the muscle-fat ratio in males and BMI in females (β [95% CI], 0.85 [0.82 to 0.88] and 0.69 [0.68 to 0.71], respectively). Thirdly, a high muscle-fat ratio correlated with decreased Rrs5 in males (β [95% CI], −0.02 [−0.03 to −0.01]), while a high BMI correlated with increased Rrs5 in females (β [95% CI], 0.05 [0.03 to 0.07]).

Causal mediation analysis indicated that the total effect of pubertal status on Rrs5 in males (β = −0.13 [95% CI = −0.21 to −0.05], p < 0.001) was due to a direct effect (β = −0.10 [95% CI, −0.20, −0.03], p < 0.001), which was complemented by the mediating effect of the muscle-fat-ratio (β = −0.03 [95% CI = −0.05 to −0.01],...
p < 0.001, portion of mediated effect = 19% [95% CI = 4% to 59%], p = 0.02). In contrast, the total effect of pubertal status on Rrs5 in females (β = −0.27 [95% CI = −0.58 to −0.05], p = 0.04) was due to a direct effect (β = −0.41 [95% CI = −0.70 to −0.17], p < 0.001), which was partially offset by the mediating effect of BMI (β = 0.14 [95% CI = 0.03 to 0.28], portion of mediated effect = −51% [95% CI = −244 to −4%], p = 0.04).

**Discussion**

Our study showed that pubertal children have sex-dependent differences in body composition due to the effects of sex hormones, which in turn affect lung function. This may explain the superior lung function of girls before puberty and that of boys after puberty. Increased testosterone levels in boys increases the muscle-fat ratio, which had a synergistic mediating effect on lowering lung resistance. Conversely, the effect of increased BMI upon sexual maturity in females had a negative effect on pulmonary function.

Thus, our study demonstrates that changes in body composition help explain the association between pubertal status and airway resistance. Specifically, the release of sex hormones increases during puberty, and there are sex-dependent immunologic differences in sex hormones. Testosterone has an immunosuppressant effect that reduces systemic and airway inflammation [19], whereas estradiol affects immune cells by promoting Th2 polarization, switching of B cells to IgE production, and degranulation of mast cells and basophils [20, 21]. In addition, puberty in adolescent males and females has different effects on body composition [4], which is consistent with our results. Increased testosterone levels in males promotes myogenic differentiation of multipotent mesenchymal stem cells, stimulates muscle protein synthesis, and inhibits proteolysis [22]. In contrast, the endocrine effects of estradiol promote fat mass accumulation predominantly in the abdomen or hip of females [23]. A proposed mechanism by which body composition could affect lung function is that high lean body mass leads to increased mechanical power of breathing.
and better resultant lung function, whereas high fat mass induces inflammation of lung tissue, causing a reduction in airway diameter [7].

Several studies have discussed connections between some of these factors, but the present study is the first to identify the links between all three factors. The presence of the links described here is easily understood and straightforward; however, to the best of our knowledge, this study is the first to verify the effect of body composition on changes in pulmonary function during puberty in adolescents from the general population.

We utilized the Rrs5 parameter of the IOS to evaluate total airway resistance. IOS requires only passive and minimal cooperation [24], thus, it is a reliable and noninvasive method to assess airway resistance in children [25]. Several studies have confirmed the usefulness of IOS in diagnosing and monitoring patients with asthma, particularly in children [26]. Although spirometry is the gold standard for the diagnosis of asthma, the Rrs5 parameter of IOS may be a useful parameter to estimate the association of pubertal status and body composition with airway resistance in children.

This study has several limitations. First, this was not a longitudinal study, so causal inferences regarding the relationship between body composition, pubertal status, and lung function cannot be made. Therefore, further studies with prospective follow-up are necessary to confirm our results. Second, there was a lack of information about demographic characteristics, including socioeconomic status and eating or exercise habits, which can affect body composition or airway resistance. However, we tried to analyze the associations between several confounding factors (prematurity, birth weight, passive smoking, allergen sensitization, history of wheezing episode, and 25-OH vitamin D levels). Third, the Tanner stage of each child was determined from a questionnaire answered by the parents rather than a physical examination by a physician. However, self-assessment was considered sufficient for our study because we only distinguished between prepuberty and puberty [12].

Our study provides new insights into the mediating effect of sex-dependent body composition changes on airway resistance during puberty. Our study will help to guide further research that examines the effects of altering body composition on pulmonary function in children, especially in adolescents with reduced lung function during puberty.

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Authors’ contributions
JHK, SWL, EY, and MYH conceptualized and designed this study. SWL, JAK, and MYH were involved in data collection, data analysis, and interpretation. JHK, EKH, and HMIJ were involved in manuscript writing and revision. MKJ, SL, and YHS supervised the data interpretation and critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from the Institutional Review Board of CHA University, Korea (2017–04‑049). All methods were performed according to the relevant guidelines and regulations (Declaration of Helsinki). Written informed consent was obtained from the parents or caregivers.

Consent for publication
Not applicable.

Competing interests
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References
1. Carey MA, Card JW, Voltz JW, Arbes SJ Jr, Germolec DR, Korach KS, et al. It’s all about sex: gender, lung development and lung disease. Trends Endocrinol Metab. 2007;18:308–13.
2. Kim YH, Jang YY, Jeong J, Chung HL. Sex-based differences in factors associated with bronchial hyperresponsiveness in adolescents with childhood asthma. Clin Exp Pediatr. 2021;64:229–38.
3. Thomas AO, Jackson DJ, Evans MD, Rajamanickam V, Gangnon RE, Fain SB, et al. Sex-related differences in pulmonary physiologic outcome measures in a high-risk birth cohort. J Allergy Clin Immunol. 2015;136:282–7.
4. Loomba-Albrecht LA, Styne DM. Effect of puberty on body composition. Curr Opin Endocrinol Diabetes Obes. 2009;16:10–5.
5. Peralta GP, Marcon A, Carsin A-E, Abramson MJ, Accordini S, Amoral AF, et al. Body mass index and weight change are associated with adult lung function trajectories: the prospective ECRHS study. Thorax. 2020;75:313–20.
6. Park JE, Chung JH, Lee KH, Shin KC. The effect of body composition on pulmonary function. Tuberc Respir Dis (Seoul). 2012;72:433–40.
7. Peralta GP, Fuertes E, Granell R, Mahmoud O, Roda C, Serra I, et al. Child‑hood body composition trajectories and adolescent lung function. find‑ings from the ALSPAC study. Am J Respir Crit Care Med. 2019;200:75–83.
8. Jeon YH, Yang HJ, Pyun BY. Lung function in Korean adolescent girls: in association with obesity and the menstrual cycle. J Korean Med Sci. 2009;24:20–5.
9. Kim JH, Lee SW, Yon DK, Ha EK, Jee HM, Sung M, et al. Association of serum lipid parameters with the SCORAD index and onset of atopic dermatitis in children. Pediatr Allergy Immunol. 2021;32:322–30.
10. Shin YH, Yoon JW, Choi SH, Baek JH, Kim HY, Jee HM, et al. Use of impulse oscillometry system in assessment of asthma severity for preschool children. J Asthma. 2013;50:198–203.
11. Ha EK, Kim JH, Lee E, Sung M, Jee HM, Baek HS, et al. Abnormal iron status is independently associated with reduced oscillometric lung function in schoolchildren. Clin Respir J. 2021;15:870–7.
12. Rasmussen AR, Wohlfahrt-Veje C, de Renzy-Martin KT, Hagen CP, Tinggaard J, Mourtis T, et al. Validation of self-assessment of pubertal maturation. Pediatrics. 2015;135:86–93.
13. Sun Y, Tao FB, Su PY, Collaboration CPR. Self-assessment of pubertal Tanner stage by realistic colour images in representative Chinese obese and non-obese children and adolescents. Acta Paediatr. 2012;101:163–6.
14. Nève V, Girard F, Flahault A, Boulé M. Lung and thorax development during adolescence: relationship with pubertal status. Eur Respir J. 2002;20:1292–8.
15. Shim YS, Lee HS, Hwang JS. Genetic factors in precocious puberty. Clin Exp Pediatr. 2021. https://doi.org/10.3345/cep.2021.00521.
16. Eto C, Komya S, Nakao T, Kikkawa K. Validity of the body mass index and fat mass index as an indicator of obesity in children aged 3–5 year. J Physiol Anthropol Appl Hum Sci. 2004;23:25–30.
17. Srdić B, Obradović B, Dimitrić G, Stokić E, Babović SS. Relationship between body mass index and body fat in children—Age and gender differences. Obes Res Clin Pract. 2012;6:e167–73.
18. Jhee JH, Joo YS, Han SH, Yoo TH, Kang SW, Park JT. High muscle-to-fat ratio is associated with lower risk of chronic kidney disease development. J Cachexia Sarcopenia Muscle. 2020;11:726–34.
19. Han Y, Forno E, Witchel SF, Manni ML, Acosta-Pérez G, Canino G, et al. Testosterone-to-estradiol ratio and lung function in a prospective study of Puerto Rican youth. Ann Allergy Asthma Immunol. 2021;127:236-42.
20. Bonds RS, Midoro-Horuti T. Estrogen effects in allergy and asthma. Curr Opin Allergy Clin Immunol. 2013;13:92.
21. Scott H, Gibson P, Garg M, Upham J, Wood L. Sex hormones and systemic inflammation are modulators of the obese-asthma phenotype. Allergy. 2016;71:1037–47.
22. Xu Y, Wen Z, Deng K, Li R, Yu Q, Xiao S-M. Relationships of sex hormones with muscle mass and muscle strength in male adolescents at different stages of puberty. PLoS One. 2021;16:e0260521.
23. Hammer L, Wilson DM, Litt IF, Killen JD, Hayward C, Miner B, et al. Impact of pubertal development on body fat distribution among white, Hispanic, and Asian female adolescents. J Pediatr. 1991;118:975–80.
24. Shin YH, Jang SJ, Yoon JW, Jee HM, Choi SH, Yum HY, et al. Oscillometric and spirometric bronchodilator response in preschool children with and without asthma. Can Respir J. 2012;19:273–7.
25. van de Kant KD, Paredi P, Meah S, Kalisi HS, Barnes PJ, Usmani OS. The effect of body weight on distal airway function and airway inflammation. Obes Res Clin Pract. 2016;10:564–73.
26. Bednarek M, Grabicki M, Porunek T, Batura-Gabryel H. Current place of impulse oscillometry in the assessment of pulmonary diseases. Respir Med. 2020;170:105952.