

The relationship between body mass index and increased airway reactivity based on methacholine challenge test results

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Abstract

Introduction: According to the reports of the United States National Bureau of Statistics regarding the prevalence of obesity among adults and children and also asthma outbreak, the relationship between asthma and obesity in developed countries is taken into consideration.

Aim: Relationship between body mass index and increased airway reactivity based on methacholine challenge test results.

Material and methods: It was a retrospective cross-sectional study done on 256 patients who were referred to the lung clinic of the Imam Khomeini Hospital of Ahvaz with symptoms of hypersensitivity of the airways. The patients, who had normal spirometry, were examined by the methacholine challenge test and then they were divided in two groups with positive and negative test results.

Results: The patients of this study were 12–84 years old and their average age was 36.3 ± 12.1 years. Their mean body mass index (BMI) was 28 ± 4.7 kg/m² in the group with positive methacholine and 26.7 ± 4.9 kg/m² in the group with negative methacholine ($p = 0.04$). It was shown that there has been a statistically significant relationship between BMI and positive methacholine challenge test results (apart from confounding effects of other variables). It seems that the positivity rate of methacholine test rises by 1.06 with an increase in BMI by each unit ($p < 0.05$).

Conclusions: According to the results of this study, it can be said that in high BMI there is a statistically significant association between gender (female) and a positive methacholine challenge test result; but there is no statistically significant association between the methacholine dose and BMI.

Key words: methacholine, body mass index, hypersensitivity of the airways.

Introduction

Asthma is the most common chronic disease around the world, so now about 300 million people are infected with this disease. For 30 years the prevalence of asthma has increased in rich countries, as currently it affects about 10–12% of adults and 15% of children. In developing countries, where the prevalence of asthma has been much lower, now it seems raised due to urbanization increase. At the same time, the prevalence of atopy and other allergic diseases has increased. A physiological disorder characterized by asthma is airway hyperresponsiveness (AHR) [1]. The bronchial constriction occurs in response to different inhaled stimuli. So, one of the goals

of asthma treatment is to reduce AHR [1, 2]. Increased bronchial hypersensitivity and bronchial constrictions occur with direct administration of bronchodilators such as histamine and methacholine, which cause constriction of bronchial smooth muscles [3]. According to stimulating factors for asthma, there is a relationship between some agents and asthma. Some factors cause asthma such as atopy, air pollution, diet lacking antioxidant, polyvalent unsaturated fats omega 3, allergens in the environment and cigarettes [4].

Recently, the relationship between asthma and obesity has been considered in developing countries and some related studies have been conducted. Vital capacity has

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a significant association with body mass index (BMI). In obese persons, their chest expansion is reduced and also they have limitations in increasing the lung volumes [5]. There are controversies about the relationship between AHR and obesity. The association between them has not been proved yet [6].

Aim

The aim of this study is to evaluate the association between BMI and increased AHR based on methacholine challenge test results.

Material and methods

Methods

This research was a cross-sectional descriptive and analytic study in which the relationship between BMI and increased airway reactivity based on methacholine challenge test results in the Khuzestan province was assessed.

Place of the study

This research was carried out in the Khuzestan province, which is one of the southwestern provinces in Iran. This research comprised the patients who were referred to the lung clinic of the Imam Khomeini Hospital, affiliated to the Ahwaz Jundishapur University of Medical Science.

Materials

Study data were collected for the adult patients who were referred to the lung clinic of the Imam Khomeini Hospital with symptoms of cough, dyspnea or wheezing and lacking previous diagnosis of asthma (forced expiratory volume in 1 s (FEV₁) < 70%, response to bronchodilator). They were selected and had the spirometry test performed based on criteria of American Thoracic Society/exercise channel test (ATS/ECT).

Procedure

After obtaining approval from the Ethics Committee of the Medical University of Ahwaz, from Jun 1, 2015 to Apr 20, 2016 all people who were referred to the lung clinic were chosen as the target population. The aim of this study was to assess the relationship between obesity and airway hyperresponsiveness to the methacholine challenge test. After participants gave informed consent and completed the testimonial, they entered the study. Then they were tested by the methacholine challenge test and the collected data were analyzed using statistical software SPSSv22.

Sample size and sampling method

The sampling method used in this study was based on the census and all 256 patients referred to the lung clinic in the Imam Khomeini Hospital were studied from Jun 1, 2015 to Apr 20, 2016.

Compliance with Ethical Standards

This study was funded by the Ahwaz Jundishapur University of Medical Sciences.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical committee of the Ahwaz Jundishapur University of Medical Sciences with reference number: IR. AJUMS. REC. 1394. 80.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Inclusion and exclusion criteria

We have excluded those patients with:

1. Spirometry test result suggesting the diagnosis of asthma.
2. Heart attack or stroke during at least 3 months.
3. Uncontrolled blood pressure (systolic blood pressure (SBP) > 200 mm Hg or diastolic blood pressure (DBP) > 100 mm Hg).
4. Known case of aortic aneurysm.

Inclusion criteria of patients in this study:

1. People who wake up at night because of shortness of breath and due to heart problems investigated but they have no heart problems.
2. Patients who have clinical symptoms of asthma (shortness of breath, wheezing and coughing) but had normal spirometry results.
3. Patients who had non-specific symptoms (chronic cough with or without shortness of breath).
4. Patients who were suspected of having occupational asthma (symptoms in the workplace).
5. Those who after contact with irritants (perfumes, detergents, air pollution, etc.) may have increased sensitivity of the airways.
6. Those who intend to get hired in sensitive jobs and are suspected to have had asthma (pilots, astronauts, or join the army, etc.).

The rest of patients took the methacholine challenge test based on the guideline of ATS/ECT taking into account contraindications.

Methacholine challenge test procedure

The methacholine challenge test was done via 2-minute tidal breath.

In our study, methacholine challenge test doses were from 0.125 to 16 mg/ml so that at each stage, dose concentration doubled in comparison with the previous stage. For statistical analysis to evaluate the association of the methacholine dose and BMI, data were classified into three groups: ≤ 1 mg/ml, 1–4 mg/ml, and ≥ 4 mg/ml. At any stage at which $FEV_1 > 20\%$ was reduced, the test was considered positive and the intensity of this reactivity was identified according to the symptoms and reduction in $FEV_1 > 20\%$ in the specified dose. In this research, the patients were asked a question about the drugs they have taken for the last 48 h. Taking drugs like Albuterol, Isoproterenol, Metaproterenol 8 h before the test, intermediate-acting bronchodilators (Atrovent) 24 h before the test, long-acting bronchodilators (Formoterol, Tiotropium bromide) 48 h before the test, Theophylline, Beta_2 Agonists, Cromolyn sodium, Nedocromil, Hydroxyzine, Cetirizine, Leukotriene modifiers 12–48 h before the test should be avoided by the patients.

Methacholine is a crystalline powder that is dissolved in normal saline solution 0.9% without phenol. Thirty minutes before the test, the methacholine solution was taken from the refrigerator and 2 cc of the initial concentration was poured in the nebulizer; the patient was asked to sit in his own place in front of the device and using the nebulizer, to inhale the solution for 5 min and then we measured FEV_1 . After each inhalation, the place of the solution was thoroughly cleaned to prevent the drug accumulation effect. If FEV_1 fell less than 20%, 2 cc of the next dose was poured into the nebulizer chamber after emptying and drying the nebulizer, and if FEV_1 fell more than 20%, the next dose was not given to the

patient and his symptoms were recorded and the albuterol inhaler was given to him, then we waited 10 min and performed spirometry. During the test, the patient's nose was closed with a nose clip. According to the ATS/ECT guideline, the intensity of airway reactivity can be described as follows:

- If the methacholine dose to response is 16 mg/ml, it means lack of AHR.
- If the methacholine dose to response is 4.0–16 mg/ml, it means borderline response to airway hypersensitivity.
- If the methacholine dose to response is 1.0–4.0 mg/ml, it means mild response to AHR.
- If the methacholine dose to response is 1 mg/ml, it means moderate to severe response to AHR [9].

Statistical analysis

For data analysis in this study, descriptive statistic determination like frequency, mean, SD and analytical statistics such as independent two-sample *t*-test, χ^2 and binary logistic regression were used. In this research, the data were analyzed with SPSS software (version 20) and *p*-value < 0.05 was considered as a statistically significant level.

Results

The average age of the participants in this study was 36.3 ± 12.1 with the age range of 12–84 years. 46.5% (119 patients) were males and 53.5% (137 patients) were females. The average BMI of the patients was about 27.3 ± 4.8 kg/m². In this research, 256 participants were divided into two groups of 128 patients based on positive and

Table 1. Demographic and clinical characteristics of the participants in the study in terms of both positive and negative methacholine

Variables	Negative methacholine (128)	Positive methacholine (128)	P-value
Age	36.7 \pm 12.1	35.8 \pm 12.1	0.86
Gender:			0.26
Male	64 (50%)	55 (43%)	
Female	64 (50%)	73 (57%)	
BMI [kg/m ²]:			0.10
≤ 25	51 (39.8%)	35 (27.3%)	
25.01–29.99	44 (34.4%)	52 (40.6%)	
≥ 30	33 (25.8%)	41 (32%)	
Methacholine inhaled dosage:			> 0.001
≤ 1	0 (0%)	85 (66.4%)	
1–4	2 (16%)	17 (13.3%)	
≤ 4	126 (98.4%)	26 (20.3%)	

negative methacholine challenge test results. The average age of the participants in the positive methacholine group was 35.8 years and in the negative methacholine group – 36.7 years. In positive and negative methacholine groups, 55 (43%) patients and 64 (50%) patients were males, respectively. Other characteristics of the participants are shown in Table 1.

The average BMI of patients in the positive group was $28 \pm 4.7 \text{ kg/m}^2$ and in the negative group it was $26.7 \pm 4.9 \text{ kg/m}^2$, this difference in mean values is significant ($p = 0.04$). Also in checking data, distribution of participants into two groups – positive and negative methacholine ones based on their BMI, distinguishing three groups of physical parameters (i.e. BMI less than 25 kg/m^2 , between 25.01 and 29.99 kg/m^2 , more than 30 kg/m^2) were investigated. The results showed that in the positive and negative methacholine groups, 33 and 41 patients had $\text{BMI} \geq 30$ and 44 kg/m^2 and 52 patients had $\text{BMI} 25.01\text{--}29.99 \text{ kg/m}^2$, respectively, and that this difference was not statistically significant ($p > 0.05$).

According to the assessment of frequency distribution of the relationship between BMI and the inhaled methacholine dose to the positive methacholine challenge test, for describing these data, it must be said that:

- A. In the positive group with $\text{BMI} \geq 30 \text{ kg/m}^2$:
 - 68.3% (28 patients) with a minimum dose of methacholine ($\leq 1 \text{ mg/ml}$), had hypersensitivity reactions of the airways (moderate to severe reactivity),
 - 12.2% (5 patients) with $1\text{--}4 \text{ mg/ml}$ dose of methacholine, had hypersensitivity reactions of the airways (mild reactivity),
 - 19.5% of the group with $\geq 4 \text{ mg/ml}$ dose of methacholine had hypersensitivity reactions of the airways (intermediate sensitivity);
- B. In the positive group with BMI between 25.01 and 29.99 kg/m^2 :
 - 71.2% (37 patients) were diagnosed with moderate to severe sensitivity,
 - 15.4% (8 patients) were diagnosed with mild sensitivity,
 - 13.5% (7 patients) were diagnosed with intermediate sensitivity;
- C. In the positive group with $\text{BMI} \leq 25 \text{ kg/m}^2$:
 - 57.1% (20 patients) were diagnosed with moderate to severe sensitivity,
 - 11.4% (4 patients) were diagnosed with mild sensitivity,

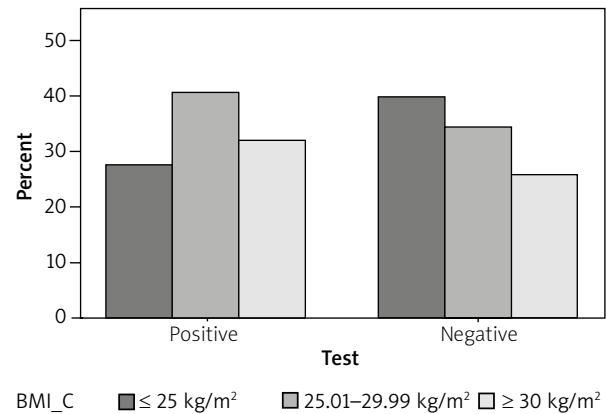


Figure 1. Individual distribution of sub-groups based on body mass index (BMI)

- 31.4% (11 patients) were diagnosed with intermediate sensitivity [7].

In data analysis, p -value was equal to 0.37, which means that in the positive methacholine test, there was no significant association between the dose of methacholine and BMI.

Also, in the survey of the relationship between the dose of methacholine and BMI, in the negative methacholine test, the results have shown no significant relationship ($p = 0.054$).

Finally, in the results of the logistic regression model to examine the variables like age, gender and BMI on the positivity rate of the methacholine challenge test, it was shown that there was a significant relationship between BMI variable and the positive methacholine challenge test in the crude analysis, which was meaningful disregarding the effect of other confounding variables. In other words, it seems that with any unit increase in BMI, the positivity rate of the methacholine challenge test rises by 1.06 (Table 2, Figure 1).

It is remarkable that in this study, there is no statistically relationship between age and sex (male-female) and the positivity rate of the methacholine challenge test ($p > 0.05$) (Table 3).

Discussion

In 2008, a study on 23 obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) and 26 non-obese persons, among the non-asthmatic people

Table 2. The results of the effects of age, gender and body mass index on the variable rate of the positive methacholine challenge test using a single and multiple logistic regression model

Variables	Crude coefficients			Adjusted coefficients		
	OR	95% CI	P-value	OR	CI	P-value
Age	0.99	0.974–1.015	0.57	0.99	0.97–1.01	0.30
Gender	1.33	0.811–2.172	0.26	1.21	0.73–1.99	0.47
BMI	1.06	1.003–1.114	0.04	1.06	1.005–1.121	0.03

Table 3. Distribution of the methacholine dose used in people with a positive methacholine test based on body mass index subgroups

Parameter	Dose met-C			Total		
	≤ 1	1-4	≤ 4			
BMI [kg/m ²]	≤ 25	Count	20	4	62	86
		% within BMI_C	23.3	4.7	72.1	100.0
	25.01-29.99	Count	37	8	51	96
		% within BMI_C	38.5	8.3	53.1	100.0
	≥ 30	Count	28	5	41	74
		% within BMI_C	37.8	6.8	55.4	100.0
Total	Count	85	17	154	256	
	% within BMI_C	33.2	6.6	60.2	100.0	

between 18 and 70 years old, was conducted in Austria. In this study, a high dose of methacholine was used to determine the sensitivity and maximum response to methacholine. Resistance and reaction of the respiratory system by using the forced oscillation technique, dyspnea by using the Borg score and lung volumes by using plethysmograph were measured. The results of this qualitative study showed that the rate of change in the airway resistance was similar in both groups, but obese people had more negative reactions to treatment and severity of their dyspnea was higher. According to the results, obesity reduces lung volume but the sensitivity and maximum lung response to methacholine do not change. Obesity increases the dyspnea symptoms [8].

An investigation in India (2014) was performed on 424 adults who did not develop asthma. The results of this quantitative test revealed a significant relationship between spirometry parameters and BMI in healthy obese people, especially in women [9].

A study in Italy (2002) was done on 1426 people aged over 24 years in relation to BMI changes. Spirometry was performed on participants and then lung volume was measured with respect to BMI and gender. The results of this quantitative study showed that BMI of men rather than of women has a significant association with lung capacity. Also, BMI is a better prediction for lung volume in men [10].

In 2012, a quantitative study was conducted on 4217 adults whose results demonstrated that obesity only in women can increase airway sensitivity and bring its moderate degree. This effect can be due to changes in obesity on the lung function [11].

A survey (2008) was performed on 861 adults with regard to obesity and AHR. Among them, 401 participants had AHR and the medium dose of methacholine was 4.16 ± 2.25 mg/ml. The results showed that obesity increases the risk of hypersensitivity airways and leads to the development of asthma [12].

A survey in Chile (2005) was conducted on 1232 individuals with respect to obesity and asthma. People in this

study suffered from atopy (skin test) and had high sensitivity of bronchi. The results of this quantitative study showed that BMI was negatively associated with airway hypersensitivity and waist size has no relationship to asthma symptoms and has a negative association with hypersensitivity of the airways [13].

In a study in India (2014) which was conducted on 158 people (90 men and 68 women) based on the impact of gender and BMI in lung volume change and PFTs were performed on all patients. It revealed that gender diversity was found significant at the normal levels of pulmonary function tests. Body mass index in men was negatively associated with forced vital capacity and the grades of BMI in women show better prediction of lung function [11].

In 2012, a study in South Korea was carried out on 852 patients with asthma to investigate the relationship between obesity and AHR. Patients were divided into 4 groups: obese, overweight, normal and underweight and also the samples were tested by the methacholine challenge test to determine AHA. The results of this quantitative study presented that obesity is generally a driving factor for asthma but obesity in people with asthma is negatively correlated with the severity of AHR and asthma symptoms. Obesity in patients with asthma is significantly associated with the prevalence of dyspnea but negatively correlated with AHR [14].

A research in America (2002) was performed with regard to BMI and the development of AHR. Sixty-one men who did not have AHR in the initial methacholine challenge test but developed AHR 4 years later. Two hundred forty-four control samples participated in this study. The effects of initial BMI and its changes in the development of AHR were evaluated. The results of this qualitative study showed that in the men's group, both low and high BMI were associated with an increase in AHR [15].

A survey in 2012 was conducted on 200 patients (100 obese men and 100 non-obese men). The results of this qualitative study illustrated that in obese people, there are different reductions in respiratory function that is due to a decrease in chest expansion power and limi-

tation in increasing the volume of the chest cavity and consequently reduction in respiratory volume and total lung volume reduction [16].

Conclusions

The results of this study show that the prevalence of AHR is higher in fat people. With increasing severity of obesity, the hypersensitivity of airways rises.

This investigation illustrates that BMI increases along with AHR. This result of this study is different from some other studies that examined the association between BMI and AHR. In the survey conducted by Salome *et al.*, it was shown that obesity causes a decrease in lung volumes, but it does not affect the response threshold of airways to methacholine.

Also the survey of Bustos *et al.* was shown that obesity and AHR has negative relationship and litonjua study demonstrated that airway hypersensitivity is more current in fat and thin men.

The result of our study is similar to the survey of Kwon *et al.* They showed that obesity is generally a risk factor for, the hypersensitivity of airways, which was lower in obese persons with asthma. This study displayed that the relationship between obesity and hypersensitivity of airways is not affected by sex. In other words, the prevalence of AHR is not different among obese men and women. Our results are against the conclusion of Kwon *et al.* We demonstrated that the association between obesity and hypersensitivity of airways is found among women.

The result of our investigation is inconsistent with the study of Kwon *et al.* about the relationship between the severity of obesity and hypersensitivity of airways due to methacholine. Our study showed that the severity of obesity has a relationship with AHR, while in the study of Kwon *et al.*, the obesity in asthma patients had a negative relationship with hypersensitivity of airways. Also it showed that obesity has been associated with intermediate sensitivity of airways among women.

In this domain, the largest study was conducted by Bruno *et al.* that demonstrated that the relationship of sex with BMI and with hypersensitivity of airways is related to multiple agents like leptin hormone and mechanical factors such as fat distribution in body of men and women and difference in airway diameter is a claim that has not been confirmed by other studies. On the other hand, however the number of patients has been high, there have not been any strong results to reject this relationship.

Also in our study, only intermediate sensitivity of airways in women has an association with obesity, so it is necessary to review other factors that influence the cause and aggravate sensitivity of airways and its relationship with asthma. It is anticipated that above risk factors or stimuli cause hypersensitivity of airways with-

out increasing the intensity or amount of stimuli or factors for hypersensitivity of airway.

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Conflict of interest

The authors declare no conflict of interest.

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