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Research Article

Is Serum Tryptase a Valuable Marker for Obesity-Bronchial Asthma Interrelationship in Children?

Abstract

Background: Asthma among obese represents a unique phenotype. Mast cells are more abundant in obese. Serum tryptase (ST) is a marker of mast cell numbers or activity. Since obesity and asthma have been linked in epidemiological studies, a possible higher mast cell activity in obesity could be a factor between the two conditions. This study was to investigate ST and its potential association between obesity and childhood asthma.

Methods: Study recruited 60 asthmatic children, their age ranged from 5-16 years. They were divided according to BMI centile to 30 obese and 30 non-obese asthmatics. Thirty healthy non-asthmatic, non-atopic and non-obese children; were included as a healthy control. Serum tryptase, atopy (skin prick test reactivity) and spirometry were assessed.

Results: Frequency of atopy and positive skin prick test significantly increased among obese more than non-obese asthmatics ($P < 0.05$, OR = 1.96, 95% CI = 1.27-3.24). FEV1% of predicted mean levels were lower among obese than non-obese asthmatics ($p < 0.05$). ST was significantly higher in asthmatics than in controls with a mean \pm SD of 53.3 \pm 13.78 ng/ml and 10.06 \pm 4.39 ng/ml respectively. ST was higher in obese than non-obese asthmatics with a mean \pm SD of 71.73 \pm 19.17 ng/ml and 34.5 \pm 8.68 ng/ml respectively ($P < 0.05$). There was a negative correlation between ST and FEV1 % of predicted and positive correlations between ST and age, BMI, and waist circumference among asthmatics.

Conclusion: Mast cells play a role in both obesity and asthma, serum tryptase, being a marker of mast cell activation, could represent a link between them.

Introduction

Asthma is determined by multiple interacting genetic and environmental factors. Obesity is a common co-morbidity that may adversely affect asthma severity and response to therapy and recent studies have also suggested that obese asthmatics respond differently to standard therapies than their non-obese counterparts. Moreover, there is mounting evidence that childhood obesity is a risk factor for the development of asthma [1].

Mast cells are found to be more abundant in subcutaneous abdominal adipose tissue from obese humans than from non-obese humans [2]. Total serum tryptase (ST) could be considered as a measure of mast cell activity [3]. Although their biological function has not yet been clarified, tryptases seem to be involved in a number of mast cell-mediated allergic and inflammatory diseases. In particular, the involvement of tryptase in asthma, an inflammatory disease of the airways often caused by allergy, has been proposed [4].

Aim of the Study

This cross sectional study was designed to evaluate serum tryptase (ST) in obese asthmatic children as a possible linkage between both obesity and asthma. Accordingly, this study may add to the pathogenesis of asthma among obese children that could be critical to guide understanding of this disease process; such studies will ultimately guide the development of new therapies to treat the obese asthmatic population.

Methods

Study design and population

Current cross sectional study has respected principles laid down in the Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, which recently amended at the 59th World Medical Assembly, Seoul, Korea; in October, 2008. The entire protocol was approved by university ethical committee. All parents and/or care-givers

provided signed an informed consent for participation in study as required. This study was carried out in Pediatric Chest Clinic, Children's Hospital, Ain Shams University. It included 60 asthmatic children diagnosed according to "GINA, 2008" [5], their age ranged from 5–16 years. They were 37 males and 23 females with male to female ratio 1.6:1. Asthmatic children were subdivided according to body mass index (BMI) [6,7], into: thirty obese asthmatic whose BMI were above the 95th percentile according to sex- and age-specific BMI reference range using charts provided by Centers for Disease Control and Prevention, and thirty non-obese children whose BMI were below the 95th percentile and above 5th percentile according to sex- and age-specific BMI reference range using same charts [6–8].

Thirty healthy non-asthmatic, non-atopic and non-obese (BMI < 95th centile for age and sex) children; age and sex matched with the patients' group were included as a healthy control group.

Exclusion criteria

Asthmatics with obesity secondary to an organic condition were excluded. We excluded also children with chronic cardio-respiratory or neuromuscular problems, and children less than 5 years (They were unable to perform spirometry maneuvers). Additionally, children who had clinical manifestations suggestive of existing acute respiratory infection or an acute asthma exacerbation at time of testing or in the previous 3 weeks, or any other associated chronic systemic illness e.g. diabetes mellitus were excluded.

Anthropometric measurements

Standing height was measured to nearest 1 cm against a wall chart, and weight was measured to nearest 0.1 kg using an electronic digital scale. Then, BMI was calculated as weight (kg) divided by square of height in meters (kg/m²).

Waist circumference is an important measure of obesity risk. It is measured at the level of the top of the right iliac crest. The measuring tape should be snug but not compressing the skin and held parallel to the floor. Its measurement is made at normal respiration. Hip circumference was measured as the maximum circumference over the buttocks. Then, waist-to-hip ratio (WHR) was calculated as ratio between these two circumferences. Anthropometric data and BMI were assessed as centile according to sex- and age-specific reference range using charts provided by Centers for Disease Control and Prevention [8].

Spirometry

Both forced vital capacity and forced expiratory volume in first second (FEV₁) were used as measures of ventilatory function [9]. All subjects performed dynamic spirometry (Jaeger, Germany). The best of three technically acceptable values for forced expiratory volume in first second (FEV₁) and forced vital capacity (FVC) were selected. They were expressed as percentages of predicted normal values [9].

Skin prick tests

Skin prick tests (SPTs) were performed to confirm atopic state among asthmatics. Atopy was defined when one or more positive skin-prick test result for common inhalant allergens (with positive histamine prick result). It was carried out using stainless-steel lancets. The panel used the Taiwan Asian panel (which was found to be the most matching panel to Egyptians that includes: House dust Mite *Farinae*, Mite pterony, Cockroach Mix, Feather Mix, Dogs' and Cats' dander, *Candida*, *Aspergillus*, *Cladosporium*, *Penicillium*, *Alternaria*, Grass Mix, Bermuda Grass, Wheat, Cod fish, Pork, Beef, Egg, Whole, Egg Yolk, Milk, Yeast Brewer, Soybean, Peanut, Vegetable Mix, Rag wd Mix II, Pine Mix, Cotton wd, Mulberry Mi, Pigweed Mix, Corn, Crab, Shellfish Mix, Shrimp, and Eucalyptus) [10,11]. Histamine solution (10 mg/ml) and glycerinated saline were used as positive and negative controls. SPTs were considered positive if there was a wheal of 3 mm in diameter or larger.

Serum tryptase assay

Five ml of venous blood were withdrawn and we used serum separator tube and samples were allowed to clot for 30 minutes before centrifugation for 15 minutes at approximately 1000 × g. Sera were either assayed immediately or stored at -20° or -80° for further assay within a week, according to manufacturer's instructions using commercial immunoassay kit "Tryptase-1 ELISA Kit, EIAab, Germany".

Statistical analysis

The data were coded, entered and processed on an IBM-PC compatible computer using SPSS software version 15 (SPSS Inc., Chicago, IL, USA). The level $P < 0.05$ was considered the cut-off value for significance. Frequency, number and percentage represented qualitative data whilst, mean and standard deviation (SD) represented quantitative data. Chi-Square test χ^2 was used to test association variables for categorical data; while, Unpaired (Student's) *t*-test was used to assess statistical significance of the difference between two population means. In addition, ANOVA (Analysis Of Variance) was used to evaluate the statistical significance of the difference between more than two population means. Correlations between data were analyzed using Spearman's rank correlation test.

Results

Data of both asthmatic subgroups and healthy control groups are shown in Table 1. Age, sex distribution did not differ among studied groups ($P > 0.05$). However, asthmatic children were significantly exposed to passive smoking in comparison to healthy controls ($P < 0.05$). Frequency of atopic history and positive skin prick test significantly increased among obese asthmatic group more than non-obese asthmatics ($P < 0.05$, OR = 1.96, 95% CI = 1.27–3.24). Most studied children belonged to an urban residence near to study center (Cairo, Egypt), so residence can't be attributed as a predisposing factor for asthma in this study.

FEV₁% of predicted mean levels were lower with statistical significance among asthmatics when compared to healthy

controls, and also among obese asthmatics in comparison to non-obese asthmatics ($p < 0.05$) (Table 1).

Serum tryptase (ST) concentrations were significantly higher in asthmatics ($n=60$) than in controls ($n=30$) with a mean \pm SD of 53.3 ± 13.78 ng/ml and 10.06 ± 4.39 ng/ml respectively. Serum tryptase levels were significantly higher in obese asthmatics than those non-obese with a mean \pm SD of 71.73 ± 19.17 ng/ml and 34.5 ± 8.68 ng/ml respectively ($P < 0.05$) (Table 1). However, ST didn't differ in both asthmatic groups as regards sex (Table 2).

There was a negative correlation between serum tryptase and FEV₁ % of predicted in asthmatics whether obese or non-obese (Table 3). There were positive correlations between ST and age, BMI, and waist circumference among both groups of asthma (Table 3).

Discussion

The concomitant rises in both obesity prevalence and asthma prevalence have led to theories on the relationship between two diseases [12]. Obesity and asthma share common etiologies, for example, common effects of fetal programming or common genetics [13]. Furthermore, asthma has a higher prevalence in overweight and obese [14]. Obesity is accompanied by adipocyte death and accumulation of macrophages and mast cells in expanding adipose tissues [15]. Tryptases are serine peptidases highly abundant in granules of human and animal mast cells [16]. Therefore, baseline serum tryptase levels are mainly an indicator of an individual's mast cell burden [17].

Current data of higher levels of serum tryptase obese asthmatic group than non-obese asthmatic and its negative correlation with FEV₁ % of predicted support the speculation that the interaction between mast cells and airway smooth muscle plays a critical role in asthma and thus tryptase is a mitogen for airway smooth muscle cells [18]. Tryptase-stimulated airway smooth muscle cells can attract mast cells through stem cell factor and TGF- β 1, providing a positive feedback mechanism that increases both smooth muscle cell and mast cell numbers in the airways [19]. Indeed, airway smooth muscle mass is increased in asthmatic airways [18], and mast cell infiltration of airway smooth muscle bundles 'mast cell myositis' appears to be a distinguishing feature of the asthmatic phenotype [19].

This comes in agreement with Sommerhoff and Schaschke [20], who provided a convincing evidence that tryptase B is not only a clinically useful marker of mast cells and their activation but that it contributes to the pathogenesis of allergic inflammatory disorders, most notably asthma. However serum tryptase levels did not relate to the degree of asthma symptom scores, PEF or FEV₁ in study of Taira et al. in 2002 [21].

A BMI for age at \geq 95th percentile of CDC reference population is a specific indicator of excess adiposity for most children and teens [22]. Central obesity has been associated with the risk of cardiovascular and metabolic disease in children and the most important index of central obesity is waist circumference [23].

Our reports that atopic history is significantly higher among obese asthmatics- whose serum tryptase levels are the highest- disagrees with Komarow and his coworkers [24], who failed to show a significant association between serum tryptase and atopy. In contrast to our study, they assessed atopic state through measuring total IgE not SPTs.

We reported that serum tryptase levels were statistically correlated and increasing with age and BMI. Higher serum tryptase levels among obese asthmatics when compared to non-obese asthmatics can not only add to the fact that low-grade inflammation and different adipokines associated with obesity could be the pathogenesis' mechanism linking obesity to asthma [25], but also can link obesity to atopic asthma and more severe grades of asthma.

Obesity might increase the number of mast cells, which in turn would make the individual more prone to a mast cell-dependent asthmatic response on allergen exposure [26]. A similar finding has been reported by Lugogo and his colleagues [27], in an elegant study categorizing obese asthmatics as a unique phenotype based on markers of airway inflammation.

Furthermore, waist circumference -which points to visceral obesity [23], was positively correlated with serum tryptase.

Table 1: Demographic and Clinical Data of Asthmatic Patients and Control Groups.

	Asthma		Control (n=30)
	Obese (n=30)	Non-obese (n=30)	
Age in years, Mean \pm SD	9.53 \pm 3.08	9.90 \pm 2.77	9.20 \pm 2.77
Sex (male/female)	19/ 11	18 / 12	34 / 26
Passive smoking*	13 (43.3%)	17 (56.7%)	18 (30%)
Positive history for atopy *	24 (80%)	13 (43.3%)	0.00
Positive skin prick test *	24(80%)	13(43.3%)	0.00
FEV ₁ % pred., Mean \pm SD *	74.50 \pm 5.04	83 \pm 4.08	94 \pm 6.02
BMI kg/m ² , Mean \pm SD*	31 \pm 1.03	18.12 \pm 2.1	17.5 \pm 3.11
Waist circumference (cm)*	86.53 \pm 13.02	57.42 \pm 8.52	58.79 \pm 6.85
Waist/Hip Ratio (WHR)*	1.1 \pm 4 0.21	0.85 \pm 0.03	0.80 \pm 0.02
Serum tryptase (ng/ml), Mean \pm SD*	71.73 \pm 19.17	34.5 \pm 8.68	10.06 \pm 4.39

FEV₁ % pred.: forced expiratory volume in first second percentage of the predicted value; * $P < 0.05$ (significant).

Table 2: Serum Tryptase in Asthmatics Groups in Relation to Gender.

Group	Serum Tryptase (ng /ml) , Mean \pm SD		P
	Male Patients (n=19)	Female Patients (n=11)	
Obese Asthmatics	76.82 \pm 16.46	68.79 \pm 20.41	0.276 \ddagger
Non-obese Asthmatics	34.33 \pm 9.86	34.61 \pm 8.42	0.935 \ddagger

\ddagger No significant difference.

Table 3: Significant Statistical Correlations between Serum Tryptase and Other Studied Parameters in Asthmatic Groups.

Correlations	Obese group		Non-obese group	
	r	P	r	P
FEV ₁ % Pred.	- 0.47	0.008*	- 0.36	0.048*
Age in years	0.531	0.007*	0.403	0.027*
BMI	0.42	0.025*	0.39	0.04*
Waist circumference (cm)	0.299	0.019*	0.47	0.125

BMI: body mass index, * significant ($P < 0.05$); r Spearman's correlation coefficient.

Obesity is accompanied by adipocyte death and accumulation of macrophages and mast cells in expanding adipose tissues. The increase in mast cells in visceral fat of obese mice [15] and in human subcutaneous abdominal fat [2], suggests their role in the pathogenesis of obesity and insulin resistance and inflammatory status [2,15]. Similarly, in an adult prospective study examining the effect of fat distribution on asthma found that abdominal obesity was a risk factor for incident asthma in males and females. They concluded that metabolic syndrome and two of its components (high waist circumference and elevated glucose) were associated with an increased risk of incident asthma in adults [28].

Conclusion

If mast cells play a role in both obesity and asthma, serum tryptase, being a marker of mast cell activation, could theoretically represent a link between them. The effectiveness of tryptase inhibitors to ameliorate allergic inflammatory reactions and obese-asthma phenotype is a considerable area for pharmaceutical researches.

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