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Research Article

Dyslipidemia, insulin resistance and metabolic syndrome in children and adolescents with asthma

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Abstract

Objective: To investigate the interaction outcome of asthma and obesity on lipid profile, insulin resistance (IR)/sensitivity, and incidence of metabolic syndrome (MS) among study groups. **Methods:** This is case-control study performed on 168 children divided into four groups: asthmatic obese (AO), asthmatic non-obese (ANO), obese controls, and non-obese controls. Serum levels of fasting insulin, fasting glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were assayed. Calculation of homeostasis model assessment-estimated insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI value) and fasting glucose/insulin ratio (G/I) was done to access insulin resistance and sensitivity. **Results:** The AO group showed significantly higher TC levels, TC/HDL, LDL/HDL ratios, higher HOMA-IR, lower G/I ratio and QUICKI values than ANO group (P values = <0.001, 0.003, 0.042, <0.001, <0.001, and <0.001, respectively). Prevalence of MS among AO patients [9 cases (21.4%)] was significantly greater than in ANO group [2 cases (4.8%)], p value <0.001. LDL levels were higher in AO group than in obese controls, but the difference was statistically insignificant. Body mass index (P value = 0.001, OR = 1.17, 95% CI: 1.07-1.28) and dyslipidemia (P value= 0.002, OR = 4.38, 95% CI: 1.74-11.00) were found to be the independent variables that predict the existence of MS. **Conclusion:** Although dyslipidemia, IR, and MS were more prevalent among obese groups regardless of presence of asthma, highlighting the necessity for obesity control, LDL levels were highest in AO group as effect of obesity on LDL levels could be enhanced by asthma.

Keywords; Asthma, Obesity, Dyslipidemia, Insulin resistance, Metabolic syndrome.

Introduction

Both asthma and obesity are major diseases and their prevalence was increased over the recent decades. Pediatric obesity is linked to the worsening of asthma and reduced responsiveness to asthma treatments[1]. Obesity also increases the incidence of insulin resistance, hyperlipidemia, and metabolic syndrome. In addition, insulin resistance has been related to asthma and atopy in children. Epithelial injury and proliferation of airway smooth muscles are examples of the several mechanisms through which hyperinsulinemia and hyperglycemia can cause airway dysfunction and enhanced airway responsiveness[2]. The prevalence of hyperlipidemia in children was increased due to the rise in childhood obesity. As high cholesterol can cause pro-inflammatory

cellular responses and the release of inflammatory cytokines, so hyperlipidemia is considered to have a pro-inflammatory role that may link both obesity and asthma. Thus lowering serum cholesterol; triglycerides and weight control by calorie-restricted diet have been associated with improved clinical findings[3]. Moreover, according to numerous studies, a decrease in lung function and asthma-like symptoms are strongly linked to metabolic syndrome [4, 5]. Thus, the target of this study was to investigate the outcome of obesity and asthma on lipid profile, insulin resistance and to determine the incidence of metabolic syndrome in asthmatic children.

Methods

Ethical considerations

The research ethics committee of Cairo University's Faculty of Medicine has approved the study (approval number: MS-59-2020; date: 29/4/2020). Informed consent was taken from the parents before the collection of clinical data and samples.

Study design

This case-control study enrolled 168 children aged between 7 and 17 years. They were recruited from Pediatric Allergy and Chest Clinic, the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU), and the General Outpatient Clinic at Cairo University Hospitals from August 2020 to August 2021. According to the presence of asthma and obesity, participants were divided into four groups as follows: asthmatic obese patients (AO group), asthmatic non-obese patients (ANO group), obese controls, and non-obese controls.

Data collection, eligibility

The patients were diagnosed and categorized based on Global Initiative for Asthma (GINA 2018) criteria [6]. Patients who had taken oral corticosteroids for at least 10 days before the testing day and those who had upper or lower respiratory infections within the last 4 weeks were excluded from the study. Using the formula weight (kg)/height (m) squared, body mass index (BMI) was determined [7]. BMI above the 95th percentile for both chronological age and sex was used for defining obesity [7]. A point halfway between the iliac crest and the costal border was chosen to measure the waist circumference horizontally. Blood pressure was measured after resting at least 5 min on the right arm, by the use of a mercurial sphygmo-manometer (Baumanometer; Baum, Copiague, NY, USA)[8]. The quantitative insulin sensitivity check index (QUICKI value) derived from the following equation: 1/log (fasting insulin) +log (fasting glucose) and fasting glucose/insulin ratio (G/I) were used in our study to assess insulin sensitivity [9]. Insulin resistance was detected by homeostasis model assessment-estimated insulin resistance [HOMA-IR] which is computed by the following formula: fasting insulin*fasting glucose)/22.5 (normal values: < 2 and < 2.6 in children and pubertal children, respectively) [10]. Metabolic syndrome was defined by 3 of the following: fasting glucose level >110**,** waist circumference ≥75 percentile**,** fasting triglyceride ≥100 mg/dl, HDL ≤ 50 mg/dl, and systolic blood pressure ≥ 90 percentile [11].

Analysis

After a fast, blood samples were taken, then were refrigerated, and were transported then measured. Serum fasting blood glucose was measured by the hexokinase method, while HDL, triglycerides, and total cholesterol concentrations were assessed using the enzymatic colorimetric method on the Cobas 6000 c501 analyzer (Roche Diagnostics, Germany)[12]. Using Friedewald's equation: TC-HDL-TG/5, LDL was calculated if TG <400 mg/dl. [13]. By dividing total cholesterol and LDL values by HDL values, we obtained TC/HDL and LDL/HDL ratios, respect-tively. Fasting insulin was assessed by a commercially available Human Insulin ELISA (Enzyme-Linked Immunosorbent assay) kit (Sinogeneclon Biotech Co., Ltd, China) and by following the manufa-cturer's protocol (normal values: < 10 and < 13 µIU/mL in children and pubertal children, respectively**)** [10, 14].

Statistical analysis

SPSS (Statistical Package for Social Science) version 21 was used to analyze the

data. Quantitative data were designated as mean and standard deviation (if parametric) or median and interquartile range (if non-parametric). Qualitative data were designated as frequencies and percentages. Parametric, non-parametric, and regression analyses were done for data accordingly. P values < 0.05 are considered statistically significant.

Results

Characteristics of included participants

This research included 168 children, 84 asthmatic (obese and non-obese), and 84 non-asthmatic (obese and non-obese) patients. No statistically significant variance was detected between asthmatics and non-asthmatics regarding age. There was male predominance in the asthmatic group as 54 (64.3%) patients were males. Asthmatic patients (N=84) presented with cough [81 cases (96.4%)] and difficulty breathing [3 cases (3.6%)]. Also, most of them [83 cases (98.8%)] presented with a positive family history of asthma (Table 1).

Table (1): **Demographic characteristics of asthmatic and non-asthmatic children and adolescents (N= 168)**

		Asthmatic group (obese and non-obese) N=84	Non-asthmatic group (obese and non-obese) N=84	P-value
Age (years), median (range)		11.0 (7.0-16.0)	11.0 (7.0-17.0)	0.57
Sex, N (%)	F	30 (35.7%)	50 (59.5%)	0.002*
	M	54 (64.3%)	34 (40.5%)	
Presenting asthma, N (%)	Cough	81 (96.4%)	0 (0.0%)	<0.001**
	Difficulty of Breathing	3 (3.6%)	0 (0.0%)	
Family history, N (%)	negative	1 (1.2%)	84 (100.0%)	<0.001**
	Positive	83 (98.8%)	0 (0.0%)	

* P < 0.05
** P < 0.001

Comparison between AO and ANO groups regarding lipid profile, insulin resistance, and prevalence of MS

In comparison with the ANO group, the AO group had significantly greater BMI and higher waist circumference with P value <0.001. Also, AO group showed significantly greater systolic and diastolic blood pressure with P values <0.001 and 0.002 respectively as presented in Table (2).

Moreover, it was observed that the AO group displayed significantly greater fasting insulin and insulin resistance (HOMA-IR) with a P value <0.001, together with lower insulin sensitivity (G/I ratio and QUICKI value) with P value <0.001 as shown in Table (2)

In addition, AO group showed higher total cholesterol levels, TC/HDL, and LDL/ HDL ratios than the ANO group (P value =<0.001, 0.003, and 0.042 respectively). Although higher triglyceride and LDL levels, besides lower HDL levels, were detected in the AO group in comparison with the ANO group, the difference was statistically non-significant. Also, we noted the higher prevalence of MS among the AO group [9 cases (21.4%)] than the ANO group [2 cases (4.8%)] with a P value < 0.001 (Table 2).

Table (2): Clinical characteristics and laboratory findings among asthmatic obese (AO) and asthmatic non-obese (ANO) groups.

	Asthmatic obese (AO) N=42	Asthmatic non obese (ANO) N=42	P value
BMI (kg/m^2)†	31.20 (25.60-39.38)	17.70 (13.40-26.40)	<0.001**
Waist circumference (cm)†	94 (78-116)	63 (52-76)	<0.001**
Systolic BP (mmHg)†	103 (90-127)	100 (90-120)	<0.001**
Diastolic BP (mmHg)†	60 (60-85)	60 (54-80)	0.002*
G/I ratio†	3.90 (1.50-12.00)	8.50 (3.00-59.40)	<0.001*
QUICKI value†	0.30 (0.27-0.36)	0.34 (0.28-0.44)	<0.001*
HOMA-IR†	5.27 (1.45-12.07)	2.24 (0.44-8.80)	<0.001*
Fasting Insulin (µIU/mL)†	23.0 (7.1-56.2)	10.2 (1.8-34.2)	<0.001*
Fasting Glucose, (mg/dl)†	89 (70-110)	91 (75-107)	0.706
Total cholesterol (mg/dl)†	193 (111-243)	160 (129-237)	<0.001*
Triglycerides (mg/dl)†	84 (47-301)	77 (21-243)	0.06
HDL (mg/dl)†	48 (23-111)	52 (35-85)	0.861
LDL (mg/dl)†	110 (31-152)	94 (62-143)	0.087
TC/HDL†	4.00 (1.07-8.35)	3.29 (1.90-5.60)	0.003*
LDL /HDL†	2.35 (0.60-6.20)	1.74 (0.30-3.97)	0.042*
Presence of MS‡	9 (21.4%)	2 (4.8%)	<0.001*

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
† Data showed as Median (range), ‡ Data showed as number (%).
* P < 0.05, ** P < 0.001.

Comparison between AO group and obese controls regarding lipid profile, insulin resistance, and incidence of MS

In our study, LDL levels tended to be greater in the AO group in comparison with obese controls but the difference was statistically insignificant with a P value of 0.087. Also, it was found that obese controls showed significantly higher values than the AO group regarding systolic blood pressure (P value = 0.003). Additionally, obese controls presented with significantly higher fasting blood glucose levels, insulin resistance (HOMA-IR), TC/HDL, and LDL/HDL ratios (P value= <0.001, 0.018, 0.005, and 0.01 respectively). Additionally, HDL levels were significantly lower in the obese group when compared with the AO group (Table 3).

Table 3: Clinical characteristics and laboratory findings among asthmatic obese (AO) and obese controls.

	Asthmatic obese (AO) N=42	Obese controls N=42	P-value
BMI (kg/m^2)†	31.20 (25.60-39.38)	32.05 (26.60-48.80)	0.129
Waist circumference (cm)†	94 (78-116)	91 (82-120)	0.111
Systolic BP (mmHg)†	103 (90-127)	100 (90-120)	0.003*
Diastolic BP (mmHg)†	60 (60-85)	60 (55-80)	0.07
G/I ratio†	3.90 (1.50-12.00)	3.85 (1.30-18.30)	0.763
QUICKI value†	0.30 (0.27-0.36)	0.29 (0.25-0.35)	0.5
HOMA-IR†	5.27 (1.45-12.07)	6.10 (1.60-23.30)	0.018*
Fasting Insulin (µIU/mL)†	23.0 (7.1-56.2)	24.5 (6.0-80.7)	0.107
Fasting Glucose, (mg/dl)†	89 (70-110)	97 (74-145)	<0.001**
Total cholesterol (mg/dl)†	193 (111-243)	196 (114-230)	0.999
Triglycerides (mg/dl)†	84 (47-301)	101 (36-256)	0.06
HDL(mg/dl)†	48 (23-111)†	42 (23-66)†	<0.001**
LDL (mg/dl)†	110 (31-152)	107 (34-180)	0.087
TC/HDL†	4.00 (1.07-8.35)	4.74 (1.70-7.70)	0.005*
LDL/HDL†	2.35 (0.60-6.20)	2.86 (0.70-5.60)	0.01*
Presence of MS‡	9 (21.4%)	21 (50.0%)	<0.001**

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
† Data showed as Median (range), ‡ Data showed as number (%).
* P < 0.05, ** P < 0.001.

Comparison between ANO group and non-obese controls regarding lipid profile, insulin resistance, and MS

It was found that there was an insignificant difference between the ANO group and non-obese controls regarding any clinical or laboratory finding (Table 4).

Table 4: Clinical characteristics and laboratory findings among asthmatic obese (AO) and asthmatic non obese (ANO) groups.

	Asthmatic non obese(ANO) N=42	Non obese controls N=42	P-value
BMI (kg/m^2)†	17.70 (13.40-24.80)	18.80 (13.00-24.58)	0.129
Waist circumference (cm)†	63 (52-76)	66 (51-75)	0.189
Systolic BP (mmHg)†	100 (90-120)	105 (90-115)	0.15
Diastolic BP (mmHg)†	60 (54-80)	60 (50-70)	0.545
G/I ratio†	8.50 (3.00-59.40)	10.95 (5.00-37.90)	0.283
QUICKI value†	0.34 (0.28-0.44)	0.35 (0.31-0.47)	0.09
HOMA-IR†	2.24 (0.44-8.80)	1.50 (0.34-4.00)	0.075
Fasting Insulin (µIU/mL)†	10.2 (1.8-34.2)	7.9 (1.9-17.0)	0.059
Fasting Glucose, (mg/dl)†	91 (75-107)	89 (68-120)	0.221
Total cholesterol (mg/dl)†	160 (129-237)	170 (111-230)	0.997
Triglycerides (mg/dl)†	77 (21-243)	83 (33-271)	0.06
HDL (mg/dl)†	52 (35-85)	46 (27-70)	0.083
LDL (mg/dl)†	94 (62-143)	106 (56-167)	0.087
TC/HDL†	3.29 (1.90-5.60)	3.68 (2.10-7.00)	0.213
LDL/HDL†	1.74 (0.30-3.97)	2.39 (0.56-4.37)	0.219
Presence of MS‡	2 (4.8%)*	2 (4.8%)	0.271

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
† Data showed as Median (range), ‡ Data showed as number (%).
* P < 0.05, ** P value < 0.001

Assessment of MS predictors

In the present study, analysis by logistic regression was carried out to find out MS predictors. BMI (P value = 0.001, OR = 1.17, 95% CI: 1.07-1.28) and dyslipidemia (P value = 0.002, OR = 4.38, 95% CI: 1.74-11.00) were found to be the independent variables that predict the existence of MS (Table 5).

Table 5: Multivariate logistic regression of potential predictors of MS

Covariates	OR	95% C.I.	P-value
Age , years	0.93	0.79-1.11	0.446
Sex (Female vs male)	0.70	0.28-1.76	0.447
BMI, kg/m^2	1.17	1.07-1.28	0.001**
G/I ratio	1.01	0.91-1.12	0.851
HOMA-IR	1.09	0.92-1.30	0.314
Fasting glucose level, mg/dl	0.99	0.95-1.04	0.725
Dyslipidemia	4.38	1.74-11.00	0.002*

OR: Odds ratio, 95% CI: 95% confidence interval, BMI: body mass index.
* P < 0.05, ** P < 0.001

Discussion

One of the most prevalent chronic diseases worldwide is asthma. A Large percentage of patients suffer from uncontrolled disease despite the availability of therapies, leading to long-term disability and impairment. Obesity is one of the factors that prevent control of symptoms and response to treatment [15].

This study revealed that the AO group showed a more disturbed lipid profile, more insulin resistance, and a higher incidence of MS than the ANO group. Total cholesterol, TC/HDL, and LDL/HDL were significantly greater in the AO group in comparison with the ANO group with P value of 0.001. In addition, LDL and TG levels in the AO group were greater than the ANO group but the difference was statistically insignificant. Our findings were similar to a study done by Chen et al.,[3] as they noted that both LDL and total cholesterol levels were significantly higher in overweight/obese asthmatic males compared to lean asthmatic males (P value 0.05 and <0.001 respectively). They focused on the adoption of preventative measures to reduce hyperlipidemia in asthmatic obese pediatrics[3]. Also, previous reports have found a link between dyslipidemia (increased total cholesterol, LDL) and development of asthma[15,16]. Possible explanations for this association include augmentation of airway inflammation by dietary cholesterol, enhancement of inflammation through hypercholesterolemia, a shift to T-helper-2 (Th2) reaction in cases with marked hypercholesterolemia and common genetic variables[17-18]. In addition, studies have revealed that lipid-lowering drugs as statins have decreased eosinophilic inflammation in the airways[19]. Moreover, a rich-fat diet has been linked to a considerable rise in triglycerides, total cholesterol, and nitric oxide; which could be a factor in the initiation of chronic inflammatory diseases of the lungs and airways [20].

In addition, the AO group showed significantly lower insulin sensitivity denoted by QUICKI value and G/I ratio in addition to higher insulin resistance denoted by HOMA-IR when compared with the ANO group with P value < 0.001. Likewise, DEL-RIO-NAVARRO et al., found that HOMA-IR is higher in AO [5.10 (4.5–5.8)] than in ANO [1.52 (1.1–1.9)] with a P value <0.05 [21]. Forno et al., reported that decreased insulin sensitivity (expressed as QUICKI) or insulin resistance (expressed as HOMA-IR) is linked to diminished lung function, especially in overweight or obese adolescents[5]. Also, other studies that included adult patients showed that participants with insulin resistance tend to have a significantly higher prevalence of restrictive pulmonary deficit [22-23].

Moreover, our research revealed that MS was more prevalent among AO in comparison with the ANO group with P value < 0.001. Forno et al., showed that in people who were overweight or obese, metabolic syndrome was significantly linked with reduced lung function tests whereas there was no significant association in patients who were normal weight [5].

In our study, LDL levels tended to be greater in the AO group in comparison with obese controls, but the difference was statistically insignificant P value 0.087. Similarly, Chen et al., reported that asthmatic obese patients had significantly higher LDL levels than obese non-asthmatics (P value = <0.001) indicating that obesity-related low-grade inflammation augmented the inflammation caused by asthma (synergism) towards hyperlipidemia. Probable explanations of this synergistic effect include the combination of a chronic inflammatory state caused by hypercholesterolemia in both obesity and asthma besides induced systemic and airway inflammation by dietary cholesterol[3].

On the other hand, the present study revealed that obese controls showed significantly higher values of fasting glucose, HOMA-IR, TC/HDL, LDL/HDL, lower HDL values, and more prevalence of MS than the AO group. Similarly, Del-Rio-Navarro et al.,[22] revealed that obese non-asthmatics had a significantly greater frequency of impaired fasting glucose than obese asthmatics (14.7% vs 3.7% respectively, P value <0.05). Alternatively, Al-Shawwa et al.,[24] stated that obese asthmatic adolescents showed more IR than obese non-asthmatic adolescents. The greater levels of fasting glucose and HOMA-IR in obese controls than the AO group could be explained by the positive influence of elevated adiponectin on insulin sensitivity in asthmatics[21]. A high level of adiponectin is commonly detected in asthmatics when compared with normal control[25].

In this study, no significant variance was detected among ANO and non-obese controls regarding lipid profiles, insulin resistance, or prevalence of MS. Likewise, Chen et al. reported that no significant difference was detected regarding the prevalence of MS in the ANO group [2 cases (4.8%)] and non-obese controls [2 cases (4.8%)] with P value 0.27[3]. Stanley et al., reported that the disease load of asthma tended to be normal in women who were normal in weight rather than women who were obese or markedly obese suggesting that the occurrence of asthma might represent a turning point along the way of progression of chronic obesity[26].

Numerous studies have investigated the relation between asthma and obesity. Adipokines such as interferon, interleukin-6, tumor necrosis factor-alpha, and leptin are overproduced from fat deposition in ectopic places in obese people and may have a role in airway inflammation and the onset of asthma[27-30]. Also, it has been demonstrated that dyslipidemia induced by fat-rich diet alters immune cell trafficking, leading to acute lung damage, asthma, and pneumonia. Additionally, medications that target cholesterol like statins have demonstrated effectiveness in the management of some respiratory conditions, including asthma[31]. Moreover, a study has shown that weight loss interventions reduced asthma exacerbations and improved the quality of life of patients[32].

Limitations

Due to a lack of financing, only a small number of people were enrolled in this study.

Conclusions

Although dyslipidemia, IR, and MS were more prevalent among obese groups regardless of presence of asthma, highlighting the necessity for obesity control, LDL levels were highest in AO group as effect of obesity on LDL levels could be enhanced by asthma.

Abbreviations

AO: asthmatic obese
ANO: asthmatic non-obese

BMI: body mass index
DEMPU: Diabetes Endocrine and Metabolism Pediatric Unit
ELISA: Enzyme-Linked Immunosorbent assay
G/I ratio: glucose/insulin ratio
QUICKI: quantitative insulin sensitivity check index
HDL: high density lipoprotein
HOMA-IR: homeostasis model assessment -estimated insulin resistance
LDL: low density lipoprotein
MS: metabolic syndrome
SPSS: Statistical Package of Social Science
Th2: T-helper-2

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