Relationship Between Cough Reflex Sensitivity and Body Mass Index in Children With Chronic Cough – a Pilot Study

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Summary

Obesity is characterized by chronic, low-grade systemic inflammation. Obesity may also be associated with chronic cough. The aim of this pilot study was to clarify relation of cough reflex sensitivity and body mass index (BMI) in children with chronic cough. Altogether 41 children having symptoms of chronic cough were submitted to cough reflex sensitivity measurement. We assessed the relation of cough reflex sensitivity (CKR) due to BMI. Cough reflex sensitivity was defined as the lowest capsaicin concentration which evoked two (C2) or five (C5) coughs. Capsaicin aerosol in doubling concentrations (from 0.61 to 1250 μmol/l) was inhaled by a single breath method (KoKo DigiDoser; nSpire heath Inc, Louisville, CO, USA), modified by the addition of an inspiratory flow regulator valve (RIFR; nSpire heath Inc, Louisville, CO, USA). BMI was calculated. Pulmonary function was within normal range. Concentrations of capsaicin causing two (C2) and five coughs (C5) were reported. Children' (22 boys and 19 girls, mean age 6.8 years) cough reflex sensitivity (median, with the Inter-Quartile Range) for C2 was 19.5 (73.4) μmol/l; for C5 it was 78.1 (605.5) μmol/l. We have noticed statistically significant relation of the cough reflex sensitivity (C5) and body mass index ($P<0.0001$); however, the effect size was small, $R^2=0.03$. Increase of body mass index in one unit is associated with -34.959 μmol/l decrease of C5. We did not find a statistically significant relation between C2 and BMI ($P=0.41$). The median value of CKR (C2) in boys is not statistically significantly different than the median value of CKR (C2) in girls (P-value 0.5). The median value of CKR (C5) in boys is not statistically significantly different than the median value of CKR (C5) in girls (P-value 0.5). Increase of body mass index in children suffering from chronic cough relates to decrease of cough reflex sensitivity (C5 value).

Key words

Cough • Chronic cough • Cough reflex sensitivity • Body mass index • Children • Atopy

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Introduction

Increase in prevalence of obesity has become a worldwide major health problem in adults, as well as among children and adolescents. Overweight and obesity in childhood and adolescence has lately developed into a global health issue (Weihrauch-Blüher *et al.* 2018). Obesity plays an important role also in the development and progression of respiratory diseases.

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In asthma, obesity is considered a major comorbidity that exacerbates the respiratory symptoms (Porsbjerg and Menzies-Gow 2017). Many epidemiological studies have shown that obese patients have a higher risk of developing asthma than the general population demonstrating that obesity is involved in the development of asthma (Beuther and Sutherland 2007). It is also established that asthma associated with obesity is a phenotype with more difficult-to-treat asthma compared to non-obese subjects (Moore *et al.* 2010).

Chronic cough is a common entity in respiratory medicine. It is a complex disorder. However, body mass index (BMI) measurement and assessment of obesity markers are not included in the evaluation of patients with chronic cough. Chronic cough places high demands on health care systems but it is not classically associated with obesity (Guilleminault 2019).

With respective prevalence of 13 % and 9.6 %, obesity and chronic cough are two common conditions worldwide. The crucial role of obesity has been highlighted in the development and progression of many respiratory diseases. According to the results of epidemiological studies, obesity, particularly abdominal obesity, may also be associated with chronic cough. Chronic cough seems to be more severe in obese patients compared to normal-weight subjects (Guilleminault 2019). It was reported that patients with a higher body mass index (BMI) experience cough more often than other patients and the cough is more severe in obese patients (Moralles-Estrella *et al.* 2017).

The link between obesity and chronic cough has been suggested in the literature. In the guidelines on chronic cough management, no difference has been highlighted between obese and normal-weight individuals. The beneficial effect of weight loss has been demonstrated in many obesity-related diseases. Weight-loss procedures may constitute part of the treatment of chronic cough in obese patients (Guilleminault 2019). The higher BMI is associated with a higher prevalence of symptoms of wheeze and cough in children (Schachter *et al.* 2003).

The aim was to determine if increased body weight, as measured by body mass index, is associated with a change of cough reflex sensitivity (activity of airway afferent nerve-endings) in children suffering from chronic cough.

Methods

Selection criteria and subjects

The inclusion criteria to enter the study were: 1) age from 3 to 15 years, 2) positive anamnesis of chronic cough, cough lasting longer than 4 weeks (Chang *et al.* 2001, Chang *et al.* 2017), 3) status without signs of acute airway inflammation and signs of respiratory disorders with exclusion of obstructive ventilatory defect verified by auscultation by pediatrician, spirometry (ZAN500 Body, nSpireHealtGmbh, Germany) and complete ENT (Ear, Nose and Throat) examination – nasofiberendoscopy (Karl Storz 11101RP2, Ø2.5 mm, Germany), inspection of oral cavity, oropharynx, otomicroscopy, tympanometry, anterior rhinomanometry, microbial cultivation, 4) good cooperation during the spirometry and cough reflex sensitivity (CRS) examination with relevant outcomes (hyporeactors were excluded), 5) negative anamnesis related to the respiratory and allergic diseases and no mentioned allergy treatment as well; outpatient examination by immuno-allergologist – total immunoglobulins E (IgE), specific IgE, pediatric panel for selected inhalation and food allergens, skin prick tests for year-round and seasonal inhalation allergens, 6) the children didn´t take any topical and systemic corticosteroids, antihistamines, antileukotrienes and decongestants during the examination and minimally 2 weeks before being examined. All children who met the given criteria underwent body height, weight (digital calibrated weight Seca 61987, Germany) and CRS measurement.

41 children (22 boys and 19 girls, age range 4-13 years, mean age 6.8 years) were included into the study. Based on outpatient examination by immunoallergologist patients were divided into subgroups of 17 atopy-negative (6 boys, 11 girls, mean age 6.9 years) and 24 atopy-positive patients (16 boys, 8 girls, mean age 6.7 years). As an atopy positive we consider a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, commonly occurring in the environment, usually proteins everyone is exposed to. Second criterion is tendency to develop typical symptoms such as asthma, rhino-conjunctivitis, or eczema/dermatitis. The term atopy was used if an IgE sensitization has been documented by IgE antibodies in serum or by a positive skin prick test (Johansson *et al.* 2004).

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia and was

performed according to the Declaration of Helsinki. Each parent of the observed child was properly informed about the study, about the possibilities of cough treatment and was asked to sign an informed consent.

Spirometry and cough sensitivity testing

All subjects underwent initial screening of their basic lung functions measured by spirometry before and after capsaicin challenge (KoKo DigiDoser-Spirometer; nSpire health Inc., Louisville, CO, USA) to rule out airway obstruction.

CRS was assessed using capsaicin cough challenge, performed in agreement with the ERS guidelines (Morice *et al.* 2007) with modification for pediatric use (Varechova *et al.* 2008) (we used a compressed air-driven nebuliser (model 646; DeVilbiss Health Care, Inc., Somerset, PA, USA) controlled by a dosimeter (KoKo DigiDoser-Spirometer; nSpire health Inc., Louisville, CO, USA) with an inspiratory flow regulator valve added (RIFR; nSpire health Inc., Louisville, CO, USA) to assign identical inspiratory flow rate during capsaicin inhalations in all subjects. Each subject inhaled saline randomly interposed among 12 inhalations of incremental capsaicin aerosol concentrations (0.61-1250 μmol/l). Each administration of saline and capsaicin aerosol was performed at 1 min intervals with the inhalation time set at 400 ms. The number of coughs within 30 s after aerosol administration was counted. The end-point of cough challenge was the inhalation of capsaicin concentration that provoked at least 5 coughs (C5) or when the maximum concentration of capsaicin (1250 μmol/l) was achieved. The concentration of capsaicin causing at least two coughs was assigned as C2 and concentration of capsaicin causing at least 5 coughs was assigned as C5. For children that did no cough at any concentration of capsaicin, CRS value was assigned 1250 μmol/l.

The CRS measurement was realized as a single-dose capsaicin test. Gradually, with the increasing concentrations of capsaicin we determined sensitivity threshold of the airway nerve endings responsible for coughing.

Body mass index percentile

BMI can be considered an alternative to direct measures of body fat. In general, BMI is an inexpensive and easy-to-perform method of screening for weight categories that may lead to health problems. After BMI is calculated for children and teens, it is expressed as a percentile which can be obtained from either a graph or a percentile calculator. These percentiles express a child's BMI relative to children in the U.S. who participated in national surveys that were conducted from 1963-1965 to 1988-1994 (Kuczmarski *et al.* 2002). Because weight and height change during growth and development, as does their relation to body fatness, a child's BMI must be interpreted relative to other children of the same sex and age.

Based on height and weight of patients we calculated BMI, BMI percentile, assigned the weight category (underweight – less than the 5th percentile; normal or healthy weight – 5th percentile to less than the 85th percentile; overweight – 85th to less than the 95th percentile; obese – equal to or greater than the 95th percentile).

Obtained parameters of CRS and BMI were mutually statistically compared and relation between CRS and weight was statistically evaluated. The results were evaluated and interpreted separately for a group of all patients, group of atopy-negative patients and for a group of atopy-positive patients.

Statistical analysis

Obtained parameters of CKR were mutually statistically compared and relation between CKR in obese and non-obese children, obese and non-obese atopic children was statistically evaluated. The results were evaluated separately for each individual and subsequently for the group as a whole. The results were expressed as median values, the level of statistical significance was determined as $P<0.05$ and $P<0.01$. Wilcoxon rank-sum test was used.

The association between CKR and BMI was visualized by a crossplot. Due to the presence of outliers and influential observations in the data, instead of the Ordinary Least Squares method we have used the robust regression (M estimator) to fit the regression line into the data. Results with p-value below 0.05 were considered statistically significant. Software used: R Core Team (2015), R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, URL – https://www.R-project.org/, R version 3.2.3, 2015-12-10), (Maechler *et al.* 2016).

Results

Forty-one children (22 boys and 19 girls, age range 4-13 years, mean age 6.8 years) suffering from

chronic cough were included into the study. Based on outpatient examination by immunoallergologist patients were divided into subgroups of 17 atopy-negative (6 boys, 11 girls, mean age 6.9 years) and 24 atopy-positive patients (16 boys, 8 girls, mean age 6.7 years).

BMI was calculated. Pulmonary function was within normal range. Concentrations of capsaicin causing two (C2) and five coughs (C5) were reported. Children' (22 boys and 19 girls, mean age 6.8 years) cough reflex sensitivity (median, with the Inter-Quartile Range) for C2 was 19.5 (73.4) µmol/l; for C5 it was 78.1 (605.5) µmol/l. There was not significant difference between obese and non-obese children in concentrations of capsaicin causing two (C2) coughs (P=0.7) and five coughs (C5) (P=0.3). There was no statistically significant difference between obese atopic children and non-obese atopic children for C2 value (P>0.9) and for C5 value (P=0.8).

But we have noticed statistically significant negative relation of the cough reflex sensitivity (C5) and body mass index (P<0.0001); however, the effect size was small, R^2=0.03. Increase of body mass index in one unit is associated with -34.959 µmol/l decrease of C5 value (Fig. 1). We did not find a statistically significant relation between CKR – C2 value and BMI (P=0.41).

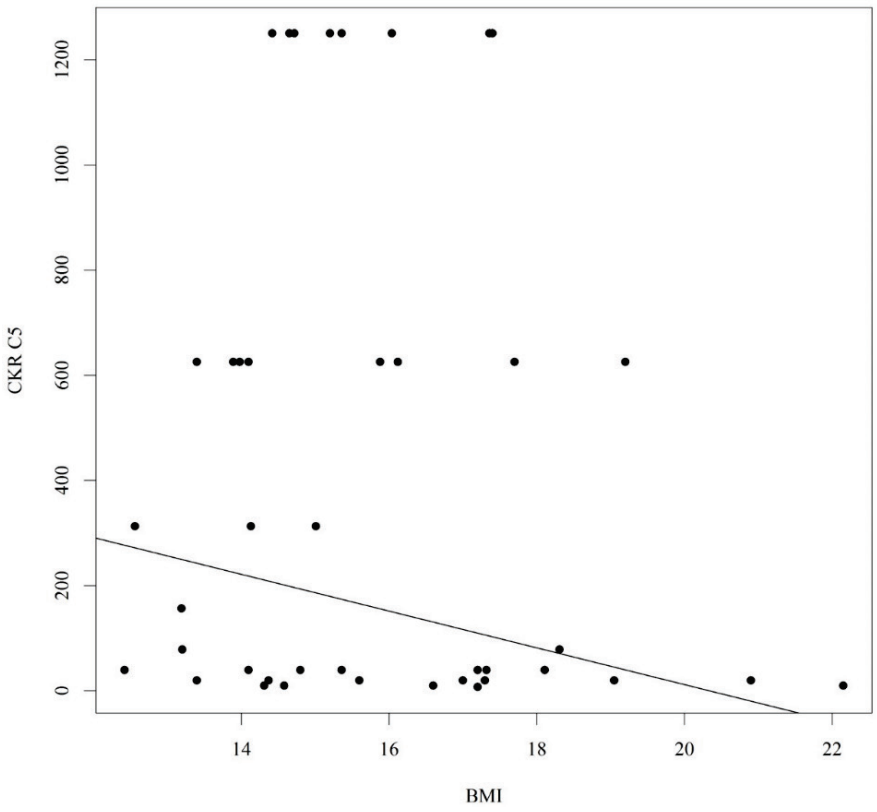

Fig. 1. Relationship between cough reflex sensitivity (CKR – C5 value) a BMI in children with chronic cough.

For the collection of 17 atopy-negative patients we did not find out statistically significant relation of the cough reflex sensitivity and BMI – C2 (P=0.43), C5 (P=0.66). For the collection of 24 atopy-positive patients we did not find out statistically significant relation of the cough reflex sensitivity and BMI – C2 (P=0.87), C5 (P=0.77). Immunoallergological status did not influence dependence between CRS and BMI.

In 17 atopy-negative children we found out 1 obese child and in 24 atopy-positive children we found out 1 obese and 8 overweight children (Table 1).

There is no statistically significant association between age composition and gender (P=0.7). The median value of CKR (C2) in boys is not statistically significantly different than the median value of CKR (C2) in girls (P=0.5). The median value of CKR (C5) in boys is not statistically significantly different than the median value of CKR (C5) in girls (P=0.5). With regard to the number of girls in the study group, there was a non-significant tendency to changes of the sensitivity of cough reflex in girls and boys.

Table 1. Proportion of children with chronic cough in weight status categories.

Alergological status	Number	Underweight (%)	Normal Weight (%)	Overweight (%)	Obese (%)
Negative and positive	41	4 (9.8 %)	27 (65.9 %)	8 (19.5 %)	2 (4.9 %)
Negative	17	2 (11.8 %)	14 (82.4 %)	0 (0 %)	1 (5.9 %)
Positive	24	2 (8.3 %)	13 (54.2 %)	8 (33.4 %)	1 (4.2 %)

Discussion

The aim of this study was to assess the relation of cough reflex sensitivity due to body mass index (BMI) in atopic and non-atopic children with chronic cough.

Chronic cough is a common entity in respiratory medicine. It is a complex disorder, the management of which has recently been defined in the guidelines of the European Respiratory Society (Morice *et al.* 2020). All the steps covering the investigations and initial treatments are detailed in these guidelines. However, body mass index measurement and assessment of obesity markers are not included in the evaluation of patients with chronic cough. Over the last years, obesity has increased worldwide and is now considered to be a genuine public health problem. Chronic cough places high demands on health care systems but it is not classically associated with obesity. In clinical practice, it is not surprising to observe the combination of two common diseases (Guilleminault *et al.* 2019). Chronic cough is reported by 10-20 % of adults and this disorder is more common in female and obese subjects (Morice *et al*. 2006). Patients with a higher BMI experience cough more often than other patients and the cough is more severe in obese patients (Morales-Estrella *et al*. 2017). Haldar *et al.* (2008) found an obese asthma phenotype with noneosinophilic inflammation. The inflammatory profile of asthma may be different in obese patients compared to non-obese patients and the role of eosinophils in inflammation may be less crucial in obese asthmatics than non-obese asthmatics. However, sub-mucosal eosinophilic inflammation has also been found in asthma patients with obesity, which indicates that the association is probably more complex (Desai *et al*. 2013). In our study immunoallergological status did not influence dependence between CRS and BMI.

In recent decades, the worldwide prevalence of allergic disease has increased considerably (Aw *et al.* 2020). There has been a significant increase in the prevalence of asthma, atopy, and obesity in children worldwide (Woolcock and Peat 1997). It is possible that these events are linked (Gennuso *et al.* 1998, Huang *et al.* 1999, Shaheen *et al.* 1999). The association between asthma and obesity is well-described, but not straightforward, and according to current guidelines asthma control is more difficult to achieve in obese patients (Ulrik 2016a). In adults, large random population studies have shown an increase in the incidence and prevalence of wheezing and diagnosed asthma in obese subjects (Schachter *et al.* 2001). Weight reduction in obese adults with asthma leads to an overall improvement in asthma control, including airway hyperresponsiveness and inflammation. Weight reduction should be a cornerstone in the management of obese patients with asthma (Ulrik 2016b). In children two meta-analyses, published in 2013 and 2019, focused on the obese asthmatic phenotype and assessed the positive correlation between asthma and childhood obesity or overweight (Chen *et al.* 2013, Deng *et al.* 2019). The association between obesity and atopy has also rarely been explored. It is possible that obesity could cause atopy or inflammation or that there is some common factor that predisposes to both obesity and atopy (Schachter *et al.* 2001).

The relationships between atopy and obesity remain uncertain, both in adults and in children. Although there are physiopathologic mechanisms which could explain how obesity could influence the immune system and promote the process of sensitization, evidences in favor of a possible role of obesity on the development of atopy have been inconsistent. Furthermore, the bulk of evidence suggests that atopy does not mediate the relationship between obesity and asthma, although in some populations, particularly in children and women, such association has been reported (Boulet 2015).

In our study there was not significant difference between obese and non-obese children suffering from chronic cough and no statistically significant difference

between obese atopic children and non-obese atopic children suffering from chronic cough. Due to the existence of subclinical inflammation, we assumed an increase in cough reflex sensitivity (C5) in obese children. This could be due to the size of the file and the fact that obesity was mild. There was no statistically significant difference in cough reflex sensitivity (CKR) between boys and girls with respect to age of children in our study (Varechova *et al.* 2008).

Limitations in this study that should be noted include the following: (1) Sampling. All cases were diagnosed with chronic cough, and there was no normal control group. (2) The unequal number of boys and girls and the sample size used in the study was rather small. Having a small sample size made the statistical results not as objective as they would be if a larger sample size had been used. (3) Direct measurement of body fat. In the future studies, these limitations should to be addressed.

Conclusions

We have confirmed in our pilot study that cough reflex sensitivity in children with chronic cough depends also from BMI. There is a statistically significant, though rather weak, negative correlation between BMI and cough reflex sensitivity and this dependence in our cohort was not influenced by atopy status. Although very little is known about relationship between chronic cough in children and obesity this observation is of interest and merits further investigation.

Conflict of Interest

There is no conflict of interest.

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