CORRELATIONS BETWEEN OBESITY AND ASTHMA CONTROL IN CHILDREN: HUNGARIAN PRIMARY CARE PILOT STUDY

KORELACIJE MED PREKOMERNO TELESNO TEŽO IN NADZOROM NAD ASTMO PRI OTROCIH: MADŽARSKA PILOTNA ŠTUDIJA V OSNOVNEM ZDRAVSTVENEM VARSTVU

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Abstract

Introduction: Asthma is often associated with overweight and obesity. The aim of this study was to find associations between asthma control, obesity and different levels of physical activity.

Methods: Using a questionnaire, 117 asthmatic patients between 6-18 years of age were interviewed. Two groups of children, normal vs. overweight, at different levels of physical activity (sport, school-based proper or light activity and full physical exemption) were compared. Asthma control was evaluated in two groups (controlled vs. non or partially controlled).

Results: The asthmatic status was generally controlled in 78%; in 81% and 72% of patients with a normal weight and overweight, respectively. Being overweight was more common among girls than boys (43.2% vs. 30.3%). A positive family history of asthma was revealed in many cases; the prevalence of asthma was found at 63% (P=0.0074) among the parents. Weight was significantly higher when the parents themselves were overweight. A lightened workload in physical education lessons at school doubled the risk of obesity (P=0.25), while full exemption increased it by six times (P=0.06). High bodyweight was found in 37% and 31% of children who had received steroid medication and other treatment, respectively (P=0.57).

Conclusion: High bodyweight and physical inactivity worsened the chances of effective asthma treatment, while sport improved it. The rates of physical activity among the surveyed patients were lower than recommended. More focus is needed; paediatricians, school-teachers and parents should pay more attention to the issue when establishing a proper family background for healthier lifestyles.

Keywords: asthma, children, Hungary, overweight, physical activity

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Izvleček

Uvod: Astmo se pogosto povezuje s prekomerno telesno težo in debelostjo. Namen te študije je bil ugotoviti povezave med nadzorom nad astmo, debelostjo in različnimi stopnjami telesne aktivnosti.

Metode: S pomočjo vprašalnika je bilo anketiranih 117 astmatičnih bolnikov v starosti od 6 do 18 let. Primerjani sta bili dve skupini otrok, z normalno in prekomerno telesno težo, na različnih stopnjah telesne aktivnosti (šport, običajna ali lažja aktivnost in popolna oprostitev od telesne aktivnosti v šoli). Nadzor nad astmo je bil ocenjen v dveh skupinah (nadzorovana vs nenadzorovana ali delno nadzorovana).

Rezultati: Astmatični status je bil na splošno nadzorovan pri 78 %; pri 81 % bolnikov z normalno telesno težo in 72 % bolnikov s prekomerno telesno težo. Prekomerna telesna teža je bila pogostejša pri dekletih kot pri fantih (43,2 % vs 30,3 %). V številnih primerih je bila odkrita pozitivna družinska zgodovina astme; obolevnost za astmo je bila ugotovljena pri 63 % (P=0,0074) staršev. Prekomerna telesna teža je bila precej večja, če so imeli prekomerno

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težo tudi starši. Manjša delovna obremenitev pri urah športne vzgoje v šoli je podvojila tveganje za debelost (P=0,25 %), medtem ko je popolna oprostitev od telesne aktivnosti to tveganje povečala za šestkrat (P=0,06). Prekomerna telesna teža je bila ugotovljena pri 37 % otrok, ki so prejemali steroidna zdravila, in 31 % otrok, ki so bile deležni drugačnega zdravljenja (P=0,57).

Zaključek: Prekomerna telesna teža in telesna neaktivnost sta poslabšali možnosti učinkovitega zdravljenja astme, medtem ko je športna aktivnost te možnosti povečala. Stopnje telesne aktivnosti med anketiranimi bolniki so bile nižje od priporočenih. Potrebna je večja osredotočenost; pediatri, učitelji in starši bi morali več pozornosti namenjati vprašanju, kdaj vzpostaviti ustrezno družinsko podlago za bolj zdrav življenjski slog.

Ključne besede: astma, otroci, Madžarska, debelost, telesna aktivnost

1 BACKGROUND

Asthma is the most common chronic inflammatory disease of the airways [1]. The risk factors include hereditary atopic liability, certain viral infections and there are some triggers such as physical load, allergens and respiratory irritants. Asthma is characterized by chronic inflammation, hyper-reactivity of the bronchial system and various stimuli generating airway obstruction. The obstruction is usually reversible spontaneously or with medical treatment, but the inflammation of the airways exists in the asymptomatic period as well [2].

There are large variations in the incidence of asthma worldwide; for example, in the UK, 32.2% of children aged 13-14, while in Ethiopia only 1.7% have been diagnosed with this disease [3]. In Europe, data from Austria (11.6%) is much lower than from the UK. The Czech Republic and Bulgaria have reported similar figures at 14% [4]. In Croatia, 11.9 % of children between 12-14 years of age are receiving treatment and there are significant differences within the country as well [5]. In 2008, the national adult prevalence of asthma was 233 thousand / 10 million (the total population of Hungary), according to the number of registered patients in the pulmonology specialist network [6]. For the prevalence of childhood asthma in Hungary, there is only data from sporadic surveys. The proportion of children with wheezing significantly increased from 6.8% in 2003 to 9.6% in 2006, and asthma may now affect 2-3 % of the total population of children [7, 8, 9]. Being overweight, the endemic of our age, contributes to the development of cardiovascular disease, diabetes and complex health problems. Genetic, familiar and environmental factors may lie in the background, but diet and a sedentary lifestyle are considered the most important causes. Based on recently published data the production of hormone-like substances increase in visceral fat and these result in the appearance of inflammatory cytokines with a major impact on asthma [2].

In the United States, the prevalence of childhood obesity has doubled since 2000 [7]. There was a significant increase in Europe as well. Approximately 20% of children and adolescents are overweight, moreover, a third of these people are obese [11]. According to recent Hungarian data, 14.4% of children were found to be overweight and 4.6% were registered as obese in 2008 [12]. Physical inactivity affects 60-70 % of the adult population and physical fitness among children has declined by 9% per decade [13].

Studies have shown that higher leptin levels in obese patients than in normal-weight ones also plays a role in the pathomechanism of asthma. Obesity due to the release of inflammatory factors may play a role in the predominant effects of asthma [2, 3]. Despite the theoretically-based interaction there is only limited data available in the literature about the clinical influence of being overweight on the control of asthma in childhood and adolescence.

The aim of our pilot study is to explore how weight surplus influences the manageability of asthma in children and young people and the connection between these common conditions, obesity related family background, and physical activity.

2 PATIENTS AND METHOD

Approximately 10,000 young patients a year – children and adolescents from East Hungary between 6 and 18 years of age – are receiving continuous care for asthma in our Paediatric Pulmonary Unit. Participants in the study were recruited from this population. They were randomized (one in five patients every Monday), between September and December in 2009. On average, eight children completed the questionnaire on these Mondays.

Refusal of participation was the sole criterion for exclusion. There were 14 patients or parents who did not want to contribute; their reasons were not questioned.

In the absence of a previously validated method, a questionnaire was developed and used in the survey; it contained questions about the asthma symptoms experienced, recent treatments, physical activity and the patients' own views about personal conditions. The concept of the questionnaire was established by the authors and was discussed with other experts in pulmonology and peadiatry. They were asked about overweight family members and the intra-familial occurrence of asthma (parents, sisters / brothers). Body weight and height were measured; BMI (body mass index) was calculated.

When structuring the questionnaire, the most important goal was to create a list of questions that were easy to understand and manage for children and parents. Participation was voluntary and anonymous, the permission of the Regional Ethical Committee having been acquired previously.

Defining variables

According to the latest GINA criteria issued in 2009, three different control levels could be defined to characterize the status of asthmatic patients: controlled, partially controlled and non-controlled groups [11]. A controlled status was considered when shortness of breath was experienced or bronchodilating medication was needed on less than two occasions in the previous week; having no complaint during physical load; no need for advanced (pulmonology) treatment in the previous year.

Overweight was considered with a BMI >25 kg/m² and obesity >30 kg/m². In children, BMI values are different. Considering gender and age; overweight was categorized at over 85 and obesity over 95 values of percentiles.

Due to the relatively small number of cases, the number of subgroups was limited in our study. Regarding asthma control there were only two groups, controlled and non- or partially-controlled groups; regarding BMI, normal and overweight (BMI >25 kg/m²) were used.

We considered proper exercise if the child took part in physical exercise (PE) lessons (45 minutes) at school without limitations, usually 2-3 times a week; sports activity if the child performed more physical exercises, plus two educational hours weekly, at least. Special lighter physical education was offered in some schools for asthmatic children. Physical exemption was considered when, upon medical or often forced parental recommendations, all kinds of physical activity were banned.

Data was processed and analysed by the Stata statistical package (StataCorp, 2007, Release 10. College Station, TX, USA). The one sided t-test and Fisher' exact test were used, 95% confidence intervals and odds ratio were given. Significance was considered when P<0.05. Correlations and odds ratios were calculated as well.

3 RESULTS

Of the 125 distributed questionnaires, 117 were filled out properly and completed for evaluation. The mean age was 12.50 y \pm 3.53 y, the distribution was characteristic of the general population and the patients treated in our centre. The gender ratio was: 51 girls (44%) and 66 boys (56%). Altogether, 47 overweight or obese children were found, 43.2% girls and 30.3% boys.

The value of overweight BMI was adjusted for gender and age, resulting in a 2.3 times higher rate for girls than boys. The parameters in Table 1 confirmed a significantly higher risk of excess weight when there is an overweight family member.

The risk of obesity was significantly affected by the level of different physical activities. Lighter PE lessons increased the risk of obesity to three, while full exemption increased it to six times higher (Table 2).

Table 1. Correlation between BMI categories in asthmatic children and their parents.

Tabela 1. Korelacija med kategorijami indeksa telesne teže (BMI) pri astmatičnih otrocih in njihovih starših.

		the chance of child being overweight (corrected for gender and age) / možnost prekomerne telesne teže pri otroku (popravljeno za spol in starost)			
Staroov o p	no of patients / št. bolnikov	odds ratio / razmerje obetov	p value / vrednost p	95% CI / 95 % IZ	
yes / da	66 (64.7%)	3.06	0.0074	0.84 - 5.28	
no / ne	36 (35.3%)	1.00	-	-	

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Table 2. Relations between physical education (PE) groups and being overweight (number and % of patients).
Tabela 2. Povezave med skupinami športne vzgoje in prekomerno telesno težo (število in % bolnikov).

physical education / sportna vzgoja	normal weight / normalna teža	overweight / prekomerna teža	odds ratio / razmerje obetov		95% CI / 95 % IZ
proper / običajna	37 (72.5%)	14 (27.5%)	1.00	-	-
lighter / lažja	24 (61.5%)	15 (38.5%)	1.72	0.25	0.60- 4.37
special / posebna	2 (40.0%)	3 (60.0%)	2.89	0.28	0.41- 20.31
exemption / oprostitev	2 (33.3%)	4 (66.7%)	6.13	0.06	0.93-40.58

No significant correlation was found between the therapeutic use of inhaled steroid-containing drugs and being overweight (Table 3).

Table 3. The connection between the administration of inhaled steroids and being overweight (number and % of patients).

Tabela 3. Povezave med uživanjem inhaliranih steroidov in prekomerno telesno težo (število in % bolnikov).

' ~	normal weight / normalna teža	Ŭ		p value / vrednost p	95% CI / 95 % IZ
no / ne	9 (69.2%)	4 (30.8%)	1.00	-	-
yes / da	56 (62.9%)	23 (37.1%)	1.44	0.57	0.40-5.23

Intra-familiar occurrence of asthma was reported by 63% of the patients.

Comparing the different types of physical activity and

asthma control, there were correlations as seen in Table 4. More physically active children had better asthmatic control and needed less medication.

Table 4. A comparison of the control level between different types of physical activities (PE)-number and % of patients.

Tabela 4. Primerjava stopnje nadzora med različnimi vrstami telesne aktivnosti (TA) – število in % bolnikov.

level of physical activity /	level of asthmati	level of asthmatic control /	
stopnja telesne aktivnosti	stopnja nadzora	stopnja nadzora nad astmo	
	controlled /	not controlled /	
	nadzorovana	nenadzorovana	
proper PE / običajna TA	49 (96 %)	2 (4 %)	
lighter PE / lažja TA	25 (64 %)	14 (36 %)	
special PE / posebna TA	4 (80 %)	1 (20 %)	
exemption from PE /	2 (33 %)	4 (67 %)	
oprostitev od TA			

The control level of the patients was generally good in 78%, while 22% of the children were none or partially controlled. Comparing the excess body weight and the respiratory status, 81% of the children with a normal weight, but only 71% of the overweight patients were controlled properly, i.e. had a good or acceptable condition. Only two patients had to be hospitalized because of exacerbation in their condition during the previous year, both of them were overweight.

Children were asked about their opinion of their own respiratory condition estimated in a subjective way. Fifty-six percent of the non-or partially controlled children rated their condition as acceptable and 44% said that it was bad. In the other group with controlled

parameters, the personal self-rating was significantly better: 43%, 41% and 15% evaluated their condition as acceptable, good and very good, respectivelly, only 1% of the patients were dissatisfied.

4 DISCUSSION

The control of asthma proved better in normal-weight children and youths vs. overweight or obese patients. A sedentary lifestyle had a strong connection with the control of asthma and excess weight, a significant relation was found between intra-familiar occurrences of obesity, but no evidence was found that inhaled corticosteroids were associated with obesity.

Genetic and family-based environmental factors, however, link asthma and obesity. The number of fat cells is of special importance in childhood while their growth in size is more characteristic in adulthood. They are regulated by neuro-hormonal, psychological and environmental factors but are influenced by genetic factors as well. In most cases, neuro-endocrinological differences cannot be detected, so obesity of familial origin develops [15]. Studies with obese children show decreasing lung capacity and pulmonary compliance [2]. Due to the inflammatory factors, being overweight can affect asthma [17, 18, 19, 20].

In our study, the chances of developing asthma for overweight girls were twice as high as in boys; 43% of the girls were overweight. In the case of girls, another survey showed a positive correlation between asthma and being overweight [7].

In our study population, the presence of an overweight parent has increased the risk of obesity threefold. Genetic susceptibility, the nutritional habits of the family and the "learned" lack of exercise also may play a role. The classification of children into different groups in PE lessons significantly determines the risk of being overweight. Children exempted from the physical education requirements are at the highest risk. Asthma by itself was the most common reason for exemption. Children suffering from asthma performed no sports activity at all, not even light physical exercise. In the case of well-treated asthmatic children, exemption from physical education is not justified. In the case of attacks provoked by physical load, however, they can get exemption from long-term running. This kind of light physical education is impossible in many places and school systems. Although breathing gymnastics, chest exercises and swimming have a good effect on asthma, performing such exercises once or twice a week does not satisfy a child's natural needs. Physical activity during childhood improves cardiovascular fitness, selfesteem, motor skills and bone development [21, 22]. In our study, a sedentary lifestyle not only increased the chances of obesity, but significantly impaired the management of asthma. The proportion of overweight children taking part in normal PE lessons was small, so the lack of physical activity significantly increased the chances of obesity.

Inhaled steroids mainly act locally (in the airways or in the lung), therefore their systemic absorption is negligible. Obesity, as a side effect of steroid use may develop if the patient receives higher doses for a long time.

The new recommendation of diagnosing the status of the asthma patient includes three control levels: controlled, partly controlled and non-controlled. It is important to be aware of the specific control level [23].

As we had a small pilot study population, the patients were allotted into only two groups: controlled, and none or partially controlled groups. In the current study, 78% of the youngsters were well-controlled, 22% were non-or partially-controlled as a result of appropriate treatment given by the specialist of the pulmonology network, which was organized in Hungary to care for both adults and children [14].

Sport and PE significantly improved the therapeutic control of asthma. Physical activity positively influences the asthmatic status of patients. According to a survey, physical fitness also influences the severity of the disease and improves its manageability [24].

The asthmatic children's opinion about their status correlated well with the control classification. They judged their condition was good, although their opinions could have been influenced by their views on their previous condition and serious symptoms experienced before the current treatment was introduced. In contrast, the AIRE survey showed significant differences between personal opinions and control group classification, with the majority of the patients considering their status as better than it actually was [25].

However, it has specific benefit for children with asthma, including reduced hospital admission, reduced school absenteeism, fewer consultation with doctors, reduced medications and an improved ability to cope with asthma [10, 11]. Despite the above, the benefits rates of physical activity among young people with asthma are lower than in their non-asthmatic peers [26,27]. Restriction was imposed because of the perceived dangers of exercising in the presence of "triggers". Physical activity was regarded as a threat to be managed rather than something beneficial. Teachers found it difficult to distinguish between children who were physically incapable of exercise due to asthma and those who were unmotivated. The lower level of activity among children with asthma was supported by the climate of fear among parents and teachers about what was safe and possible for the child [28, 29].

It cannot be excluded that parents of the study population with a higher proportion overweight and with their own asthma rarely support the active lifestyle of their asthmatic children as experienced in other studies, in other countries [30, 31, 32].

Asthmatic episodes have seasonality; usually they are frequent in the autumn. We believe that this higher ratio could affect both groups (overweight and normal weight) in the same way and amount.

Some other limiting factors should also be mentioned here:

 there were a limited number of participants within the study population, 146 Zdrav Var 2012; 51

- time and diagnosis of asthma and the development of excess weight / obesity were not evaluated,
- the questionnaire has not been validated and needs further improvement in the future when following these evaluations in a wider range.

5 CONCLUSIONS

When examining the impact of obesity on the management of asthma, we found that excess body weight and a sedentary lifestyle undermined the effectiveness of therapy. In the case of patients of normal weight, the number of days with symptoms was lower; their physical activity was higher, so despite their disease, their quality of life could be better than that of overweight people's.

Our results support the conviction that offering appropriate physical activity and giving proper treatment for children with asthma can significantly improve the manageability of asthma and decrease the chances of obesity.

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References

- Pinnock H, International Primary Care Respiratory Study Group. Research Needs Statement 2010. Prim Care Resp J 2010; 19 (Suppl 1): S1-S20.
- Canöz M, Erdenen F, Uzun H, Müderrisoglu C, Aydin S. The reletionship of inflammatory cytokineas with asthma and obesity. Clin Invest Med 2008; 31: E373-9.
- Leonardi GS, Houthuijs DBNJV, Rudnai Z, Zejda J, Gurzau E, Fabianova E, Fletscher T, Brumekreef B. Respiratory symptoms, bronchitis and asthma in children of Central and Eastern Europe. Eur Resp J 2002; 20: 890-8.
- Patei SP, Järvelin MJ, Little MP. Systematic review of worldwide variations of prevalence of wheezing symptoms in children. BMC Environ Health 2008; 7: 57.
- Munivrana H, Vorko-Jovic A, Munivrana S, Kursar M, Medlobi-Gluhak M, Vlahek P. The prevalence of allergic diseases among Croatian school children according to the ISAAC phase one questionnaire. Med Sci Monit 2007; 13: CR505-9.
- Herjavecz I. Pulmology diseases which waiting for cure. Országos Korányi Tbc és Pulmonológia Intézet. Accessed on February 15th 2010 at: http://www.magyosz.org/dokumentumok/ Nep_Herjavecz_Iren.pdf.
- Endre L, Láng S, Vámos A, Páldy Z, Varró J, Farkas I, Collinsné Horváth Z. Increase of prevalence of children's asthma in Budapest between 1995 and 2003 considering the air pollution and pollen data. Orvosi Hetilap 2007; 148: 211-216.
- Harangi F, Lőrinczy K, Lázár A. The prevalence of children's asthma in Baranya county between 2003 and 2006. Orvosi Hetilap 2007; 148: 1643-1648.
- The Hungarian Bord of Pulmonology. Guidelines of the diagnose, treatment of asthma and attendance. Accessed on February 15th 2010 at: http://www.kk.pte.hu/servlet/download.

 Crespo CJ, Smit E, Troiano RP. Television watching, energy intake and obesity in US children: results from third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adol Med 2001; 155: 360-365.

- Jakson-Leach R, Lobstein T. Estimated burden of pediatric obesity and co-morbidites in Europe. Part 1: The increase in the prevalence of child obesity in Europe is itself increasing. Int J Pediatr Obesity 2006: 1: 26-32.
- Kovacs VA, Gabor A, Fajcsik Z: Role of waist circumference in predicting the risk of high blood preassure in children. Int J Pediatr Obesity 2009; in print. Accessed on February 18th 2010 at: http:// www.informaworld.com/smpp/.
- Donaldson I. On the state of public health: annual report of the Chief Medical Officer. London: Department of Health, 2010.
- GINA 2009, Consensus Statement of Pediatrician Pulmonology.
 Accessed on February 22th 2010 at: www.tudogyogyasz.hu/ upload/tudogyogyasz/document/konszenzus_fuzet.pdf.
- Sallai A. Obesity in childhood. Accessed on February 20th 2010 at: www.medlist.com/HIPPOCRATES.
- Delgado J, Barranco P, Quirce S. Obesity and asthma. J Investig Allergol Clin Immunol 2008; 18: 420-5.
- von Behren J, Lipsett M, Horn-Ross PL. Obesity, waist size and prevalence of current asthma in the California Teachers Study Cohort. Thorax 2009; 64: 889-893.
- 18. Langmár Z. The diagnosis and therapy of Polycysic Ovarium Syndrome. Orvosi Hetilap, 2010; 151: 584-586.
- Molnár D, Erhardt É. Severe childhood obesity: what are the keys for management? Int J Pediatr Obesity 2008; 3 (Suppl 2): 9-14.
- Katona É, Settakis G, Varga Z, Paragh G, Bereczki D, Fülesdi B, Páll D. Target-organ damage in adolescent hypertension. J Neurol Sci 2006; 247: 138-143.
- Poskitt E, Edmunds L. Management of childhood obesity. Cambridge: University Press, 2008.
- 22. Ilyés I, Blatniczky L, Tobisch B. Obesity and the metabolic syndrome. In: Péter F, editor. Chilhood endocrinology. Budapest: Semmelweis Publishing House, 2010: 371-384.
- 23. Tamási L, Orosz M, Gálffy G.The not suitable asthma controll's background in our patient's population. Medicina Thoracalis 2008. Accessed on February 22th 2010 at: https://www.doki.net/tarsasag/tudogyogyasz/folyoirat.aspx.
- Mezei G, Balla K. The obesity frequence in asthma, orthopedic abnormal and health among the children. Medicina Thoracalis 2008. Accessed on February 25th 2010 at: https://www.doki.net/ tarsasag/tudogyogyasz/folyoirat.aspx.
- Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE). Eur Respir J 2000; 16: 802-7.
- Wells L, Kemp JG, Roberts EG. Effects of physical conditioning on children and adolescents with asthma. Sports Med 2005; 35: 127-141.
- 27. Smyth RL. Asthma: a major pediatric health issue. Respire Res 2002; 3 (Suppl 1): S3-S7.
- Williams B, Hoskin G, Pow J, Neville R, Mukhopadhyay S, Coyle J. Low exercise among children with asthma: a culture of over protection? Br J Gen Practice 2010; 60: 578-583.
- 29. National Asthma Campaign. An audit for children's asthma in the UK. Asthma J 2002; 8: 3-11.
- Felszeghy E, Juhász E, Káposzta R, Ilyés I. Alterations of glucoregulation in childhood obesity--association with insulin resistance and hyperinsulinemia. J Pediatr Endocrinol Metab 2008: 21: 847-53.
- Glazeebrook C, McPherson AC, MacDonald JA. Asthma as a barrier to children's physical activity: implication for body mass index and mental health. Pediatrics 2006; 118: 2443-2449.
- Lang DM, Butz AM, Duggan AK, Servint JR. Physical activity in urban school-aged children with asthma. Pediatrics 2004; 113: 341-346.