Original Article

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TANAFFOS

Associations between Occupational Asthma and Obesity in the Central Region of Tunisia

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Background: Risk factors for the severity of occupational asthma (OA) are often attributed to occupational exposure. However, some recent epidemiological data suggest a link with obesity. The study aimed to analyze the relationship between obesity and the severity of (OA) assessed by non-specific bronchial provocation.

Materials and Methods: We conducted an epidemiological descriptive retrospective study including patients who were referred to the Occupational Medicine Department of Farhat Hached University Hospital of Sousse, for (OA) and who have completed a non-specific bronchoprovocation test to metacholine.

Results: Our population consisted of 131 cases of (OA) with a female predominance. The average BMI was 27.34 ±5.30 kg. Obesity was observed in 29.8% of cases. The non-specific metacholine bronchial provocation test revealed an average dose of PD20 at 750.4 ±656.3 µg. Severe (OA) was observed in (35.1%). After univariate analysis, obesity in asthmatics had a significant association with age (p<0.001), marital status (p=0.005), average professional seniority (p<0.001), the evolution of complaints (p=0.035) and abnormal initial spirometry (p=0.044). As for the severity of (OA), the univariate analytical study did not show a significant link with obesity (p=0.68).

Conclusion: The association between obesity and OA is not an easy task and should be made using more accurate tools to measure body fat percentage. The preventive role of the occupational physician is essential in factories in order to make more prudent decisions when employing workers with a high BMI in high-risk occupations. Hence the importance of regular monitoring of weight in workers exposed to asthmatics during periodic examinations.

Keywords: Occupational asthma; Obesity; Nonspecific bronchial provocation test

INTRODUCTION

Occupational asthma (OA) is one of the most frequent respiratory diseases in the workplace in industrialized countries. It represents a major health problem with significant socio-economic impacts (1). OA is characterized by airway inflammation, variable bronchial obstruction, and bronchial hyperreactivity triggered by agents and work-related situations (2). This multifactorial and complex disease results from the effects and interactions of multiple genetic, environmental, and behavioral factors (3). Severe forms of asthma are increasingly frequent and life-threatening.

The severity of asthma is multidimensional: biological, physiological, functional, and economic (4). To assess the

severity of asthma in our study, we used the severity criteria of the non-specific bronchoprovocation test to methacholine (5).

The incidence of asthma and obesity has increased significantly over two decades in most countries around the world. Nevertheless, a number of epidemiological, clinical, and pathophysiological data support a real association between the two conditions (6). To our knowledge, no survey has yet analyzed obesity as a severity factor for work-related asthma; however, substantial attention has been given to obesity as a risk factor for asthma due to the observed dyspnea in obese individuals (7).

In this context, we carried out a retrospective epidemiological study on all the cases of OA diagnosed in the Occupational Medicine Department of Farhat Hached University Hospital of Sousse between 2004 and 2012 in the perspective of analyzing the relationship between obesity and severity of OA assessed by a non-specific bronchoprovocation test to methacholine.

MATERIALS AND METHODS

Study Population

Our survey is a descriptive retrospective study, covering all patient records referred to the Occupational Medicine Department of Farhat Hached University Hospital of Sousse for occupational asthma during 2004-2012.

Included cases were patients diagnosed with occupational asthma in accordance with the diagnostic approach of occupational asthma of the Tunisian consensus on the diagnosis and compensation of occupational asthma established in January 2003. It includes the use of respiratory functional tests (spirometry, non-specific bronchoprovocation test to methacholine) (8).

Data Collection

The data collection was carried out using a pre-established questionnaire on several items: socio-demographic, occupational, and medical characteristics, test results of complementary investigations (spirometry; reversibility test, non-specific bronchoprovocation test to methacholine); as well as information related to the declaration of the occupational disease.

Definition of variables

Our study used the classification adopted by the WHO (9). BMI appeared to be a good proxy for adiposity and overweight-related problems. To measure the height a medical measuring rod was used, the patient stands upright with his feet joints back to the wall and without shoes. The moving part of the measuring board is brought back into contact with the head. To calculate the weight, the patient places himself undressed on the scales symmetrically and remains motionless until the measurement stabilizes. The measurement conditions were identical (same operator, same equipment, same calibration, etc.) (10).

According to the National Health Authority (HAS), the diagnosis of obesity and the characterization of its level is no longer based only on the measurement of BMI and waist circumference. In addition to these two criteria, the level of severity of the associated pathologies, the functional impact, the psychopathological context, the existence of a disability, eating behavior, and the impact on the quality of personal or professional life are new parameters now making it possible to characterize obesity (11). In our study, we relied merely on the measurement of the BMI as presented in Table 1.

Table 1. BMI Classification by the WHO

WHO Classification	BMI (kg/m²)
Malnutrition	16.5
Underweight	16.5-18.4
Normal weight	18.5 – 24.9
Overweight	25 – 29.9
Obesity	>=30
Class 1 (Moderate)	30 – 34.9
Class 2 (Severe)	35 – 39.9
Class 3 (Very Severe)	>40

The severity of OA was assessed according to the PD20 classification (Provocative dose causing a 20% drop in FEV1) as follows (5):

-Severe: Dose of Methacholine (<300 µg)

-Moderate: Dose of Methacholine (300 µg -1500 µg)

-Low: Dose of Methacholine (>1500 µg)

This survey was approved by the ethics committee of the Faculty of Medicine of Sousse and has respected the consent of the participants.

Statistical analysis

All statistical analyses were performed using SPSS statistics version 24.0. Frequencies and percentages were calculated for qualitative variables and means, standard deviations, medians, and range of extreme values were calculated for quantitative variables.

RESULTS

During the study period, 131 patients with OA were collected at the occupational medicine department of the Farhat Hached University Hospital. The mean age was 38.31 ± 8.55 years with extremes of 16 and 58 years. A female predominance was noted with a sex ratio of 0.48. Most of our patients were married (71%) and 23.7% were single.

As for occupational data, the majority of workers were employed in the textile sector (66.4%) followed by the wood industry (6.9%) and automotive and mechanical industry (4.6%).Only 3.8% of the population worked in food, hotels, and rubber industries, while 3.1% worked in the chemical industry. Metallurgical, leather, and shoe manufacturing were the occupations of only 2 individuals. The other occupations, such as plastic, paper, construction, electronics, and healthcare sectors, each reported only one case of OA.

More than half of our population (61.8 %) has no professional qualification, while only 6.9 % were skilled with an average professional seniority of 16.01 ± 8.9 years. Vegetable textile dusts (cotton dusts) were the most common etiological agent found in 66.4% of the cases. Wood and cork represented 6.9% of the agents involved and acrylic resins were responsible in only 4.6% of the cases of OA. Overall, high molecular weight agents were incriminated in 74.8% and 25.2% were attributed to low molecular weight agents.

Respiratory complaints of our patients, appearing after an average delay of 10.75 ± 8.4 years, were respiratory discomfort in 42%, followed by expiratory dyspnea in 27.5% and typical seizure in 16% of cases, while dyspnea on exertion was observed in only 4.6% of cases. These complaints followed an occupational rhythm in 60.3% of cases.

Physical respiratory examination was normal in almost all of our population (82.9%), while the presence of wheezing was noted in only 16 patients (12.2% of cases). The mean BMI was 27.34 ± 5.30 Kg/m2 with extremes of 17.10 and 41.32 Kg/m^2. One-third of the population (34.4%) had a normal BMI, 32.8% were overweight, and obesity was observed in only 29.8% of the population (Moderate: 21.4%, Severe: 6.9%, and very severe: 2 cases).

Regarding additional investigations, basic respiratory functional explorations were normal in 63.4% of cases, while obstructive syndrome was found in only 33.6% of cases. The average of FEV1, CV, and DEM25-75 values were 92.55 ± 13.87%, 94.23 ± 13.35%, and 73.41 ± 18.63%, respectively. The reversibility testing was performed only in 10 patients (7.7%) and was positive in 9 cases (6.9%). The non-specific bronchoprovocation test with methacholine revealed that the mean dose of PD20 was 750.4 ± 656.3 µg with extremes of 50 and 2600 µg. Thus, 65 patients had moderate OA (49.6%), 46 cases had developed severe asthma (35.1%), and low form was observed in only 20 cases (15.3%).

In terms of compensation, the recognition of occupational diseases was made for 105 patients (80.2%) out of the study population. Permanent partial disability rates were attributed to 101 cases of OA (77.1%) during the study period with an average of 21 ± 6.8% and extremes of 11% and 40%. Univariate analysis revealed significant associations between BMI and the variables (Table 2).

The severity of OA had no statistically significant association with studied variables (Table 3). Indeed,

patients with severe OA were older, female, had longer job tenure, and were mainly exposed to high molecular weight asthmagens, although the differences were not statistically significant (p=0.7; p=0.45; p=0.81; p=0.8 respectively). Similarly, the severity of OA was not significantly correlated with rhinitis (p=0.33) and smoking (p=0.89).

Table 2. Variables statistically associated with obesity among OA patients

Variables	p	r
Age	$<10^{-3}$	0.37
Professional seniority	$<10^{-3}$	0.3
The delay for the development of signs	0.035	0.2
Marital status	0.005	
Pathological base line spirometry	0.044	

Table 3. Statistical analysis between the severity of OA and the studied variables

		Severe OA	Non severe OA	p
Age		40.1 years	37.3 years	0.7
Gender	Female	29	59	0.45
	Male	17	26	
Sector	Textile	31	56	0.86
	Other	15	29	
Professional Seniority		16.16	15.87	0.81
Molecular weight	Low	11	22	0.8
	High	35	63	
Rhinitis	Yes	23	50	0.33
	No	23	35	
Smoking	Yes	4	8	0.89
	No	42	77	
BMI		27.08	27.80	0.68

Although the average BMI was higher in patients with non-severe OA than in patients with severe OA (27.8 vs. 27.08 kg/m^2), this difference was not statistically significant (p =0.68). On the other hand, the average PD20 in obese patients was lower than in non-obese patients (733 µg vs. 757.8 µg) but without a statistically significant difference (p=0.84).

Multivariate analysis did not show any statistical association between OA severity and the studied variables.

DISCUSSION

OA incidence varies between countries (from 13 new cases per million workers in Quebec to 178 new cases per million workers in the United States) and industries (1.8 cases per 100 person-years for healthcare workers using latex gloves and 4.1 cases per 100 person-years among workers exposed to wheat flour) (12). Approximately, up to 25% of adult-onset asthma is work-related (13, 14).

In Tunisia, the prevalence of OA was estimated at 7.17% of all occupational diseases and 44.19% of reported respiratory diseases (15). In our study, among the 131 collected cases of OA, only 35.1% had severe asthma and 29.8% were obese, with no statistically significant association between obesity and asthma severity (p =0.68).

Obesity has been recognized as a chronic disease since 1997 by the WHO. According to this organization, the prevalence of obesity almost tripled globally between 1975 and 2016. Generally, about 13% of the world's adult population is obese (16). Diagnosis of obesity is usually established by calculating a BMI ≥ 30 kg/m^2 (17).

In the workplace, obesity has become a major concern due to its significant socioeconomic impact. In our study, 29.7% of participants were obese. Similar results were found in an American study conducted in 29 states, where the prevalence of obesity was 27.8% among employees, and 39% of those working in the transport sector (18).

This sudden rise in the prevalence of obesity has affected the epidemiology of many pulmonary diseases. Asthma is one of the best-characterized diseases related to obesity. The relationship between obesity and asthma was first described in 1999 by Camargo et al. (19). Since then, several studies have shown the significant risk of asthma in obese children and adults (20). A meta-analysis involving over 300000 adults found that obesity and asthma are related, and the risk of asthma increased with increasing BMI (21). Although a minor proportion of asthmatic patients suffer from severe asthma (22), it carries the majority of morbidity and use of care as well as a high rate of work absenteeism compared to patients with mild or moderate asthma (23).

However, the association between obesity and the severity of asthma assessed by the BHR is still the subject of much research with some persistent ambiguities (24).

Our results were similar to those found in the Australian study by Schachter et al. showing that there is

no relationship between obesity and BHR (25). There is no increased risk of BHR in people who are overweight or obese. A cohort study carried out by Kwon et al. in Korea on a total of 852 asthmatic patients diagnosed based on the BHR confirmed by a methacholine bronchial provocation test had shown that obesity in asthmatics was negatively correlated with the intensity of BHR and not related to the severity of asthma. Obesity is rather positively related to wheezing but negatively related to BHR (26). Other studies have consistently shown no relationship between obesity, asthma, and BHR (27, 28).

In our study, the non-specific bronchoprovocation test with methacholine revealed that 65 patients had moderate OA (49.6%), 46 cases had developed severe asthma (35.1%), and low form was observed in only 20 cases (15.3%). The univariate analytical study did not show a significant link with obesity (p=0.68). These inconsistent results may be attributable to the heterogeneity of the study populations, possibly including sex distribution, the proportion of normal weight, the regional origins, the definition of asthma, and the obesity measurement tool.

Obesity can be categorized into different types assessed by a corresponding obesity index, and different types of obesity can influence asthma risk differently (29). Most previously published studies have used BMI as an index of obesity due to its clinical utility (30, 31). However, BMI may not be an accurate method for measuring body fat, especially in men, and has several limitations and is no longer the best marker of obesity (32). This problem may be responsible for the absence or weak correlation between BMI and OA in our study. Gonzalez-Barcala et al. (30) have stated that BMI would not perfectly estimate adiposity, would not distinguish muscle from fat, and would not reflect body fat distribution (33). Assessing body fat distribution with other measures such as waist circumference or waist-to-hip ratio can improve the assessment and diagnosis of obesity and also more accurately understand its relationship with asthma (17).

On the other hand, numerous studies have evaluated the possible correlation between obesity and asthma (24), such as the one carried out in France on 398 patients who had a bronchial provocation test with methacholine in the Department of Physiology Functional Explorations of the Cochin Hospital, where there was a relationship between obesity and BHR. Obese women and overweight men had a significantly higher risk of BHR compared to subjects with normal weight (34). This same positive association was also found by Jarvis et al. in their ECRHS (European Community Respiratory Health Survey) study (35), and also by Sood et al. in their survey of 1141 obese adults in the United States (36).

Another meta-analysis of 7 prospective studies in adults showed that the prevalence of asthma increases with higher BMI in adults. In overweight subjects (BMI of 25 to 29.9), the risk of asthma increased by 38% in comparison to normal-weight subjects; in obese (BMI≥30) individuals this risk increased by 92% (21).

In comparison to overweight or normal-weight asthmatics, obese asthmatic patients experience more severe respiratory symptoms with higher frequency, greater number of exacerbations, and decreased quality of life due to asthma (37).

Recent studies suggest that the interaction between obesity and asthma is more complex and goes beyond a simple association between excess weight and asthma. Several mechanisms have been proposed to explain this positive correlation: the first incriminated factor is purely mechanical: mass loading of the chest wall and abdomen with adipose tissue decreases the functional residual capacity of breathing and may increase airway reactivity (38). However, patients with obesity breathe at similarly low lung volumes regardless of asthma status (39), so other factors must also be involved. Obesity can also cause chronic systemic inflammation attributable to increased expression of pro-inflammatory mediators and adipokines such as leptin and TNF-alpha and may aggravate BHR (26). High levels of circulating IL-6 produced by adipose tissue macrophages are associated with poor asthma control (40, 41). These pro-inflammatory cytokines provide a possible mechanism in BHR in obese persons (42).

According to some published studies, the American Thoracic Society estimates that 15% of asthma cases in adults are due to occupational exposures (43). Environmental exposure or exposure to some chemical compounds such as indoor and outdoor pollutants can also contribute to the association of obesity and OA (44-46). A study assessing the correlation between the prevalence of OA and BMI among 551 workers in a cable manufacturing company has shown that the prevalence of OA could be higher among workers with a higher BMI who are exposed to occupational asthmatics. The prevalence of asthma in exposed subjects with a BMI>=25kg/m^2 was found to be significantly higher than in exposed workers with a BMI<25kg/m^2 ($p<0.01$) (47).

In addition, data in the literature suggest some other responsible factors for severe forms of OA. The molecular weight of the handled products admits a questionable role. In our study, patients with severe OA had longer job tenure and were mainly exposed to high molecular weight asthmagens, but with no statistical significance ($p=0.8$). This was confirmed by the results of Descatha et al. (48) and Maghni et al. (49). However, according to a prospective study of 99 cases of OA, a less favorable evolution was noted when the causal agent was a high molecular weight allergen (OR: 0.17, CI 95 %: 0.03- 0.99, p=0. 04) (50).

Therefore, the effects of obesity on the clinical features of asthma must be determined in asthmatic patients in order to provide improved management of the growing number of obese or overweight individuals with asthma.

Gender was also suspected. In our study, women had a higher risk of severe OA than men but without a statistically significant relationship ($p = 0.45$). Our results were different from those found in the literature which attests to the significant role of the female gender in asthma severity and BHR. Diem et al found that obese women had a significantly higher risk of BHR compared with normal-weight women (OR = 2.83; 95%CI =1.08 –7.39) (24). Some authors have put forward some explanations.

Anatomically, women's airways are smaller than men's (51). Women's airways are influenced by their sex hormones and also by their cyclical fluctuations (52). In obesity, estrogen concentrations are increased due to the peripheral flavoring of androstenedione to estrogen and testosterone to estrogen in the adipose tissue stroma (21). In addition, the decrease in sexual hormones combined with the globulin found in obesity results in the amplification of the effect of estrogen on sensitive tissues (51). In fact, during menstrual cycles, maximum levels of estrogen have been associated with increased symptoms of BHR and decreased lung function in asthmatic women (36).

Study limitations

The retrospective nature of the study does not allow us to objectify causal relationships. We had also selection bias since only OA cases referred to the occupational medicine department of Farhat Hached University Hospital were considered. Other cases (not having been consulted or referred and followed up in other consultations) could not be collected, and only cases that were explored by non-specific bronchial provocation test with methacholine were included.

The lack of random sampling does not allow generalization of the result at the end of the study, because the study population was constituted by convenience, including cases consulting the Occupational Medicine Department.

In addition, the method used to characterize asthma and obesity may have a relevant impact on the results of our study aimed at evaluating the association of asthma and obesity. Obesity can vary widely, depending on the criteria used to assess body mass. Like any other measure, BMI it is not perfect because it is only dependent on height and weight and it does not take into consideration different levels of adiposity based on age, physical activity levels, and sex. For this reason, it is expected that it overestimates adiposity in some cases and underestimates it in others. Other measures can complement BMI estimates and allow

us to better estimate the relationship between asthma and obesity.

CONCLUSION

This was the first study in Tunisia to assess the correlation between obesity and asthma from the point of view of occupational exposure. In this study, we used BMI as a convenient and easy method of screening and used the WHO definitions for obesity and overweight. Determining the association between obesity and asthma is not an easy task and should be done scientifically using proper and standardized techniques. The lack of such a correlation between obesity and OA may be due to other factors and different occupational exposures may somehow account for this problem.

The discussion of the links between OA and obesity is important in the workplace, given the preventive role of the occupational physician and his awareness-raising actions which can be useful in making more cautious decisions when employing workers with high BMI in occupations with high exposure to asthmatics. Emphasis should be placed on the weight loss of workers exposed to asthmatics during periodic examinations. Given the importance of this issue, larger studies are recommended with more accurate and effective measurement tools to measure body fat percentage rather than BMI.

Conflict of Interest

There is no conflict of interest to declare.

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