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Original article

METABOLIC SYNDROME IN CHILDREN WITH ASTHMA

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Abstract

The association between asthma and obesity is well known, with several underlying mechanisms. The aim of the study was to evaluate whether metabolic syndrome may be other underlying mechanism related to this association. The study included 112 children (73 boys and 39 girls, mean age 11.1 ± 2.4); out of them 41were overweight, 38 had asthma and a normal body mass index (BMI), and 33 were overweight asthmatics. Serum leptin, adiponectin, glycemia, insulinemia, lipid profile levels (cholesterol and triglycerides) and the homeostasis model assessment (HOMA) index were analyzed as parameters of metabolic syndrome. BMI, waist circumferences (WC), and waist to hips ratio (WHR) were measured as parameters of obesity. Levels of BMI, WC, WHR, HOMA-IR (insulin resistance), and HOMA-AD (adiponectin) were significantly higher in overweight group ($p<0.001$) and overweight with asthma group compared to asthma ($p<0.05$). Asthma group had significantly lower level of leptin ($p=0.00001$) and significantly higher level of glycemia ($p=0.0001$) compared to overweight group and also compared to overweight with asthma group ($p=0.00001$ and $p=0.001$, respectively). A strong positive correlation was observed between leptin, BMI and WC in all three groups as well as between insulinemia and BMI in overweight ($r=0.384$) and asthma group ($r=0.603$). A significant strong correlation was also found between HOMA-IR and HOMA-AD with BMI in asthma group for consequently $r=620$ and $r=531$.

Undoubtedly, there is an association with some parameters of the metabolic syndrome in childhood asthma. However, obesity has been shown to be a major driver of metabolic changes.

Keywords: asthma, body mass index, children, HOMA index, metabolic syndrome, obesity, overweight

Introduction

Asthma is one of the most common chronic diseases in children. According to the International Study of Asthma and Allergy in Childhood - ISAAC, prevalence is different between the countries, and has been gradually increasing in last decades. This trend continues in economically undeveloped and developing countries, and it has reached a plateau in western countries[1]. Concomitantly the obesity rates have reached epidemic proportion with more than 1.9 billion overweight adults, and over 650 million obese of them, worldwide. In 2016, 39% of adults aged 18 years and over (39% of men and 40% of women) were overweight[2]. Obesity is also a problem in children and the prevalence has been increasing at an alarming rate. Globally, in 2020, the number of overweight children under the age of 5 was estimated at more than 39 million, as well as 340 million children and adolescents aged 5 to 19 years.[2] In the last two decades, the Republic of North Macedonia as a low-income country has been following the trend of prevalence of both, asthma and obesity in children[3-5]. These two chronic diseases are undoubtedly associated. Obesity increases the risk of asthma in both, adults and children, but it also makes burdensome the treatment and control of the disease. Their association seems to be complex and is still debating. Many factors are involved such as mechanical effects of abdominal fat and abnormal ventilation, genetics, hormonal influences, systemic inflammation in both chronic inflammatory conditions and comorbidities such as gastroesophageal reflux[6]. Numerous studies in adults indicate metabolic changes specific for obesity and define metabolic syndrome, however, similar studies in children are insufficient considering the number of involved subjects, quality of analyses and length of follow-up. Obesity is associated with hyperinsulinemia, insulin-resistance and dyslipidemia as parameters of metabolic syndrome, which underline cardiovascular disorders and diabetes mellitus (DM). Although the definition of metabolic syndrome in children is difficult, hyperinsulinemia and insulin-resistance, defined as a condition in which higher than normal insulin concentrations are needed to achieve normal metabolic responses, play a central role in metabolic disorders in overweight children. Leptin and adiponectin as hormones produced in adipose tissue and major regulators of insulin sensitivity and glucose and lipids metabolism also are considered reliable indicators of metabolic syndrome in children[7,8].

Is metabolic syndrome also associated with childhood asthma?

Dyslipidemia and hyperinsulinemia can influence both, innate and adaptive defense mechanisms in the respiratory tract, thus promoting the expression of multiple proinflammatory cytokines and chemokines, reduced endogenous anti-inflammatory activity and increased innate airway hyperresponsiveness (AHR)[9]. AHR and variably and/or reversible bronchoconstriction are major features in asthma, and it is conceivable that early life abnormalities in lipid or glucose metabolism may contribute to the pathogenesis of asthma in childhood[10].

Leptin stimulates T-cell proliferation and activation, monocyte redirection, and angiogenesis through expression of leptin receptors. It supports inflammation in the lungs that may correlate with the inflammatory cascade and T-cell function in asthma. In contrast, adiponectin is decreased in obesity and its decreased anti-inflammatory effects may be the underlying link between obesity and asthma. Moreover, adiponectin inhibits the proliferation of cultured vascular smooth muscle cells and the decrease in adiponectin in obese individuals could contribute to increased smooth muscle mass in asthmatic individuals[11].

The aim of the study was to evaluate the metabolic syndrome and its parameters (glucose, insulin, triglycerides, cholesterol, leptin, adiponectin and HOMA index) in children with asthma,

and to analyze correlations of these parameters with parameters of obesity - BMI, WC, and WHR.

Material and methods

A prospective study with 112 children aged 7-17 years was performed at the University Children's Clinic, Skopje, Republic of North Macedonia, during 2019. Ethical approval was obtained by the Ethics Committee at the Faculty of Medicine in Skopje and written informed consent for inclusion in the study was signed by the parents.

Patients were divided in three groups. The overweight group consisted of 41 overweight children, the asthma group consisted of 38 children with asthma and normal BMI, and the overweight + asthma group consisted of 33 overweight children with asthma.

The diagnosis of asthma was assessed by the Global Initiative for Asthma (GINA) and International Consensus on (ICON) Pediatric Asthma guidelines[12,13].

BMI was calculated according to the standard formula, defining overweight for those over 25 kg/m^2 and obesity for those above 30 kg/m^2 at 18 years of age[14]. For abdominal obesity assessment, WC was measured in centimeters between the lower border of the ribcage and midline of the iliac crest; HC was measured in the centimeters from the widest point of the hips, and then WHR was calculated[15]. WHO reference values by sex and age were used, defining abdominal obesity as over the 90th percentile[16].

In each child, leptin and adiponectin were determined by Luminex technology. All standards and recommendations were followed in accordance with the manufacturer's instructions [Immuno-Biological Laboratories (IBL) (Hamburg, Germany)]. Reference values for leptin by sex and age in ng/ml were used[17]. Insulin levels were measured with the immunoturbidimetry method, by automated Vidas Biomerieux immunoassay analyzer (IU/ml). Fasting blood glucose and lipid profile (cholesterol and triglycerides) were analyzed by Architect c4000 (Abbott, USA) (mg/L).

The homeostasis model assessment-insulin resistance (HOMA-IR) and the homeostasis model assessment - adiponectin (HOMA-AD) indices were calculated using standard formulas[18,19]. HOMA-IR = [insulinemia (U/l) × glycemia (mmol/l)]/22.5 and HOMA-AD = [insulinemia (U/l) × glycemia (mmol/l)]/Adiponectinemia (g/ml)[3].

The data was statistically analyzed with the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). Quantitative series were present as mean, median and standard deviation. The Shapiro-Wilk W test was used to determine the normality of frequency distribution of investigated variables. The Difference test was used to compare the proportions. Pearson's Chi square test was used to determine the association between certain variables in the groups of subjects. Two and more independent numerical variables with non-normal distribution of frequencies were compared with the Mann Whitney U test and Kruskal-Wallis H test. Pearson's correlation was used as a measure of the strength and direction of association that exists between two numerical variables with normal distribution of frequencies. A two-sided analysis with a significance level of $p<0.05$ was used to determine the statistical significance.

Results

We studied a sample of 112 children, aged 7-17 years, divided into three groups as overweight - 41 (36.6%), with asthma - 38 (33.9%), and overweight with asthma - 33 (29.5%). There was no significant age difference between the groups (p=0.4565). There was no significant association between the group to which children belonged and sex (p=0.7162), premature birth

(p=0.7162), and breast feeding (p=0.5371). No percentage differences were found between the groups related to birth weight ≥3.500 gr, although the proportion of patients with this birth weight in overweight group as well as in overweight with asthma group was higher compared to asthma group. We found the family history of DM to be significantly more associated with overweight with asthma compared to asthma group [OR=3.5294 (1.25-9.95) 95% CI]. All other groups combination, for p>0.05, showed no significant association with DM in the family. The number of passive smokers in the family was not significantly different between the groups (p=0.0994).

Analyses between groups and the parameters of obesity – BMI, abdominal obesity – WC, WHR and metabolic syndrome – glycemia, insulinemia, triglycerides, cholesterol, leptin and adiponectin, are shown in Table 1.

Table 1. Analyses of the groups and parameters of obesity and metabolic syndrome

	Groups	Mean	Standard Deviation	Percentiles			P
				25th	50th (Median)	75th	
BMI	Overweight	30.39	5.64	26.7	29.1	32.3	$X^2(2)=68.502$; p=0.00001*
	Asthma	19.09	2.88	16.8	19.4	20.8	O/A:Z=-7.438; p=0.00001*
	Overweight + asthma	29.22	5.34	25.8	28.0	32.3	O/OA: Z=-0.788; p=0.4301 A/OA: Z=-6.744; p=0.00001*
WC	Overweight	98.15	13.78	90.5	99	103.0	$X^2(2)=49.438$; p=0.00001*
	Asthma	69.03	12.52	62.0	69	76.0	O/A: Z=-6.328; p=0.0001*
	Overweight + asthma	92.73	11.63	87.0	92.0	100.0	O/OA: Z=-1.482; p=0.138 A/OA: Z=-5.713; p=0.0001*
WHR	Overweight	0.94	0.11	0.9	0.9	1.0	$X^2(2)=18.351$; p=0.0001*
	Asthma	0.83	0.07	0.8	0.8	0.9	O/A: Z=-4.284; p=0.0001*
	Overweight + asthma	0.91	0.11	0.8	0.9	0.9	O/OA: Z=-1.869; p=0.062 A/OA: Z=-2.634; p=0.008*
Glycemia mmol/L	Overweight	4.69	0.75	3.4	7.1	4.3	$X^2(2)=8.7183$; p=0.0128*
	Asthma	4.90	0.44	4.0	5.8	4.6	O/A: Z=-1.654; p=0.098
	Overweight + asthma	4.51	0.62	3.2	5.9	4.1	O/OA: Z=-1.327; p=0.185 A/OA: Z=-2.969; p=0.003*
Insulin IU/ml	Overweight	20.4	18.86	2.0	100.0	10.5	$X^2(2)=18.5779$; p=0.0001*
	Asthma	12.70	18.73	3.1	119.0	6.4	O/A: Z=-3.955; p=0.0001*
	Overweight + asthma	18.94	16.04	7.2	78.7	8.8	O/OA: Z=-1.158;

							p=0.247 A/OA: Z=-3.246; p=0.001*
Triglicerid mmol/L	Overweight	1.33	0.67	0.6	3.6	0.9	
	Asthma	1.05	0.51	0.3	2.5	0.7	$X^2(2)=5.1711$; p=0.0754
	Overweight + asthma	1.38	0.79	0.3	4.0	0.8	
Cholesterolmmol/L	Overweight	4.13	0.97	0.8	5.9	3.6	$X^2(2)=6.5718$; p=0.0374* O/A: Z=-2.208; p=0.027*
	Asthma	3.66	0.85	1.2	5.5	3.1	
	Overweight + asthma	4.15	0.99	1.3	6.8	3.7	O/OA: Z=-0.033; p=0.974 A/OA: Z=-2.214; p=0.027*
Adiponecti n g/ml	Overweight	4.56	1.55	1.1	9.3	3.8	
	Asthma	5.56	2.67	1.0	14.9	3.6	$X^2(2)=3.6558$; p=0.1607
	Overweight + asthma	5.20	2.25	1.2	10.1	3.9	
Leptin ng/ml	Overweight	30.62	21.56	1.07	90.4	15.3	$X^2(2)=6.5718$; p=0.0374* O/A: Z=-6.260; p=0.00001*
	Asthma	9.19	16.17	1.20	101.0	2.3	
	Overweight + asthma	31.09	20.32	1.49	98.4	20.1	O/OA: Z=-0.364; p=0.718 A/OA: Z=-6.099; p=0.00001*
HOMA-IR	Overweight	4.32	4.23	2.14	2.95	4.46	$X^2(2)=15.041$; p=0.0005* O/A: Z=-3.689; p=0.0002*
	Asthma	2.74	3.77	1.30	1.73	2.71	
	Overweight + asthma	3.83	3.39	1.80	1.28	5.44	O/OA: Z=1.223; p=0.221 A/OA: Z=-2.640; p=0.0083*
HOMA-AD	Overweight	26.69	32.71	10.33	14.39	29.15	$X^2(2)=13.473$; p=0.0012* O/A: Z=3.542; p=0.0004*
	Asthma	15,51	23,26	4,74	6,12	13,15	
	Overweight + asthma	24,79	31,74	6,29	9,89	21,05	O/OA: Z=1.484; p=0.138 A/OA: Z=-2.255; p=0.0261*

Asthma group (A): N=41; Overweight group (O): N=38; Overweight + asthma group (OA): N=33
BMI=body mass index; WC=waist circumference; WHR=waist to hip ratio; The homeostasis model assessment-insulin resistance (HOMA-IR); The HOMA-adiponectin (HOMA-AD); Z=Mann-Whitney U test; X2=Kruskal-Wallis H test; *significant for p<0,05

Levels of BMI, WC, WHR, HOMA-IR, and HOMA-AD were significantly higher in the overweight group (p<0.001) as well as overweight with asthma group compared to asthma (p<0.05), but with no significant differences between the overweight group compared to overweight with asthma group (Table 1). Asthma group had a significantly lower level of leptin compared to overweight (p=0.00001) and overweight with asthma group (p=0.00001). Asthma group had a significantly higher level of glycemia compared to overweight as well as with

overweight to asthma group for p=0.0001 and p=0.001, respectively. We found a significantly higher level of insulinemia, as another parameter of metabolic syndrome, in overweight group compared to other two groups. There was no significant differences between the three groups related to triglycerides (p=0.0754) and adiponectin (p=0.1607) as parameters of central obesity.

Correlation between parameters of obesity and parameters of metabolic syndrome adjusted to sex and age are shown in Table 2.

Table 2. Correlation between parameters of obesity and parameters of metabolic syndrome

Parameters	Partial correlations – age and sex adjusted		
	Overweight (N = 41)	Asthma (N = 38)	Overweight + asthma (N = 33)
Glycemia			
BMI	r (37)=0.074; p=0.653	r (34)=0.035; p=0.838	r (29)=0.313; p=0.086
WC	r (36)=0.176; p=0.290	r (26)=0.139; p=0.480	r (29)=0.462; p=0.009*
WHR	r (36)=0.172; p=0.301	r (26)=0.111; p=0.572	r (29)=0.013; p=0.943
Insulinemia			
BMI	r (37)=0.384; p=0.016*	r (34)=0.603; p=0.000*	r (29)=0.014; p=0.942
WC	r (36)=0.052; p=0.754	r (26)=0.257; p=0.187	r (29)=0.144; p=0.440
WHR	r (36)=0.089; p=0.594	r (26)=0.248; p=0.203	r (29)=0.042; p=0.821
Triglycerides			
BMI	r (37)=0.055; p=0.739	r (34)=0.226; p=0.185	r (29)=0.130; p=0.485
WC	r (36)=0.319; p=0.051*	r (26)=0.359; p=0.061	r (29)=0.007; p=0.968
WHR	r (36)=0.032; p=0.850	r (26)=0.035; p=0.858	r (29)=0.217; p=0.240
Cholesterol			
BMI	r (37)=0.100; p=0.545	r (34)=0.008; p=0.964	r (29)=0.003; p=0.989
WC	r (36)=0.150; p=0.368	r (26)=0.111; p=0.572	r (29)=0.052; p=0.780
WHR	r (36)=0.166; p=0.318	r (26)=0.144; p=0.463	r (29)=0.188; p=0.312
Adiponectin			
BMI	r (37)=0.008; p=0.963	r (34)=0.079; p=0.648	r (29)=0.082; p=0.661
WC	r (36)=0.035; p=0.834	r (26)=0.252; p=0.193	r (29)=0.296; p=0.105
WHR	r (36)=0.035; p=0.833	r (26)=0.063; p=0.750	r (29)=0.024; p=0.900
Leptin			
BMI	r (37)=0.629; p=0.000*	r (34)=0.559; p=0.000*	r (29)=0.542; p=0.002*
WC	r (36)=0.536; p=0.001*	r (26)=0.510; p=0.006*	r (29)=0.509; p=0.003*
WHR	r (36)=0.016; p=0.935	r (26)=0.035; p=0.858	r (29)=0.098; p=0.603
HOMA-IR			
BMI	r (37)=0.293; p=0.070	r (34)=0.620; p=0.000*	r (29)=-0.056; p=0.764
WC	r (37)=0.160; p=0.330	r (34)=0.282; p=0.096	r (29)=-0.065; p=0.727
WHR	r (37)=0.004; p=0.980	r (34)=0.157; p=0.359	r (29)=-0.216; p=0.242
HOMA-AD			
BMI	r (37)=0.258; p=0.113	r (34)=0.531; p=0.001*	r (29)=0.065; p=0.726
WC	r (37)=0.136; p=0.410	r (34)=0.281; p=0.097	r (29)=0.186; p=0.318
WHR	r (37)=0.010; p=0.951	r (34)=-0.169; p=0.324	r (29)=-0.123; p=0.509

*significant for p<0.05; BMI=body mass index; WC=waist circumference; WHR=waist to hip ratio; The homeostasis model assessment-insulin resistance (HOMA-IR); The HOMA-adiponectin (HOMA-AD)

After adjusting for sex and age, a significant positive strong correlation was observed between leptin and BMI as well as between leptin and WC in all three groups. No significant correlation was found between leptin and WHR. Only in the overweight with asthma group, we founded a mild positive correlation between glycemia and WC for r=462. A significant positive strong correlation was found between insulinemia and BMI in overweight (r=0.384) and asthma group (r=0.603). Between triglycerides and WC in overweight group a significant linear mild correlation was observed (r=0.319). We found no significant correlations of cholesterol as well as adiponectin with parameters of obesity in all three analyzed groups. Significant strong correlations were found between HOMA-IR as well as HOMA-AD with BMI in asthma group for consequently r=620 *vs*. r=531.

Discussion

Asthma and obesity are worldwide parallel epidemic chronic diseases both in adults and in children. Their association is well recognized, but mechanisms of their associations are still being debated. In 2020, Shan *et al*[20]. In a meta-analysis concluded that there was a bidirectional association between obesity and asthma during childhood and adolescence, suggesting that childhood obesity drives an increase in the onset of asthma, and childhood asthma may also increase risk of obesity in children and adolescents. The "obese asthma" phenotype is complex and modifies asthma characteristics with more frequent and severe exacerbations, poor response to inhaled corticosteroids, lower quality of life and worse control[21].

Obesity is characterized by metabolic changes, and defining of metabolic syndrome in childhood is challenging. However, glucose intolerance and insulin-resistance have been confirmed as central events driving metabolic disturbance in overweight children and increased risk of type II diabetes. The mechanisms underlying the relationship between metabolic syndrome and asthma are still not well understood. Several clinical studies suggested that hyperinsulinemia and insulin resistance are associated with impaired lung function[22] even in non-diabetics and also after reducing of BMI[23,24]. These studies suggest that obesity and asthma may be related through common inflammatory pathways associated with insulin resistance and hyperinsulinemia and resulted in airway hyperresponsiveness (AHR) as a major asthma feature. Insulin resistance promotes development of Th1 inflammatory response through the production of proinflammatory molecules such as IL-6, TNF-α[25]. Insulin resistance results in hyperinsulinemia, which is responsible for inhibition of pre-synaptic M2 muscarinic receptors, leading to bronchial hyperreactivity[21,26]. Therefore, the increased prevalence of asthma in children could result from peripheral tissue insulin resistance and hyperinsulinemia. Perez *et al*. [21] go further and talk about "metabolic asthma".

In this study, we processed the biochemical parameters of the metabolic syndrome in overweight children with asthma and confirmed a significant difference between the three groups of patients in terms of insulinemia and glycemia level. A significantly higher insulinemia value was obtained in the overweight groups, with asthma and without asthma, compared to asthma group which was consistent with other studies[20-22]. A significant strong correlation was observed between insulinemia and leptin with BMI, as well as between leptin, adiponectin and triglycerides with WC, as a parameter of central, abdominal obesity. Moreover, the metabolic syndrome was associated with WC values, regardless of BMI[27]. Bustos *et al*. confirmed leptin association with BMI but not with WC[28].

There was a significant difference between the groups in terms of glycemia, due to the significantly lower value in overweight children with asthma compared to asthma group. Several

clinical studies have shown that elevated plasma glycemia level in diabetes mellitus patients was associated with impaired lung function[20,29,30].

Insulin resistance was determined by HOMA-IR and HOMA-AD. Although HOMA-IR and HOMA-AD indexes had higher values in overweight groups in our study, a significant strong positive correlation of those insulin resistance indexes was found with BMI in asthma group. There are numerous studies confirming insulin resistance and impaired lung function in overweight children with asthma[31,32], but also studies with no associations between HOMA-IR, HOMA-AD and BMI in children with current asthma[33,34].

In addition to hyperinsulinemia and insulin-resistance, metabolic syndrome is characterized by dyslipidaemia[35]. This was confirmed during the analysis of the results in our study. Thus, hypercholesterolemia and hypertriglyceridemia were present in overweight groups, in contrast to the group of children with asthma and normal BMI. But there is evidence that asthma association with elevated serum triglycerides levels was confirmed regardless of BMI. Many children who are metabolically obese despite having a deceptive normal weight are predisposed to the same cardiovascular and respiratory comorbidities typical of their overweight peers[16,36]. Dyslipidemia is also associated with Th-2 immune response, major immune drive in pediatric asthma[37,38]. Vinding *et al.*[39] reported hypercholesterolemia with poor lung function, allergic sensitization, and AHR correlation in overweight children with asthma, and confirmed serum lipid levels, asthma and allergy association as a basis of systemic chronic inflammation.

Leptin as a major proinflammatory mediator and regulator of insulin sensitivity was significantly higher in the overweight groups, with and without asthma, and adiponectin as a major anti-inflammatory mediator was significantly lower in the same groups, which is consistent with a large number of studies[7,8,40-41].

None of the children in the study had DM, as that was one of the exclusion criteria. However, the analysis data showed 33.9% family history of DM. A statistical significance was confirmed in the group of overweight children with asthma, compared to the other groups. Additional analysis indicated that DM in family was 3.35 times more common in overweight children with asthma compared to the group of children with asthma and normal BMI. Family history of DM is associated with impaired glucose-metabolism and insulin-resistance, independent of BMI in children and adults.[42] Metabolic syndrome increases the risk of chronic cardiovascular diseases and DM later in life, so early detection of metabolic risk factors may include certain dietary and therapeutic interventions to prevent them[7,43,44].

In conclusion, undoubtedly there is an association with some parameters of the metabolic syndrome in childhood asthma. However, obesity has been shown to be a major driver of metabolic changes. Hyperinsulinemia, insulin resistance and dyslipidemia were present in overweight groups. Leptin and adiponectin correlated with WC as parameter of abdominal obesity. Thus, an endocrinologist should be involved in asthma treatment to assess and treat obesity, in order to identify as early as possible each component of the metabolic syndrome to reduce the risk of uncontrollable and difficult to treat asthma, as well as to prevent comorbidities such as DM and cardiovascular disease in those children.

Conflict of interest statement. None declared.

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