

Asthma and menopause

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The progressive ageing of our population is forcing us to review a whole array of concepts and modes of thinking and operating. This is the case with bronchial asthma, traditionally considered a problem prevalently related to children and adolescents, but that we find today present and of significance in adults and even in the elderly.

In this perspective, also the classic concepts related to the link between menopause and asthma are undergoing major review. That a special link exists between female sex and bronchial asthma cannot be denied: one has simply to think of the influence that menarche, pregnancy and the menstrual cycle have on this disease. There is a clearly greater risk of developing bronchial asthma after puberty in women than in men [1]. Hence it comes as no surprise that women have greater recourse to medical care and hospitalization than men at the same age [2, 3]. The reasons for this difference are complex, but it is clear that female sex hormones play a particularly important role [4, 5]. Not by chance, in menopause we observe asthma exacerbations (where asthma already pre-exists) and also cases where the disease makes its appearance for the first time: in fact there is a peak in the frequency of asthma onset reported in adults aged in their forties [6].

Both exacerbation and first-time onset of asthma post menopause seem linked, at least in part, to elevated serum 17-beta-Estradiol. This hormone can in fact exert an asthmogenic action through its contribution to the increase of prostaglandin F₂-alpha and other proinflammatory mediators derived from the arachidonic acid metabolic cascade [7, 8].

Asthma insurgence in the menopausal age seems to have specific clinical characteristics. As with asthma in the elderly in general, but to a still greater extent, there is a frequent association with negative allergological history, recurrent sinusitis, urticaria and/or angioedema, and with an incomplete drug response with more frequent steroid dependence. In addition, it is not uncommon to find intolerance to acetylsalicylic acid and other non steroid antiinflammatories [9, 10].

There is particular debate about the treatment of asthma in post menopause. There are two crucial aspects: on the one hand, the effects of hormone replacement therapy (HRT) and, on the other,

the risk of severe side effects with administration of corticosteroids.

HRT is practised by a growing number of women: one British study reports that 60% of women aged between 51 and 57 years use it [11], while in the United States approximately 38% of women in post menopause do so [12]. The therapy is especially indicated for the prevention of the cardiovascular disease of osteoporosis [13, 14] but it carries an increased risk of asthma insurgence. In fact from the *Nurses Health Study* it emerged that women using HRT for 10 years or more had a two-fold higher risk (age-adjusted) of developing bronchial asthma post menopause than women who did not practise HRT [15]. Still under debate, however, is the relationship between HRT and asthma with onset prior to menopause. In the study of Lieberman et al. 15 women in post menopause affected by mild-moderate asthma who underwent HRT showed a deterioration in their clinical and functional conditions [16]. A different conclusion was reached by Hepburn et al.: in 20 asthmatic women they observed no significant variation in clinical and spirometric values with HRT use. The issue remains open and hence further studies in large cohorts are needed to clarify definitively the role of HRT in post menopausal asthma [17].

The second question is the increased risk of osteoporosis for asthmatic women in post menopause. Systemic corticosteroid assumption has been widely demonstrated to increase the risk of osteoporosis [18], but recent reports indicate that also inhaled corticosteroids at high dosage can reduce bone mineral density in post menopause and thus increase the risk of osteoporosis and fractures [19]. Amongst other authors, Fujita et al. reported that the sole assumption of beclomethasone for at least one year leads to a significant reduction of bone mass in post menopausal as compared to pre menopausal women [20].

Considering the need to be able to carry out an early diagnosis of osteoporosis and in order to prevent correlated fractures, the G.I.N.A. guidelines recommend, for some patient groups, specific screening with follow-up every 1 or 2 years according to clinical severity [21]. The same document also recommends smoking cessation, regular physical exercise, use of the lowest dosage of cor-

ticosteroids, and an adequate dietary intake of calcium.

As one can see, these are "hot" topics on which are focalized different interests in relation to the growing health demand from the population in the middle to elderly age and also to the growing concern about the sustainability of costs of health care for these people who are obviously destined to live longer and longer. Studies are thus welcome that increase our stock of knowledge on the subject and help us design more specific strategies to counter the phenomenon. In this issue, Balzano et al. [22] have focused experimental research on the differences between subjects with post menopause asthma onset and age-matched controls with pre menopause onset. In both groups the clinical condition necessitated pharmacological treatment. Subjects and controls were matched for age and for asthma severity as based on evaluation of symptoms, lung function tests and the need for drugs.

The topic of the study is of great interest, and a rigorous selection of both subjects and controls was carried out. The findings confirm that women with asthma onset post menopause have a lower prevalence of atopy [23]. It was also observed that asthma with post menopause onset is associated more frequently to recurrent chronic sinusitis and thus can induce a more severe clinical picture. In fact, the association of asthma and sinusitis signifies a risk of frequent exacerbations and severer symptoms poorly controlled by drugs [24, 25]. In Balzano et al.'s study, women with post-menopausal asthma onset presented numerous exacerbations such as to require systemic corticosteroid treatment at a higher dosage than the control group.

An interesting idea for future research stems from one of the study's findings: the higher eosinophil count in induced sputum found in women with asthma in menopausal age. This finding suggests a different dynamic of the inflammation that could have clinical value, as suggested by the fact that in both groups the asthmatic exacerbations during the 12 months of follow-up were correlated to the percentage of eosinophils present in sputum.

The significance of this increase of eosinophils is open to debate. A high eosinophil sputum count is in fact associated to a more favourable response to corticosteroids [26, 27]. However, as proposed by the authors, the hormonal variations typical of menopause can induce metabolic alterations that render subjects with elevated sputum eosinophil levels less responsive to treatment.

The authors acknowledge that the small study population constitutes a study limitation: it reflects, however, the difficulties encountered in dealing with a phenomenon generally unknown, poorly understood or misunderstood such as asthma in the middle or elderly age-group. As an example of the lack of interest that this issue raises still today in the scientific world, it is sufficient to cite the fact that a bibliographic research carried out in PubMed using the terms "Asthma" and "Menopause" identified only 80 articles.

It is true that it is complex to make a diagnosis of asthma in subjects over 50 years of age on account of the frequent presence of diseases (e.g. COPD, heart failure and angina pectoris) that not infrequently manifest with the same signs and symptoms as asthma.

In particular, the difficulty of carrying out a correct differential diagnosis between asthma and COPD in this age group is due to several factors, including the less frequent atopy, the low specificity of dyspnea, and the reduced reversibility of airways obstruction at spirometry.

In fact, in the middle and elderly age-group obstruction of the bronchi can become persistent due to chronic inflammation which over the course of the years can induce a remodelling of the airways.

The SARA study, conducted in a population of 128 patients aged > 65 years with confirmed diagnosis of asthma, found that only just over half of the patients had had a correct diagnosis, while 20% of the study group received an erroneous diagnosis of COPD and in 27% of the asthmatics no diagnosis at all of respiratory disease had been made [28].

It should in any case be stressed that diagnosing asthma in the elderly will constitute an increasing challenge in the next few years under the pressure of the demographic revolution. It is necessary therefore to become equipped methodologically, starting with a wider knowledge of the specific characteristics of the phenomenon: Balzano et al.'s study is certainly a useful contribution in this sense.

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