의학석사 학위논문

가습기 살균제 관련 폐 손상 환아의 평가를 위한 폐확산능의 임상적 유용성

Clinical usefulness of the diffusing capacity of the lung for carbon monoxide (DLco) in the identification of humidifier disinfectant-associated lung injury in children

울산대학교 대학원

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Abstract

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Title: Clinical usefulness of the diffusing capacity of the lung for carbon monoxide (DLco) in the identification of humidifier disinfectant-associated lung injury in children

Background: Humidifier disinfectant-associated lung injury (HDLI) is classified as an interstitial lung disease due to pulmonary fibrosis, which may be characterized by decreased DLco levels. Then, DLco can be a possible clinical marker of HDLI. However, there is no published information on DLco levels in HDLI children compared with controls. The purpose of this study was to establish a reference equation for DLco in healthy Korean children and to evaluate the levels of DLco in a national cohort of HDLI survivors and to compare those data to controls

Methods: DLco were performed in a nationwide cohort of HDLI survivors aged from 5 to 12 years. To investigate the reference value of DLco in controls, we recruited age- and sex-matched outpatients who had no exposure history of HD and underlying respiratory disease.

Results: The study population consisted of 67 HDLI survivors and 216 controls, respectively. Height is the most significant factor to influence the log-transformed DLco (LnDLco) in both sexes (boys, R^2=0.724; girls, R^2=0.734, respectively). Multiple regression equations were obtained for LnDLco using variables including age, height, and weight in both sexes (boy, R^2=0.736; girl, R^2=0.755, respectively). To compare HDLI survivors with controls, HDLI children have lower DLco than control groups. In particular, the mean difference is significantly higher in boys taller than 130cm (130–139cm, 12.6 vs. 9.5, P=0.055; 140–149cm, 16.4 vs. 12.8, P<0.001; 150cm≤, 20.3 vs. 16.2, P=0.050. respectively).

Conclusion: The DLco value increases with increased height, but the rate of increase in HDLI children is less than that of the control groups. DLco may be considered a useful pulmonary function test for HDLI survivor in children for the diagnosis and follow-up of HDLI.

Key words: Diffusing capacity, humidifier disinfectant, lung injury, children

차 례

표 및 그림목차

약어

HDLI : humidifier disinfectant-associated lung injury

DLco : diffusing capacity of the lung for carbon monoxide

ILD : interstitial lung disease

LnDLco : Log-transformed DLco

Introduction

Humidifier disinfectant-associated lung injury (HDLI) is a distinctive interstitial lung disease (ILD) associated with humidifier disinfectant use that was recently described among children and adults in Korea[1,2]. The main histological features of the cases were a bronchiolocentric distribution, an obliterative bronchiolitis pattern, subpleural and peripheral alveolar reservation, an organizing pneumonia pattern, a diffuse alveolar damage pattern, and temporal homogeneity of the fibro-inflammatory process[2]. Originally, humidifier disinfectants, marketed for cleaning a humidifier's water tank but instead used by the public as a water additive to suppress microbial growth, affect the potential for occupational or environmental lung disease in workers and the general public who inhale agents with unanticipated pulmonary toxicity.

An impaired diffusing capacity of the lung for carbon monoxide (DLco) has been reported in adults with HDLI[2] and can be affected by pulmonary fibrosis, which decreases alveolar volume and directly affects the rate constant for carbon monoxide uptake from alveolar gas[3]. Several studies have focused on the significance of DLco in early diagnosis of ILD, even in the case of normal functional volume capacity (FVC)[4] and correlation with patient

outcome in ILD[5]. Thus, DLco measurements are important in the diagnosis and follow-up of HDLI.

However, there is no published information on DLco in HDLI children compared to unexposed healthy children. Additionally, although their interpretation is highly dependent on reference equations, the previously published reference equations might be inappropriate for today's pediatric population, especially in Korean children. Reference data, which were often collected decades ago, could be outdated. Furthermore, measurement protocols have improved and analytical techniques have progressed. The current predictive equations are also based on data from Caucasian children and are thus unlikely to be accurate for Asian children[6,7,8]. Lung volumes in Asian subjects are smaller than those in Caucasian subjects of the same height[9].

Therefore, to prevent misinterpretation and avoid the misdiagnosis of HDLI in clinical practice, we aimed to generate new reference values for DLco in children, prospectively collected pulmonary function measurements, using standardized measurement protocols. In addition, we evaluate the DLco in a national cohort of HDLI survivors and to compare those data to unexposed healthy children.

Materials and methods

Subjects and design

HDLI survivors

The Korean Government completed the third round of investigation (first: July 2013 through April 2014; second: July 2014 and April 2015; and third: September 2015 through August 2016) on the association between HDLI and the use of HD by collecting information on individuals who presumed their condition was related to the use of HD and determined whether these registered cases were indeed associated with the use of HD. Further, the investigation committee evaluates the degree of damage by compiling results from individual tests, such as environmental exposure, histopathology, radiology, and clinical tests. The classifications for being identified as having lung disease caused by HD and the definitions of the respective categories of judgement are definite, probable, possible, and unlikely and are discussed in our previous paper[10]. Of 360 registered children (169, 66, and 125 individuals from the first-, second-, and third-round investigations, respectively), 161 individuals (44.7%) were classified as “definite” or

"probable." Among 161 patients HDLI with "definite" or "probable," 75 patients were available for the routine testing of DLco as a part of pulmonary function. Eight patients aged 13 years or older were excluded to match the age of the control group. Finally, 67 patients aged 5 to 12 years were included in this study. The study protocol was approved by the Institutional Review Board of the Asan Medical Center (approval number: 2015-0510), which waived the requirement for informed consent because the study was retrospective in design and all patient records were anonymized and de-identified prior to analysis.

Controls

As the control group, age- and sex-matched subjects were recruited from outpatients in Asan Medical Center from June 2016 through Sep 2017. All subjects were born at full term and had no history of HD exposure. Subjects had no acute or chronic cardio-respiratory disease, no history of chest cage deformity or thoracic surgery, no history of hematological disorders, and no other diseases known to influence the respiratory system, either directly or indirectly. Finally, 216 subjects aged 5 to 12 years were included in this

study. Table 1 demonstrates the detailed information on the control subjects.

Table 1. Comorbidities of control subjects

Group	Frequency	%
Only AD	46	21.3
Only FA	1	0.5
Only AR	61	28.2
AD and AR, but no history of asthma	46	21.3
AD, FA, and AR, but no history of asthma	5	2.3
Urticaria	3	1.4
Tic	2	0.9
Health check-up	52	24.1

AD, atopic dermatitis; FA, food allergy; AR, allergic rhinitis;

DLco measurement

DLco was measured by the single-breath method using a Vmax229D instrument (SensorMedics, Yorba Linda, CA, USA) following the European Respiratory Society and American Thoracic Society criteria protocol recommendations[11]. The breath-holding time

was at least 10 s, and the washout volume was 0.75 l. The interval between measurements was 5 min, and the tests were performed in standing position. The predicted values of DLco and corrected DLco were calculated from Polgar's equation[12].

Statistical Analysis

Variables are expressed as mean ± standard deviation (SD). The t-test or chi-square test was used to compare the variables, as appropriate. DLco was transformed as the natural log diffusing capacity of the lungs to carbon monoxide (LnDLco) due to nonlinear relationship with height and age. Multivariate linear stepwise and enter regression models were used to define the relationship of height, age, and weight with each of LnDLco for boy and girls. The prediction models derived in this study were compared to other studies in which the diffusion capacity was derived using the single-breath technique and in which regression equations for at least two of DLco, alveolar volume (V_A), and DLco/V_A were reported[6,7,8]. All statistical analyses were performed using SPSS software 24.0 (SPSS Inc., Chicago, IL, USA). P-values of less than 0.05 were considered statistically significant.

Results

Characteristics of study subjects

The demographics of clinical data and DLco indices for study subjects included in the analysis from HDLI survivors and controls are summarized in Table 2. The study population consisted of 67 HDLI survivors and 216 controls with a mean age of 8.0 and 7.1 years, respectively. Although children from HDLI survivors were older and taller than controls, the predicted value of DLco and corrected DLco were significant lower in HDLI than controls (49.7% vs. 54.6%, P=0.001; 69.3% vs. 78.4%, P<0.001, respectively).

Table 2. Demographics and DLco indices compared between HDLI survivors and controls

	HDLI survivors (n=67)		**Controls (n=216)**		**P-value**
	Mean	SD	Mean	SD	
Age (years)	8.0	2.4	7.1	1.7	0.003
Boy (%)	55.2	NA	58.3	NA	<0.001
Height (cm)	130.9	15.0	124.7	11.0	0.002
Weight (kg)	30.7	10.2	26.3	7.4	0.001

DLco (ml/min/mmHg)	10.3	3.5	10.2	3.1	0.910
DLco (pred %)	49.7	10.3	54.6	10.8	0.001
Corrected DLco (ml/min/mmHg)	10.6	3.5	10.8	3.2	0.664
Corrected DLco (pred %)	69.3	13.8	78.4	13.4	<0.001
V_A (L)	1.8	0.7	1.8	0.6	0.486
DLco/V_A (ml/min/mmHg/L)	5.8	0.9	5.9	0.7	0.118

DLco, diffusing capacity of the lung for carbon monoxide; pred, predicted; V_A, alveolar volume; L, liter; Data are shown as mean ± standard deviation; comparison between groups has been made using a t-test or chi-square test, as appropriate.

Regression equation of DLco according to height, weight, and age

The mean DLco (ml/min/mmHg) is illustrated in Figure 1 according to age at performance.

The range of DLco was between 7.8 and 20.4 for boys and between 6.8 and 17 for girls.

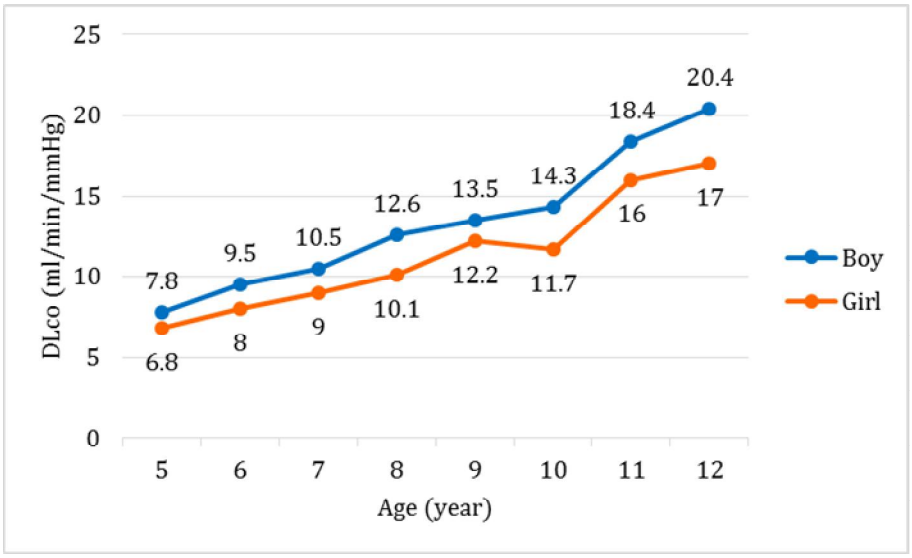


Figure 1. Results of the DLco levels (mean value) in controls according to age at performance.

The results of the regression analysis and significant predictors of DLco in boys and girls are summarized in Tables 3 and 4, respectively. In simple regression analysis, LnDLco was significantly influenced by height, age, and weight in both boys (height, R^2=0.724, P<0.001; age, R^2=0.623, P<0.001, weight R^2=0.596, P<0.001, respectively) and girls (height, R^2=0.734, P<0.001; age, R^2=0.638, P<0.001, weight R^2=0.605, P<0.001, respectively). Among them, height is the most significant factor to influence the LnDLco in both sexes (R^2=0.724, R^2=0.734, respectively). Multiple regression equations were obtained for LnDLco using variables including age, height, and weight. The regression

equation for all cases was P<0.001, and the explanatory power was the highest when all three variables were analyzed by a multiple enter regression model in both sexes (boy, R^2=0.736; girl, R^2=0.755, respectively). In addition, Figures 2 also illustrates that an increasing height was associated with increasing DLco in boys (R_2=0.761, P<0.001) and girls (R_2=0.760, P<0.001) using simple regression analysis.

Table 3. Regression equations for DLco in boys as controls

	Parameter	Estimate	Standard error	P-value	R^2	SEE
LnDLco (simple)	**Height**	0.021	0.001	<0.001	0.724	0.1398
	Age	0.133	0.009	<0.001	0.623	0.1634
	Weight	0.027	0.002	<0.001	0.596	0.1691
LnDLco (multiple, enter)	**Constant**	0.263	0.302	0.384	0.736	0.1354
	Height	0.014	0.004	<0.001		
	Age	0.035	0.017	0.041		
	Weight	0.005	0.003	0.135		

Ln, natural log; DLco, diffusing capacity of the lungs for carbon monoxide; VA, alveolar volume; SEE, standard error of the estimate. Height, age, and weight are expressed in cm, years, and kilograms, respectively

Table 4. Regression equations for DLco in girls as controls

	Parameter	Estimate	Standard error	P-value	R^2	SEE
LnDLco (simple)	**Height**	0.021	0.001	<0.001	0.734	0.1501
	Age	0.033	0.003	<0.001	0.638	0.1752
	Weight	0.127	0.011	<0.001	0.605	0.1831
LnDLco (multiple, enter)	**Constant**	0.179	0.289	0.538	0.755	0.1456
	Height	0.013	0.004	0.001		
	Age	0.031	0.017	0.064		
	Weight	0.009	0.005	0.074		

Ln, natural log; DLco, diffusing capacity of the lungs for carbon monoxide; VA, alveolar volume; SEE, standard error of the estimate. Height, age, and weight are expressed in cm, years, and kilograms, respectively.

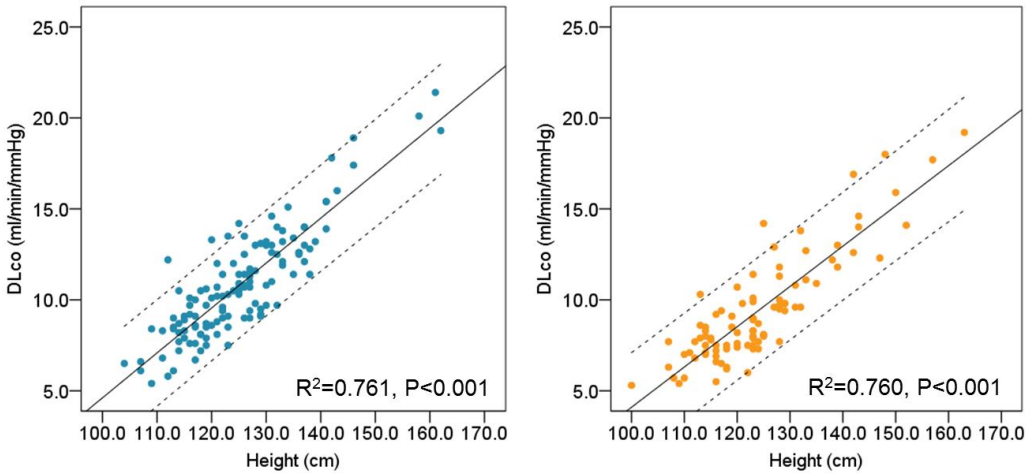
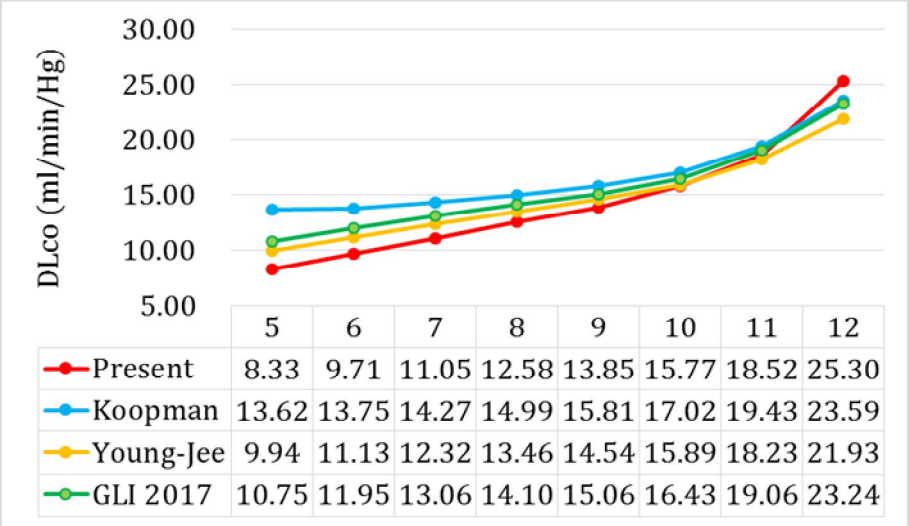


Figure 2. Correlation between DLco and height for boys (blue circles) and girls (orange circles). Dotted lines represent 95% CI.

Comparison regression equation of DLco in the present study with other studies

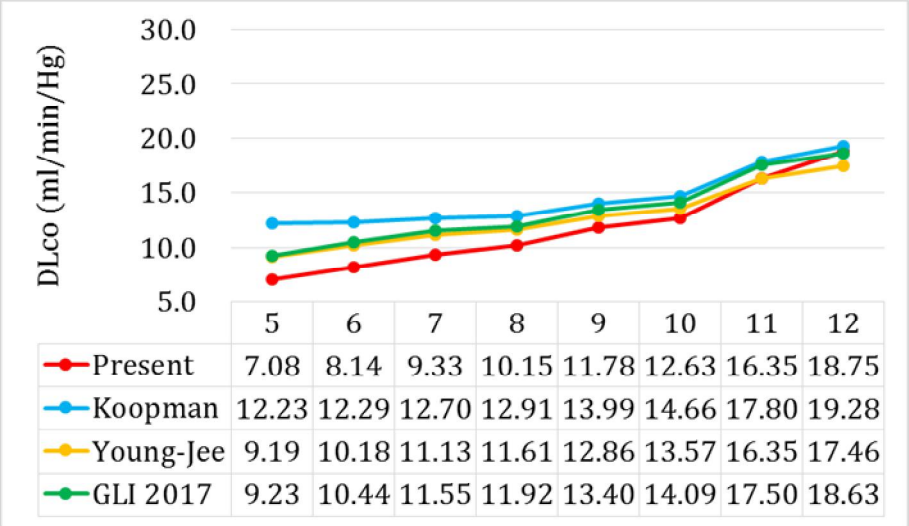
The agreement between DLco for boys and girls for this study and previously reported studies[6,7,8] is shown in Figures 3 and 4, respectively. This study showed lower DLco levels than Young et al. in younger boys (aged 5–7 years), and mean differences ranged from 1.27 to 1.61 ml/min/mmHg for DLco. However, mean differences ranged less than 1 ml/min/mmHg in boys aged 8–10 years, and the predicted value of DLco is even higher in those aged 11–12 years compared with Young et al. In girls, the predicted value of DLco is lower than Young et al., and mean differences ranged from 0.94 to 2.11 ml/min/mmHg in

those aged 5–10 years. However, the predicted value is the same as Young et al. in 11 year olds, and DLco is higher in 12 year olds. In particular, a similar trend is observed in comparison with Koopman et al. and GLI 2017 in both sexes[7,8].



	5	6	7	8	9	10	11	12
Present	8.33	9.71	11.05	12.58	13.85	15.77	18.52	25.30
Koopman	13.62	13.75	14.27	14.99	15.81	17.02	19.43	23.59
Young-Jee	9.94	11.13	12.32	13.46	14.54	15.89	18.23	21.93
GLI 2017	10.75	11.95	13.06	14.10	15.06	16.43	19.06	23.24

Figure 3. DLco in boys (n=126), plotted against age. Red lines represent the predicted values based on this study. Other lines represent the predicted values based on the reference equation by Koopman 2011 (blue), Young-Jee 2012 (yellow), and GLI 2017 (green).



	5	6	7	8	9	10	11	12
Present	7.08	8.14	9.33	10.15	11.78	12.63	16.35	18.75
Koopman	12.23	12.29	12.70	12.91	13.99	14.66	17.80	19.28
Young-Jee	9.19	10.18	11.13	11.61	12.86	13.57	16.35	17.46
GLI 2017	9.23	10.44	11.55	11.92	13.40	14.09	17.50	18.63

Figure 4. DLco in girls (n=90), plotted against age. Red lines represent the predicted values based on this study. Other lines represent the predicted values based on the reference equation by Koopman 2011 (blue), Young-Jee 2012 (yellow), and GLI 2017 (green).

Comparison DLco of HDLI survivors with controls

The mean DLco (ml/min/mmHg) is illustrated in Figure 5 according to age at performance. The range of DLco is 7.8–16.2 ml/min/mmHg for boys and 6.7–14 ml/min/mmHg for girls. Figures 6 demonstrates the correlation between HDLI and control according to increasing height, the most significant influence factor. The mean difference between HDLI survivors and controls is increased as height increases in both sexes.

We also compared the DLco per 10cm height increase in HDLI survivors with controls (Figure 7). In all categories of height for boys, HDLI survivors decreased the DLco compared to healthy controls. In particular, the mean difference is the higher in boys over 130cm tall (130–139cm, 12.6 vs. 9.5, P=0.055; 140–149cm, 16.4 vs. 12.8, P<0.001; 150cm≤, 20.3 vs. 16.2, P=0.050. respectively). Although statistically insignificant in girls, HDLI survivors had lower DLco than healthy controls.

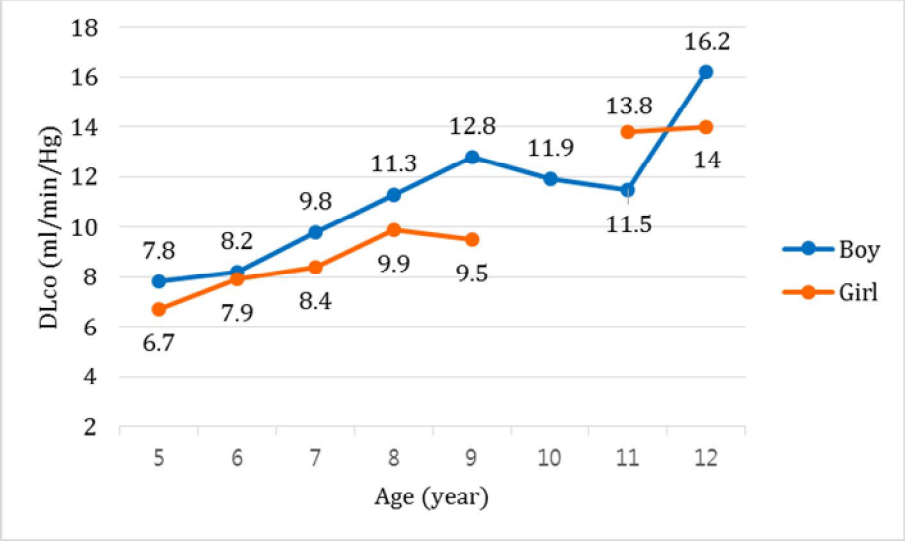


Figure 5. Results of the DLco (mean) in HDLI survivors according to age at performance.

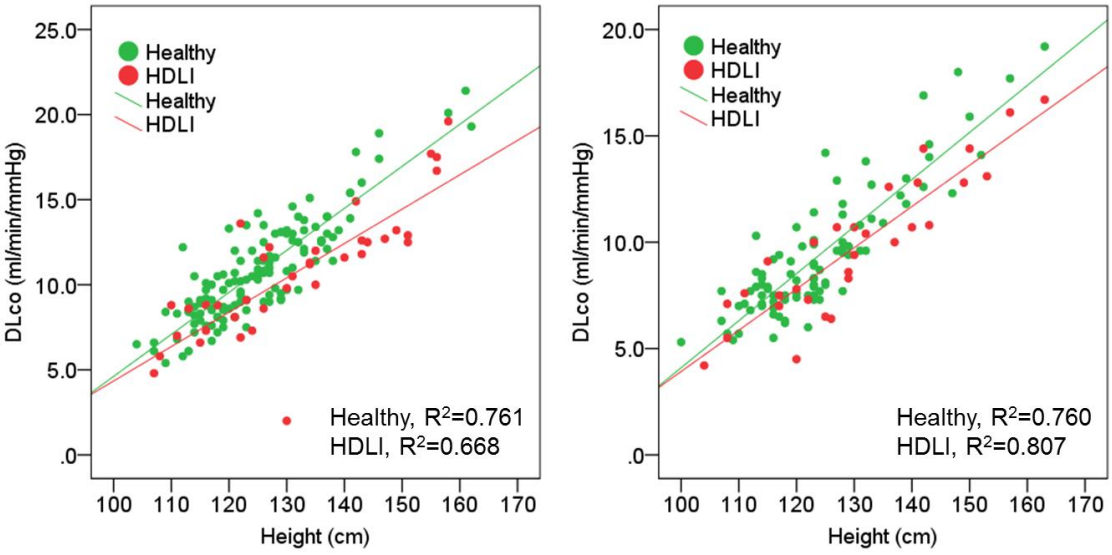


Figure 6. Correlation between DLco and height for control (green) and HDLI (red) children.

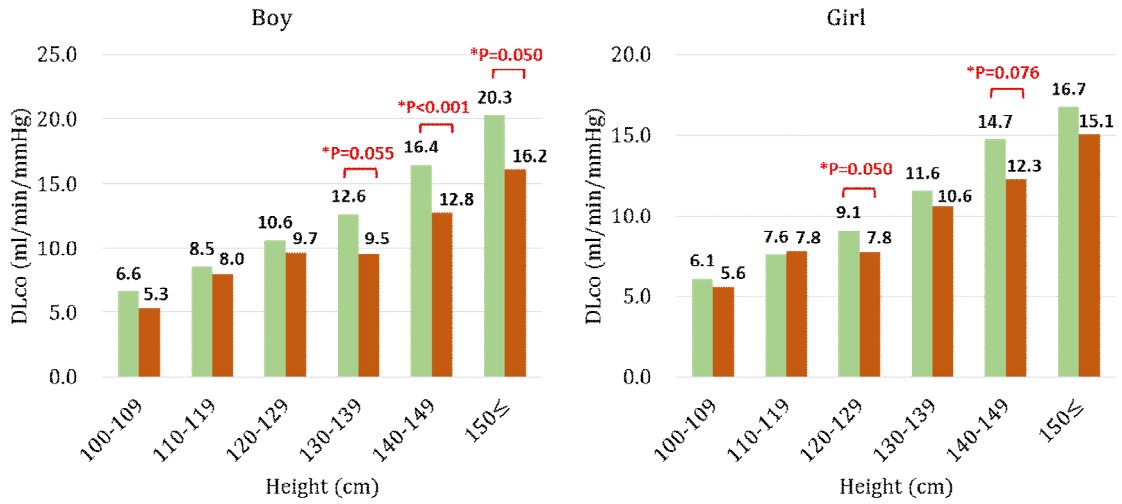


Figure 7. Comparison of DLco measurement (mean value) between the two groups (HDLI (red bar) vs. healthy (green bar).

Discussion

In the present study, we have evaluated DLco in Korean children using modern equipment and following the most recent international testing guidelines. Our data indicate that as children grow in height, a significant influencing factor, from early childhood to school age, the DLco correspondingly increases. We also reported the multiple regression equations for calculating predicted DLco values for children from height, age, and weight. In a comparison between HDLI and controls, we showed that DLco is significantly reduced in children with HDLI when compared to controls, which is consistent with adult patients. In particular, taller boys had a statistically significant reduction of DLco. These findings suggest that a consistent reduction in height growth is important in diagnosis and follow-up of HDLI, reflecting that the diffusing capacity has not recovered to normal levels in adolescence. To our knowledge, this is the first time in Asia that a study has been done to calculate reference equations for the DLco in healthy children and such a comparison has been observed and reported in pediatric patients with HDLI.

Humidifier disinfectants were dissolved in water and then dispersed into the air by a humidifier's aerosolizer as nano-sized particles. The small size of these particles allowed

them to reach the distal airways easily[14]. These findings are compatible with prior publications' results on HDLI addressing small airway involvement on computed tomography and a restrictive pattern on spirometry in adults[2,15]. In addition, a previous study showed that bronchiolar destruction and a centrilobular distribution of alveolar destruction following HD exposure were documented by lung biopsy[16]. Abnormalities in DLco reflect pathological changes in the lung parenchyma and are often correlated with patient outcome[17]. More recently, the DLco has been proposed as an early indicator of lung parenchymal changes and for detecting emphysema in its early stages.

However, reference equations for DLco in children are scarce. Although predicted values of DLco for children have been published[13,18,19,29,21,22], these equations were obtained between 1960 and 1990. Due to improved nutrition and better health in general, DLco will have changed over the past decades. Two larger studies recently produced reference equations for the more frequently used outcomes of DLco[6,7,8] However, these studies are not generalizable to non-Caucasian children, as ethnic differences in lung function exist[9] Therefore, it is important to continue to develop normative data for children of differing races.

The primary strength of this study is the large and acceptable age distribution of control children. Furthermore, this study was completed in both HDLI and control groups with identical equipment. The same two technicians performed all measurements, resulting in a high level of repeatability and a systematic approach. In addition, we included children as young as 5 years of age, expanding our ability to adequately evaluate advanced pulmonary function in this age group. Finally, our calculated reference equations for DLco corresponded well to recently published equations. We hope that having reliable reference equations for DLco will lead to improved diagnostic evaluation and provide a monitoring tool for the treatment of children presenting with HDLI.

Although promising results were obtained, we are aware that this study has several limitations. First, decreased DLco could not represent the unique finding of HDLI, suggesting the existence of diffuse interstitial lung disease entities, such as acute respiratory distress syndrome, hypersensitivity pneumonitis, and bronchiolitis obliterans organizing pneumonia. To differentiate the diagnosis of other conditions, we should investigate the distinguishable pattern of DLco in HDLI to explore the follow-up data and the long-term clinical significance with respect to DLco associated with HDLI. However,

we believe that we were able to distinguish other conditions because we also performed CT for all HDLI survivors in this investigation.

The second limitation is the fact that measurements were merely obtained in children. These new reference equations do not connect smoothly with the used reference equations for adolescence and highlight the need to collect new data in adolescence.

In summary, our study demonstrates that HDLI children have lower DLco than healthy children of the same gender, height, age, and weight. In addition, we provide regression equations that include race as a predictor. These results should improve our ability to predict DLco in HDLI children and therefore more accurately identify lung disease in children. It may be a useful marker for diagnosis and prognosis during follow-up.

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국문요약

제목 : 가습기 살균제 관련 폐 손상 환아의 평가를 위한 폐확산능의 임상적 유용성

배경 : 가습기 살균제 관련 폐 손상은 폐 섬유증으로 인한 간질성 폐 질환으로 간주되며 이는 폐확산능의 감소를 특징으로 한다. 따라서, 폐확산능은 가습기 살균제 관련 폐 손상의 임상지표가 될 수 있을 것으로 사료된다. 그러나 대조군과 비교한 가습기 살균제 관련 폐 손상 환아에서 폐확산능에 대한 비교 연구는 아직 보고되지 않은 상태이다.

목적 : 한국 어린이에서의 폐확산능에 대한 참조 방정식을 수립하여 대조군 데이터를 구하고, 대조군 데이터를 통해 국가 코호트 연구의 가습기 살균제 관련 폐 손상 환아들의 폐확산능을 평가하는 것이다.

방법 : 폐확산능은 5 세에서 12 세 사이의 가습기 살균제 관련 폐 손상군에서 수행되었다. 건강한 소아에서 폐확산능의 기준치를 조사하기 위해 우리는 가습기 살균제 및 기저 호흡기 질환의 노출력이 없는 외래 환자를 대상으로 폐확산능을 시행하였다.

결과 : 연구 집단은 가습기 살균제 관련 폐 손상군 67 명과 대조군 216 명으로 구성되었다. 신장은 폐확산능에 영향을 미치는 가장 중요한 요인으로 조사되었고 (남아, R^2 = 0.724, 여아, R^2 = 0.734), 연령, 신장, 체중을 포함한 변수들을 이용하여 폐확산능에 대한 다중 회귀 방정식을 얻었다. (남아, R^2 = 0.736, 여아, R^2 = 0.755). 가습기 살균제 폐 손상 남아는 모든 신장 범주에서 대조군에 비해 폐확산능이 감소되어 있었고, 특히 그 평균 차이는 130cm 이상 (130-139cm, 12.6 vs 9.5, P = 0.055, 140-149cm, 16.4 vs 12.8, P <0.001, 150cm≤, 20.3 vs 16.2, P = 0.059) 에서 통계적으로 유의하게 차이가 큰

것을 확인하였다. 여아에서도 통계적으로 유의하지 않지만 가습기 살균제 관련 폐 손상군에 대조군에 비해 폐확산능이 감소된 것으로 조사되었다.

결론 : 가습기 살균제 관련 폐 손상군에서 폐확산능의 감소를 보였으며 그 평균차이는 신장이 커짐에 따라 증가하였으며, 특히 남아에서 현저한 것으로 나타났다. 폐확산능은 소아 가습기 살균제 관련 폐 손상군에서 폐 손상 평가의 임상적 지표로서 활용 가능할 것이며, 향후 다른 폐기능 지표와 달리 장기 추적에서도 도움이 될 것으로 생각한다.