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Asthma in Menopausal Women: Clinical and Functional Particularities

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Background: Hormonal changes in women, especially at menopausal transition, may have significant consequences on respiratory function. This issue in asthmatic patients is more frequent, more severe, and less controlled after menopause. Tunisian data regarding this issue are limited; therefore, we assessed the clinical and functional particularities of asthma at menopausal transition.

Materials and Methods: This descriptive-analytical study was performed for two years (2016-2017) on 82 asthmatic women followed up in the pulmonology department of Charles Nicolle hospital of Tunis. According to hormonal status, two groups were defined: G1 (menopausal patients) and G2 (non-menopausal patients). Asthma control and severity of asthma as well as other variables including gender, age, body mass index (BMI), comorbidities, allergenic status, spirometry results, health care use in the past 12 months, and prescribed medications were evaluated.

Results: The mean age of patients was 50 years and half of them (60%) were menopausal women. Allergy was the most common cause of asthma (82%). A mean of 2.3 exacerbations per patient was recorded. Asthma was well controlled in 58% of patients and was moderate to severe in 80% of them. Menopausal asthmatic women had more comorbidities (p=0.006), particularly arterial hypertension (p<0.0001). Atopy was more common in non-menopausal women and they were all allergic (p=0.01). Menopausal asthmatic patients had more airflow obstruction with lower forced expiratory volume 1 and forced vital capacity (p<0.0001). They also had more exacerbations (p<0.0001) with lower PaO2 (p=0.006). Univariate analysis showed that menopause was a predictive factor of severity (p=0.01) and bad control of asthma (p=0.03). Multivariate analysis confirmed that menopause was a predictor of severity (p=0.01; OR=5.02, IC [1.36-18.46]) but not control of asthma despite the tendency to significance (p=0.07).

Conclusion: Our results confirm that menopause is a factor influencing the control and severity of asthma.

Key words: Asthma; Menopause; Control; Severity

INTRODUCTION

Asthma is a multifactorial chronic inflammatory disease of the bronchi. It is a common disease with an increasing prevalence worldwide. According to the World Health Organization (WHO), about 300 million people worldwide have asthma (1). In Tunisia, asthma affects 3 to 6% of adults (2). Male predominance is noted during childhood. However, in adulthood, female predominance

is clear. Hormonal changes in women, especially during menopause, may have important consequences on respiratory function. It may also be responsible for increasing the risk of chronic respiratory disease or the aggravation of a pre-existing one. Hormonal changes in patients with asthma are more common, more severe, and less controlled after menopause (3). Natural menopause according to the WHO is defined as a permanent cessation of menstruation due to a loss of ovarian follicular activity (4).

Limited data is available about this subject in Tunis; therefore, this study was done to assess the clinical and functional features of asthma in peri- and postmenopausal women.

MATERIALS AND METHODS

This descriptive-analytical study was conducted in the pulmonology department of Charles Nicolle Hospital in Tunis.

Women with asthma were included in the study and divided into two groups according to their hormonal status:

- G1: women in peri- or postmenopausal period
- G2: non-menopausal women

Male patients, smokers, those presenting clinical or radiologic features suggestive of other respiratory diseases, especially chronic obstructive pulmonary disease (COPD), bronchiectasis, and pulmonary tuberculosis, and also patients with extra respiratory symptoms suggestive of systemic disease were excluded.

A pre-established sheet was used to collect data from patients' case histories.

The primary dependent variables were asthma control and severity that were defined according to the Global Initiative for Asthma criteria (GINA; 2018) (5). Asthma control was assessed as controlled, partly controlled, and uncontrolled. Asthma severity was classified according to the therapeutic load as mild, moderate, and severe.

The primary independent variable was hormonal status. Peri-menopause was defined as the absence of or irregular menstrual cycles after the age of 45 years. Menstrual cycle disorders before the age of 45 years may be related to hormonal disturbances other than menopause (6); therefore these women were not included. However, non-menopausal women were included regardless of age. When hormonal status was not available in patients' files, they were contacted by phone.

The secondary independent recorded variables were gender, age, body mass index (BMI), comorbidities, allergenic status, spirometry results, health care use in the past 12 months (emergency room and hospitalization), and prescribed medications.

A multivariate analysis was performed for major confounding factors, such as comorbidities and obesity. Patients with fixed airway obstruction were not included in our study in order to avoid confusion with COPD disease.

RESULTS

The subjects' characteristics

Clinical data of 82 asthmatic patients were obtained. The mean age of participants was 50.55±16.19 years (ranged 18-88). Forty percent of the patients (N=33) were in the period of genital activity and 60% (N=49) were in (perimenopause period, of whom 37% were in the postmenopausal period.

Atopy was noted in 56% of patients. Asthma was allergic in 82% of cases. The most prominent allergens were mites (71%), pollen (43%), and animal dander (25%). Polysensitization was documented in 36% of patients. Spirometry was without anomalies in 30% of cases. Also, 24% of the cases showed obstructive syndrome.

In addition, 189 patients had exacerbations in the last 12 months, with an average of 2.3±2.17 exacerbations per patient. Exacerbations were moderate to severe requiring hospitalization in 44% of cases. The mean hospitalization length was 10.49±8 days.

Asthma was well-controlled in 58% of patients and not well-controlled or poorly controlled in 42% of patients. All patients used short-acting beta-agonists (SABA), 99% of patients used inhaled corticosteroids (IC), and 63% used long-acting beta-agonists (LABA). Antileukotrienes were

prescribed in 5 patients, as well as xanthine bases and oral corticosteroids. According to the prescribed treatment, asthma was classified as moderate to severe in three-fourths of patients (80%).

Characteristics of the participants according to the hormonal status

The mean age of both groups of G1 and G2 was 61.12±11 and 34.85±7.47 years, respectively. Menopausal asthmatic women had more comorbidities (p=0.006), especially arterial hypertension (p<0.0001), heart disease (p=0.03) and diabetes (p=0.02). They had an average BMI of 30.43 kg/m2 compared with 28.78 kg / m2 in non-menopausal women (p=0.09).

Asthma occurred during the perimenopausal period in 30% of patients, of whom 83% (or 41% of the total population) had novo asthma, appearing after the age of 40 years. Only 70% of the patients had old asthma.

Personal atopy (p=0.01), as well as familial atopy (p=0.01), were more common in premenopausal women. The allergic etiology of asthma was correlated with hormonal status (p=0.004). Indeed, asthma had an allergic origin in all non-menopausal patients against 62% of menopausal ones.

Obstructive ventilatory defect was more common in the G1 group (47%), compared with 23% in G2 group (p = 0.06). Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1 / FVC ratio were statistically lower in the G1 group (p<0.0001, p <0.0001, and p=0.03, respectively).

Exacerbations were more frequent (p<0.0001) and more severe with a lower oxygen blood pressure (p=0.006) in postmenopausal asthmatic patients. Similarly, hospitalization for exacerbation was longer in this group (p=0.09).

The combination of LABA and IC association was more prescribed in postmenopausal women (75% in the G1 vs. 52% in the G2 group, p=0.02).

In univariate analysis, asthma was better controlled in non-menopausal women (49% in the G1 group vs. 72% in the G2 group, p=0.03). A relation was also found between asthma severity and hormonal status. Thus, perimenopause was associated with more severe asthma (p=0.01).

In multivariate analysis, asthma control was no longer associated with menopause when co-morbidities, obesity, and gastroesophageal reflux (GER) were considered, despite the trend was toward significance (p=0.07; OR=2.75, 95% CI [0.92-8.24]). However, severity remained significantly associated with menopause (p=0.01, OR=5.02, 95% CI [1.36-18.46]) (Tables 1 and 2).

Table 1.Patients characteristics according to the hormonal status

Groups characteristics	G1 (n=49)	G2 (n=33)	P
Comorbidities (%)	61	30	0.006
Heart Disease (%)	18	3	0.03
Arterial hypertension (%)	35	3	<0.0001
Diabetes (%)	29	9	0.02
GER (%)	18	21	0.48
BMI (Kg/m2)	30.43	28.78	0.09
Familial atopy (%)	15	40	0.01
Personal atopy (%)	33	61	0.01
Rhinitis (%)	20	67	<0.0001
Conjunctivitis (%)	10	28	0.03
Spirometry			
Mean FVC (l)	2.18±0.62	2.98±0.66	<0.0001
Mean FEV1 (l)	1.77±0.66	2.58±0.62	<0.0001
Mean FEV1/FVC (%)	77.80±9.72	83.11±7.78	0.03
Exacerbations			
Mean exacerbation number/Patient	3±2.39	1.27±1.20	<0.0001
Hospitalisation (%)	47.8	41.7	0.40
Mean hospitalisation length (days)	12,06±9,50	8.27±4.69	0.09
Mean oxygen blood pressure (mmHg)	66,25	78.64	0.006
Severity of asthma			
Mild (%)	10	33	
Moderate (%)	49	46	0,01
Severe (%)	41	21	

GER: Gastroesophageal reflux

BMI: body mass index

FVC: forced vital capacity

FEV1: forced expiratory volume in one second volume

Table 2. Multivariate analysis of factors associated with control and severity of asthma

	Control			Severity		
Variables	OR	IC 95 %	P	OR	IC 95 %	P
Comorbidities	0.80	0.27 - 2.30	0.68	0.57	0.13 - 2.42	0.45
Obesity	0.88	0.31 - 2.45	0.81	0.28	0.07 - 1.09	0.06
GER	1.11	0.30 - 4.11	0.87	0.36	0.03 - 3.37	0.37
Menopause	2.75	0.92 - 8.24	0.07	5.02	1.36 -18.46	0.01

GER: Gastroesophageal reflux

DISCUSSION

Asthma in women is closely related to the hormonal variations experienced by them during the genital life from puberty to menopause (7). Menopause is characterized by a drop in ovarian hormones (progesterone and estrogen) and an increase in pituitary gonadotropins (FSH and LH). It affects about 18% of asthmatic women in the world, according to WHO (4). The prevalence of asthma in menopausal women compared with all women with asthma has been estimated at 15 to 22% (8,9).

There is conflicting evidence in the literature regarding the risk of developing asthma during menopause (10). Two prospective studies conducted in 1995 and 2010 reported a decrease in the incidence and prevalence of postmenopausal asthma in women with natural menopause (11,12). In contrast, the link between menopause and the risk of developing asthma has been demonstrated in several other studies (3, 13,14). The most recent study is a meta-analysis conducted by McCleary et al. in 2018, in which it was concluded that hormone replacement therapy in postmenopausal women is associated with a higher risk of asthma (OR= 1.57, 95% CI 1.07-2.30) (15). These contradictions in the literature can be explained by the fact that the studies on the incidence of asthma during menopause were essentially based on questionnaires. In addition, in this period, the symptoms of asthma can be confused with other pathologies expressing dyspnea, like COPD and heart disease. In our study, asthma appeared after the age of 40 years in 41% of cases, and in the perimenopause period in 30% of them.

Asthma during menopause affects a significant portion of older women who often have one or more comorbidities. In our study, menopausal women with asthma had more comorbidities (p=0.006), especially arterial hypertension (p <0.0001).

In addition to cardiovascular and metabolic comorbidities, GER is frequently observed during menopause, especially in women who are overweight or obese (16). In our study, 91% of postmenopausal women were overweight or obese (p = 0.09). In contrast, regarding GER, there was no significant difference compared with no-menopausal patients.

The asthmatic menopausal group had more symptoms compared with others (7). They had more exacerbations and require more hospitalizations (17). Asthma in these women is often severe and poorly controlled (18). In our study, menopausal women compared with non-menopausal women had more severe asthma (p=0.01, OR=5.02, CI [1.36-18.46]) and their disease was less controlled (p=0.07, OR=2.75, CI [0.92-8.24]). They had more exacerbations (p<0.0001) requiring longer hospitalizations (p=0.09).

In addition, asthma development at menopause is often characterized by the absence of atopy or a history of asthma in the family (18,19). These results are consistent with those found in our study, where familial and personal atopy were less common in postmenopausal women (p=0.01). This non-allergic character of asthma could be related to the type of bronchial inflammation, which according to Foschino Barbaro et al's study was neutrophilic (9).

Regardless of the duration of asthma in menopausal women, physiological and degenerative changes associated with aging can contribute to a gradual decline in lung function. These changes could lead to a decrease in expiratory flows, mainly FVC and FEV1, with a tendency towards obstruction, parallel to an increase in the residual volume (3, 20). Our results are in line with those reported in the literature. In fact, FVC, FEV1, and FEV1/FVC were lower in menopausal women with p<0.0001, p<0.0001, and p=0.03, respectively.

With increasing age, gas exchange is changed with a linear decrease in PaO_2 until the age of 70 years and a decrease in carbon monoxide release capacity (21). In our patients, PaO_2 in postmenopausal women was lower (p=0.006).

On the other hand, with increasing age, the immune defense function of the respiratory system may impair leading to an increase in the risk of respiratory infections (22). In fact, in our study, menopausal women had more exacerbations that were essentially infectious (p<0.001).

In addition to the aging of the respiratory system, the worsening of pre-existing asthma during menopause can be explained by the process of tissue remodelling, which can be responsible for the progressive thickening of the bronchial wall (23). Clinically, remodelling could increase the asthma exacerbations frequency and the frequency of emergency treatment. Functionally, the fixity of anatomical lesions can lead to irreversible obstructive syndrome and even sometimes, the inefficacy of inhaled corticosteroids (23,24).

Apart from this anatomical hypothesis, another hypothesis, involving sex hormones, has been advanced. The role of sex hormones seems to be major. It is now admitted that sex hormones are decreased during menopause that may influence asthma and may even explain its onset during this period (13,25). Several mechanisms have been proposed to elucidate the role of female hormones in the risk of asthma. In fact, there are estrogen and progesterone receptors in the lungs; especially in the epithelium and the bronchial smooth muscle. These hormones have an effect on bronchial contractility, bronchial inflammation, and cilia (26). Thus, estrogen, causing a bronchodilatation at physiologic concentration, has an inverse effect on high rate (27). Similarly, according to the cell types, the estrogen concentration, and the target organ, estrogen appears to have both anti and pro-inflammatory effects (26). At a physiologic dose, it has anti-inflammatory action. However, at low or very high concentrations, such as during menopause or hormone replacement therapy, estrogen has pro-inflammatory effects (28).

As for estrogen, progesterone, at a physiologic dose, has an anti-inflammatory effect. It causes the relaxation of the smooth muscle and regulates the cilia. At low doses, it becomes pro-inflammatory (26).

In addition, estrogen has been shown to inhibit insulin resistance, resulting in the inhibition of inflammation mediators and the decreased risk of developing asthma symptoms. Therefore, the decline in estrogen levels during menopause can be responsible for the increase in insulin resistance, and therefore an increase in systemic and bronchial inflammation (29,30).

These different mechanisms associated with individual susceptibility could explain the diversity reported in the literature regarding the influence of menopause and hormone replacement therapy on asthma.

CONCLUSION

Asthma is a chronic and common respiratory disease. In adulthood, the female predominance is clear. Hormonal changes in women, especially during menopause, have important consequences on respiratory function in general and asthmatic disease in particular. Through our study, we were able to highlight the characteristics of asthma in women during menopause. Indeed, late-onset asthma beyond the age of 40 years and during perimenopause is common. Certainly, our study had some limitations, especially in the definition of the two groups. In fact, to definite perimenopause, we only referred to anamnesis data and age without using hormonal tests. However, aging does not seem to be sufficient to explain the risk of developing asthma after menopause. A drop in sex hormones could explain this risk with many contradictions in the literature. Our data demonstrated that asthma during menopause is more severe, less controlled, and commonly non-allergic. Thus, asthma during menopause is a particular pathophysiological condition requiring appropriate and oriented management.

Nevertheless, further data are needed to explain the exact impact of menopausal hormonal changes on asthma incidence and severity.

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