Dyslipidemia Associates with Respiratory Resistance Assessed by Forced Oscillation Technique in Asthmatic Children

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Abstract

Purpose: This study evaluated the correlation between dyslipidemia and pulmonary function parameters assessed by spirometry and force oscillation technique in asthmatic children.

Methods: Asthmatic children (aged 5–18 years old) were measured for fasting serum lipid profiles, including low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP). Pulmonary function tests were assessed by spirometry and forced oscillation technique (FOT).

Results: One hundred forty-one asthmatic children were enrolled with the mean (sd) age of 11.82 (3.38) years. Eighty-eight children (62.4%) were males, 64 children (45.4%) had dyslipidemia, and 20 (14.2 %) children were obese. Of 64 children with dyslipidemia, high LDL-C was the most common dyslipidemia (65.6%), followed by TC (57.8%), non-HDL-C (53.1%), TG (35.9%), and low HDL-C (15.6%). There were no significant differences in spirometry parameters and FOT parameters between asthmatic children who had dyslipidemia and normal lipid levels. Asthmatic children who had high LDL-C had significantly higher expiratory phase respiratory resistance at 5 Hz (R_5), whole breath R_{20} and expiratory phase R_{20} evaluated by FOT than those with normal LDL-C ($p < 0.05$). There were no significant differences in weight, height, obesity status, and CRP level between children with high and normal LDL-C.

Conclusion: The prevalence of dyslipidemia in children with asthma is high. LDL-C is associated with more elevated respiratory resistance assessed by FOT in asthmatic children. Intervention lowering LDL-C may have a benefit on lung function in asthmatic children.

Introduction

The prevalence of dyslipidemia in children has increased in recent years due to the global epidemic of childhood obesity. Among children and adolescents in the United States, approximately 20% of children and adolescents aged 8 to 17 have abnormal lipid values of at least one or more lipid values[1]. Dyslipidemia, defined as abnormal lipid values of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) levels, or high-density lipoprotein cholesterol (HDL-C), or triglycerides (TG), or non-HDL-C.

There is recently conflicting evidence on the association between dyslipidemia and asthma[2, 3]. The prospective cohort study in children born to mothers with a doctor's diagnosis of asthma has demonstrated the increased airway obstruction in children with high LDL-C. Children with high HDL-C had better lung function and less bronchial responsiveness [2]. While a recent epidemiologic study in China found no associations between serum lipid levels and pediatric asthma [3]. Non-HDL-C and the TG/HDL-C ratio are practical addition lipid measures in evaluating dyslipidemia in children[4]. Non-HDL-C and TG/HDL-C ratios were proposed to be robust markers of cardiometabolic risk in children [5, 4]. A recent study has shown the higher prevalence of asthma in children with a higher TG/HDL-C ratio [6].

Assessment of pulmonary function test using the Forced Oscillation Technique (FOT) has been recently introduced. It is a simple, non-invasive technique performed during tidal breathing that is easy to apply and less cooperative with the patient. FOT can measure respiratory system resistance and lung reactance [7]. FOT measurement was suggested to be more sensitive than spirometry in detecting subtle changes in lung function in children [8]. There is no previous study evaluating the association of FOT parameters and dyslipidemia in asthmatic children before. We hypothesize that dyslipidemia asthmatic children may have peripheral airway dysfunction which can be detected by FOT but not from spirometry. The current study was aimed to evaluate the correlation between dyslipidemia and pulmonary function, assessed by spirometry and FOT in asthmatic children, and find the prevalence of dyslipidemia in pediatric asthma.

Methods

This cross-sectional study was conducted from January 2019 to December 2019. One hundred and forty-one asthmatic children (aged 5–18 years old) who had clinically controlled asthma in the past 4 weeks were enrolled. The diagnosis of asthma and the definition of clinically controlled asthma are based on GINA 2018. The exclusion criteria were children with other underlying chronic diseases (Diabetes Mellitus, chronic liver diseases, and chronic kidney diseases). Demographic data, atopic history, and medications were recorded. The Pediatric Asthma Control Test (PACT) and the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) were used to assess asthma control. Ethical approval was provided by the Human Rights and Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (ID: MURA2019/55). Written informed consent and informed written assent for children aged 7 years or older were obtained for all participants and their parents.

Anthropometric measurements were performed. Height and weight were measured. Body mass index (BMI) and BMI z-score were calculated. Obesity children have defined as BMI z-score > 2.00 standard deviations (S.D.) according to the World Health Organization (WHO) Report of the Commission on Ending Childhood Obesity [9].

Blood samples were collected from the subjects after fasting for at least 8 hours. Serum lipid profiles and C - reactive protein (CRP) were measured. Definition of pediatric dyslipidemia based on the above normative data of; TC $\geq$ 200 mg/dL, LDL-C $\geq$ 130 mg/dL, TG $\geq$ 100 mg/dL for aged 0–9 years and $\geq$ 130 mg/dL for aged 10–19 years, or non-HDL-C $\geq$ 145 mg/dL, or below normative level of HDL-C < 40 mg/dL. [9] Aeroallergen sensitization was evaluated by skin prick test to aeroallergen. Spirometry and forced oscillation technique (FOT) were performed.

Pulmonary Function Test Assessments

Because of the possible effects of forced expiratory maneuvers on the bronchial motor tonus, first FOT and then spirometry was performed. FOT, using MostGraph-02; Chest M.I., Co Ltd, Tokyo, Japan, was performed according to European Respiratory Society criteria [10]. FOT was performed during

spontaneous tidal breathing. During data acquisition, pressure and flow traces were graphically displayed in real-time. Measurements were accepted when the tracings showed uninterrupted breathing during data acquisition. Measurements were rejected if disturbed by coughing, breath-holding, swallowing, or vocalization. FOT parameters including respiratory resistance at 5 Hz (R_5), respiratory resistance at 20 Hz (R_{20}), and respiratory reactance at 5 Hz (X_5), area of reactance (ALX), and resonance frequency (F_{res}) were recorded. The spirometry, using Spiromaster PC-10; Chest M.I., Co Ltd, Tokyo, Japan, was then performed. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), % FEV_1 /FVC ratio, and forced expiratory flow at 25–75% of FVC (FEF_{25-75}) were measured.

Statistical analysis

Statistical analysis was performed using SPSS software, version 18. Differences between groups were examined using the Chi-square test, student *t*-test, or Mann-Whitney Test.

Results

One hundred forty-one asthmatic children were enrolled with the mean (S.D.) age of 11.87 (3.40) years. Eighty-eight children (62.4%) were males, 102 children (72.3%) were atopic asthma. Only 20 children (14.2%) were obese. The mean (S.D.) PACT and score PAQLQ were 23.88 (1.93), 6.60 (0.41), respectively. Sixty-four children (46.7%) met the criteria for dyslipidemia. Of 64 children with dyslipidemia, 14 children (21.9%) were obese, 42 children (65.6%) had high low-density lipoprotein cholesterol (LDL), 37 children (57.8%) had high total cholesterol, 34 children (53.1%) had high non-HDL-C, 23 children (35.9%) had high triglycerides, and 10 children (15.6%) had low high-density lipoprotein cholesterol (HDL). Baseline characteristics of the enrolled children were summarized in Table 1. There were no significant differences in the baseline characteristics between children with or without dyslipidemia (Table 2).

Table 1
Baseline characteristics of the participants

Patient features	N = 141
Age (years)	11.87 (3.40)
Gender: Male	88 (62.4)
Female	53 (37.6)
BW (kg)	47.00 (19.18)
Height (cm)	148.57 (17.07)
BMI (kg/m ²)	20.49 (5.15)
Obesity	20 (14.2)
Severity of asthma	103 (73)
• Mild	38 (37)
• Moderate to severe	
Atopic Asthma	102 (72.3)
Dyslipidemia	64 (45.4)
• High TC	37 (26.2)
• High LDL-C	42 (29.8)
• High Non-HDL-C	34 (24.1)
• High TG	23 (16.3)
• Low HDL-C	10 (7.1)
CRP (mg/dL)	0.65 (0.23,1.77)
PACT* (score)	23.88 (1.93)
PAQLQ** (score)	6.60 (0.41)
Data present as mean (S.D.), median (IQR) or n (%) PACT*: Pediatric Asthma Control Test, PAQLQ**: Pediatric Asthma quality of life questionnaire, C- Reactive protein (CRP), high-density lipoprotein cholesterol (HDL)	
low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG)	

Table 2
Comparison between asthmatic children with dyslipidemia and non-dyslipidemia group

Parameters	Dyslipidemia N = 64	Non-dyslipidemia N = 77	P-value
Age (year)	11.55 (3.37)	12.14 (3.37)	0.302
Body weight (kg)	47.87(21.52)	46.28(17.12)	0.626
Height (cm)	146.68(17.18)	150.14 (16.93)	0.231
BMI (kg/m ²)	21.17(5.78)	19.93(4.53)	0.156
Obesity	14 (21.9)	6 (7.8)	0.027
Atopic asthma	42 (65.6)	60 (77.9)	0.131
PACT (score)	23.89 (1.8)	23.88 (2.1)	0.779
PAQLQ (score)	6.61(0.36)	6.58(0.44)	0.791
CRP (mg/dL)	0.71 (0.28, 1.92)	0.45 (0.20, 1.48)	0.104
Spirometry			
• FEV ₁ (L)	1.99 (1.59,2.72)	2.20 (1.68,2.82)	0.312
• FVC(L)	2.36 (1.87,3.09)	2.59 (1.97,3.26)	0.298
• FEV ₁ /FVC (%)	86.79 (83.63,89.77)	87.02(81.37,91.03)	0.516
• FEF ₂₅₋₇₅ (L)	2.37 (1.78,3.05)	2.47 (1.86,3.13)	0.340
FOT parameters			
R ₅ (cmH ₂ O/L/s)	5.43 (4.02, 8.03)	5.13 (3.36, 7.32)	0.194
• Whole-breath	5.05 (3.78, 7.15)	4.76(3.21–6.71)	0.291
• Inspiratory	5.82(4.42, 8.75)	5.24 (3.55–7.86)	0.168
• Expiratory			
R ₂₀ (cmH ₂ O/L/s)	4.99 (3.86, 6.54)	4.55(3.43, 6.21)	0.203
• Whole-breath	4.66(3.72, 6.23)	4.36 (3.41,5.87)	0.157
• Inspiratory	5.30(3.96, 6.64)	4.73(3.55–6.45)	0.283
• Expiratory			

Parameters	Dyslipidemia N = 64	Non-dyslipidemia N = 77	P-value
X ₅ (cmH ₂ O/L/s)	-0.92 (-1.47 to -0.43)	-0.75 (-1.40 to -0.39)	0.490
• Whole-breath	-0.96 (-1.63 to -0.54)	-0.84 (-1.48 to -0.48)	0.777
• Inspiratory	-0.67 (-1.26 to -0.31)	-0.56 (-1.21 to -0.21)	0.452
• Expiratory			
Fres (Hz)	10.29(7.78, 15.88)	10.33(7.33– 14.54)	0.649
• Whole-breath	10.86(8.59, 14.93)	10.12(7.72, 14.59)	0.689
• Inspiratory	9.97(7.21,17.52)	9.53(6.30, 14.74)	0.435
• Expiratory			
ALX (cmH ₂ O/L/sXHz)	4.12 (1.61, 9.47)	3.52(1.28, 8.49)	0.483
• Whole-breath	4.37 (2.29, 10.09)	3.72(1.55, 8.45)	0.796
• Inspiratory	2.71(1.08, 8.81)	2.44(0.67, 8.22)	0.348
• Expiratory			

Comparison of spirometry and FOT parameters between dyslipidemia and non-dyslipidemia children

Spirometry and FOT parameters were compared between children with and without dyslipidemia. There were no significant differences in spirometry and FOT values between subjects with dyslipidemia and those with normal blood lipids (Table 2). Subgroup analysis in type of dyslipidemia, there were no significant differences in spirometry, and FOT parameters between children having high TC, TG, HDL-C, non-HDL-C, and those having normal value. Only children with high LDL-C had a significantly higher expiratory phase R₅, whole breath R₂₀, and expiratory phase R₂₀ than those with normal LDL-C (Table 3). There were no significant differences in the baseline characteristics between children with high LDL-C and normal LDL-C (Table 3).

Table 3
Comparison between asthmatic children with high LDL-C and normal LDL-C group

Parameters	High LDL-C N = 42	Normal LDL-C level N = 99	P-value
Age (year)	11.57 (3.40)	12.00 (3.40)	0.492
Body weight (kg)	47.65 (21.19)	46.72 (18.38)	0.796
Height (cm)	146.61(17.70)	149.41 (16.82)	0.378
BMI (kg/m ²)	21.02 (5.68)	20.26 (4.92)	0.423
Obesity	7 (16.7)	13 (13.1)	0.603
Atopic asthma	24 (57.1)	78(78.8%)	0.013
PACT (score)	23.97 (1.50)	23.84 (2.09)	0.779
PAQLQ (score)	6.69 (0.25)	6.55 (0.45)	0.07
CRP (mg/dL)	1.05 (0.29, 1.89)	0.59 (0.22, 1.58)	0.367
Spirometry			
• FEV ₁ (L)	1.99 (1.55,2.79)	.2.20 (1.68,2.82)	0.397
• FVC (L)	2.38 (1.74,3.13)	2.59 (1.97,3.26)	0.558
• FEV ₁ /FVC (%)	87.13 (,84.43,90.24)	87.02 (81.37,91.03)	0.489
• FEF ₂₅₋₇₅ (L)	2.43 (1.80,3.33)	2.47 (,1.86,3.13)	0.960
FOT parameters			
R ₅ (cmH ₂ O/L/s)	5.55 (4.45, 8.35)	5.13 (3.39, 7.18)	0.062
• Whole-breath	5.23 (3.93, 7.96)	4.76 (3.23, 6.66)	0.110
• Inspiratory	6.08 (4.58,8.95)	5.24 (3.54,7.84)	0.042
• Expiratory			
R ₂₀ (cmH ₂ O/L/s)	5.21 (4.02,6.85)	4.55(3.42, 6.14)	0.042
• Whole-breath	5.13 (3.74, 6.78)	4.44 (3.39, 5.78)	0.075
• Inspiratory	5.56 (4.12,7.03)	4.78 (3.53, 6.30)	0.026
• Expiratory			

Parameters	High LDL-C N = 42	Normal LDL-C level N = 99	P-value
X ₅ (cmH ₂ O/L/s)	-0.93 (-1.50 to -0.51)	-0.75(-1.34 to -0.37)	-
• Whole-breath	-0.94 (-1.86 to -0.58)	-0.84 (-1.49 to -0.48)	0.335
• Inspiratory	-0.69 (-1.21 to -0.39)	-0.56 (-1.24 to -0.22)	0.558
• Expiratory			0.397
Fres (Hz)	10.29 (8.27, 16.18)	10.33(7.40, 15.35)	0.543
• Whole-breath	10.86 (8.65,15.24)	10.55 (7.73, 14.67)	0.480
• Inspiratory	10.64 (7.50,17.41)	9.38 (6.56, 15.01)	0.430
• Expiratory			
ALX (cmH ₂ O/L/sXHz)	4.26 (2.03,9.82)	3.52(1.26, 8.81)	0.331
• Whole-breath	4.37 (2.44,10.77)	3.74 (1.55,8.46)	0.521
• Inspiratory	2.80 (1.34,7.73)	2.43 (0.71,8.55)	0.285
• Expiratory			

Comparison of spirometry and FOT parameters between obese and non-obese children

Obese asthmatic children had significantly lower % FEV₁/FVC, but there were no significant differences in all FOT parameters. Obese children also had a considerably higher CRP level than those having a normal weight. No significant differences in PACT and PAQLQ scores were observed. Interestingly, among blood lipids only the level of TG was significantly different between obese asthmatic children and non-obese asthmatic children (Table 4).

Table 4
Comparison between obese asthmatic children with and non-obese asthmatic children

Parameters	Obese N = 20	Non-obese N = 121	P-value
Age (year)	11.20 (3.82)	11.98 (3.33)	0.341
Body weight (kg)	63.83 (21.92)	44.22 (17.27)	< 0.001
Height (cm)	147.04 (16.94)	148.82 (17.15)	0.666
Atopic asthma	13 (65)	89(73.6)	0.429
PACT (score)	23.45 (1.79)	23.96 (1.95)	0.495
PAQLQ (score)	6.66 (0.26)	6.59 (0.42)	0.278
CRP (mg/dL)	1.85 (0.82,5.26)	0.42 (0.21,1.51)	< 0.001
Lipid Profiles			
• TC (mg/dL)	181.45 (34.42)	182.11 (30.52)	0.930
• LDL-C (mg/dL)	116.80 (39.42)	113.45 (29.41)	0.654
• Non-HDL-C (mg/dL)	128.00 (40.16)	124.27 (27.91)	0.606
• TG (mg/dL)	123.30 (61.96)	80.15 (31.48)	< 0.001
• HDL-C (mg/dL)	53.45(26.69)	57.83 (11.95)	0.223
• TG/HDL-C	2.73 (1.91)	1.47 (0.73)	< 0.001
Spirometry			
• FEV ₁ (L)	1.99 (1.55,2.79)	.2.20 (1.68,2.82)	0.738
• FVC (L)	2.38 (1.74,3.13)	2.59 (1.97,3.26)	0.421
• FEV ₁ /FVC (%)	87.13 (,84.43,90.24)	87.02 (81.37,91.03)	0.035
• FEF ₂₅₋₇₅ (L)	2.43 (1.80,3.33)	2.47 (,1.86,3.13)	0.673
FOT parameters			
R ₅ (cmH ₂ O/L/s)	5.64 (4.46,8.82)	5.30 (3.61,7.62)	0.375
• Whole-breath	5.34 (3.82,8.27)	4.80 (3.45,6.86)	0.396
• Inspiratory	6.11 (4.78,8.98)	5.54 (3.78,8.13)	0.420
• Expiratory			

Parameters	Obese N = 20	Non-obese N = 121	P-value
R ₂₀ (cmH ₂ O/L/s)	4.99 (4.27,6.73)	4.70 (3.58,,6.23)	0.543
• Whole-breath	4.88 (3.82,6.62)	4.53 (3.48,5.89)	0.577
• Inspiratory	5.10 (4.52,6.86)	4.94 (3.66, 6.58)	0.499
• Expiratory			
X ₅ (cmH ₂ O/L/s)	-1.05 (-1.76 to -0.61)	-0.76 (-1.39 to -0.38)	0.109
• Whole-breath	-1.26 (-1.96 to -0.72)	-0.82 (-1.58 to -0.48)	0.088
• Inspiratory	-0.83 (-1.48 to -0.47)	-0.59 (-1.16 to -0.22)	0.110
• Expiratory			
Fres (Hz)	11.95 (8.72,18.40)	10.19 (7.32,13.87)	0.097
• Whole-breath	11.75 (9.73,17.49)	10.20 (7.76,14.52)	0.111
• Inspiratory	12.12 (8.26,19.36)	9.39 (6.47,14.73)	0.096
• Expiratory			
ALX (cmH ₂ O/L/sXHz)	4.77 (2.19,12.62)	3.58 (1.32,8.41)	0.105
• Whole-breath	6.32 (2.78,13.70)	3.63 (1.58,8.69)	0.091
• Inspiratory	3.91 (1.59,11.31)	2.52 (0.71,7.19)	0.109
• Expiratory			

Discussion

We have demonstrated that asthmatic children with high LDL-C had a higher value of respiratory resistance at 5 Hz and 20 Hz evaluated by FOT independently from obesity status. There were no significant differences in spirometry parameters between asthmatic children with high or normal LDL-C. Our finding may support the previous reports on the association of LDL-C and pulmonary function in asthmatic patients. A recent study in children has shown an association of a high LDL-C level with childhood asthma and specific airway resistance[2]. A study in asthmatic adults has demonstrated the negative association of LDL-C subclass 3, a pro-inflammatory LDL-C, and FEV₁[11]. However, we did not evaluate for the LDL subclass in the present study. FOT measurement was suggested to be more sensitive than spirometry in detecting subtle lung function changes in children [8]. The difference in the finding of the association between LDL-C and spirometry parameters between adult and childhood asthma may explain from the fact that pro-inflammatory effect of LDL-C on lung functions changes in childhood asthma may be minimal to be seen by spirometry.

We have demonstrated that obese asthmatic children had a lower % FEV₁/FVC which may explain by the airway dysanapsis, the incongruence between the growth of the lung tissue and airway caliber [12]. Obesity has a significant effect on lung function in children and it could associate with airway dysanapsis independently of asthma [13, 14].

We did not found the differences in FOT parameters between obese asthmatic children and non-obese asthmatic children. Studies regarding the effect of obesity or BMI on FOT parameters showed conflicting results [15, 16]. A recent cohort study in children has shown no association between trajectories of BMI and FOT parameters [17]. In this study, we have found that almost half of asthmatic children (45.4%) had dyslipidemia which is much higher than the prevalence of dyslipidemia in Thai children (11.8 %) [18]. Interestingly, 50 out of 64 dyslipidemia children (78%) were not obese. Only 20 children (14.2%) among 141 children met the criteria for the diagnosis of obesity. This result would suggest that dyslipidemia and obesity has an impact on pulmonary function test on the different mechanism.

Our study has limitations in that we did not have a control group who are non-asthmatic and non-dyslipidemia. However, the association of dyslipidemia and the prevalence of asthma have already been confirmed in several meta-analyses and studies [19–21]. Additionally, there was only 4% of our enrolled children who had obesity but having normal lipid profile. The study sample size in the current study may not large enough to differentiate the effect of obesity and dyslipidemia on pulmonary function parameters in asthmatic children.

In conclusion, the prevalence of dyslipidemia in asthmatic children is higher than in normal children. The majority of dyslipidemia asthmatic children are not obese. Abnormal LDL-C but not for other blood lipids affect the value of R₅ and R₂₀ irrespectively from obesity status. Intervention for improvement of LDL-C level may have a benefit on lung function parameters in asthmatic children.

Abbreviations

Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), forced expiratory flow at 25-75% of FVC (FEF₂₅₋₇₅). Pediatric Asthma Control Test (PACT), Pediatric Asthma Quality of Life Questionnaire (PAQLQ), C- Reactive protein (CRP), high-density lipoprotein cholesterol (HDL)

low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), force oscillation technique (FOT), respiratory resistance at 5 Hz (R₅), respiratory resistance at 20 Hz (R₂₀), and respiratory reactance at 5 Hz (X₅), area of reactance (ALX), and resonance frequency (Fres)

Declarations

Clinical Trial Registration: TCTR20200305005 date of registration 03-04-2020 retrospectively registered

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Conflict of Interest: The authors have no conflict of interest to declare

Availability of data and material (data transparency): Yes the linked will be provided

Authors' contributions: PNC, W.K. and W.M. designed the study. PNC, W.J. and P.K. contributed to data collection. PNC, AS, and W.M. performed the statistical analysis and interpretation of the results. PNC, and W.M. draft the manuscript. W.M. edited the final manuscript. All authors read and approved the final manuscript.

Ethics approval: Ethical approval was provided by the Human Rights and Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (ID: MURA2019/55) (include appropriate approvals or waivers)

Consent to participate : Written informed consent and informed written assent for children aged seven years or older were obtained for all participants and their parents

Consent for publication: Written informed consent and informed written assent for children aged seven years or older were obtained for all participants and their parents

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