Sex, Asthma and Exercise

Subjects: Allergy | Physiology | Others

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Exercise-induced bronchoconstriction (EIB) is a common complication of athletes and individuals who exercise regularly. It is estimated that about 90% of patients with underlying asthma (a sexually dimorphic disease) experience EIB; however, sex differences in EIB have not been studied extensively. With the goal of better understanding the prevalence of EIB in males and females, and because atopy has been reported to occur at higher rates in athletes, in this study, we investigated sex differences in EIB and atopy in athletes. A systematic literature review identified 60 studies evaluating EIB and/or atopy in post-pubertal adult athletes (n = 7501). Collectively, these studies reported: (1) a 23% prevalence of EIB in athletes; (2) a higher prevalence of atopy in male vs. female athletes; (3) a higher prevalence of atopy in athletes with EIB; (4) a significantly higher rate of atopic EIB in male vs. female athletes. Our analysis indicates that the physiological changes that occur during exercise may differentially affect male and female athletes, and suggest an interaction between male sex, exercise, and atopic status in the course of EIB. Understanding these sex differences is important to provide personalized management plans to athletes with underlying asthma and/or atopy.

asthma exercise sex gender

1. Introduction

Asthma is one of the most common chronic non-communicable diseases of the airways, affecting about 339 million people worldwide [1]. The global prevalence of self-reported and physician-diagnosed asthma in adults is 4.3% (95% CI 4.2–4.4), with wide variation among countries [2]. Asthma is generally characterized by airway smooth muscle constriction (bronchospasm), excessive inflammation of the airway, and increased mucus production, although it presents in a variety of phenotypes and endotypes, ranging from mild and intermittent to severe and uncontrolled [3]. The diagnosis of asthma is determined by the history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitations [4][5].

Asthma is a heterogeneous disease, usually characterized by chronic inflammation. The clinical course of asthma is influenced by several factors, including genetics [6], environmental and occupational exposures [7], sex and gender [8], and hormones [9]. Atopy is also frequently associated with asthma [10]. Different from an allergy (i.e., the exaggerated immune response to a foreign antigen regardless of mechanism), atopy is characterized by an exaggerated IgE-mediated response to an allergen. Worldwide, 80% of childhood asthma and over 50% of adult asthma has been reported to be atopic [11]. In the United States, 56.3% of asthma cases have been attributed to atopy, a percentage that is greater among male patients than female patients [12].

Exercise and physical exertion are some of the most common triggers of bronchospasm in patients with asthma [13][14]. Bronchial hyperreactivity, a basic feature of bronchial asthma, occurs more often in athletes than non-athletes, especially in swimmers and winter sports athletes [15][16]. Exercise-induced respiratory symptoms usually involve acute narrowing of the airways that occurs during or after exercise and include exercise-induced bronchoconstriction (EIB) [17].

EIB is defined as the acute onset of bronchoconstriction occurring during or immediately after exercise [18]. Although EIB has been estimated to occur in up to 90% of patients with underlying asthma, it also occurs in subjects with no prior history of asthma and no symptoms outside of exercise [19]. Similarly, there is a subset of patients who have only exercise-induced asthma, but not chronic daily asthma [18]. Overall, while the epidemiology of asthma has been widely reported and studied worldwide, the epidemiology of exercise-induced asthma and EIB has not been well described.

Sex and gender differences in the incidence, prevalence, and severity of lung diseases have been noted for years [20]. The terms "sex" and "gender" are oftentimes used interchangeably in research studies, although they represent different concepts. "Sex" refers to the underlying biological differences between males and females, including sex organs, XY chromosomes, and expression of endogenous hormones, while "gender" is a social construct that imparts roles and behaviors as masculine or feminine within the framework of historical or cultural contexts. The recent implementation of regulations and policies encouraging the incorporation of sex as a biological variable in research studies has permitted the identification and characterization of sex-specific mechanisms of lung diseases, including asthma, across the lifespan. Among children, the prevalence of asthma is higher in males than in females [21]. However, after puberty, the prevalence is about 20% higher in females than males, indicating a potential contribution of sex hormones [22]. Regarding the response to exercise, research studies evaluating sex differences have reported that the male and female body differ in cardiovascular, respiratory, thermoregulatory, metabolic, and neuromuscular responses that have clear implications for understanding sex-specific adaptations to exercise for athletic performance and overall health [23]. Gender, on the other hand, can potentially influence an individual's behavior or preference towards a specific sport or physical depending on societal beliefs.

Although asthma has been widely reported to be more prevalent and severe in adult females than males [21][22], very few studies to date have addressed sex differences in EIB and/or the overall effects of exercise in male and female patients with asthma. One study reported that female adolescents, but not males, with EIB experience a lower health-related quality of life and poorer lung function than those without EIB [24]. Others reported that female athletes exhibit more severe symptoms of EIB than males, especially in the luteal phase of the menstrual cycle [25]. However, there is still no consensus in the literature on an established sexual dimorphism for EIB, nor studies addressing the mechanisms underlying potential sex differences in EIB prevalence and/or severity. Because minute ventilation rises with exercise [14], EIB likely results from changes in airway physiology triggered by the large volume of relatively cool, dry air inhaled during vigorous activity [26]. This is supported by research findings concluding that the main determinant of the occurrence and degree of bronchoconstriction is not the type of exercise, but rather the ventilation demand and humidity of the inspired air during exercise [27][28][29].

2. Discussion

Exercise-induced bronchoconstriction occurs in the presence or absence of clinically recognized asthma. A sex disparity exists in individuals suffering from asthma throughout life, calling for the question of whether sex also influences EIB. In this review, we studied the prevalence of EIB in adult professional and recreational athletes and its relationship with atopic status in males and females enrolled in 60 studies. Our analysis of the literature confirmed the previously described positive association of atopy and EIB in athletes [30] and showed that while the prevalence of EIB does not display an overall sex dimorphism, atopy is more prevalent in male athletes than in female athletes. Moreover, our analysis indicates that male athletes are twice as likely to present with atopic EIB than females. These results indicate that potential sex-specific mechanisms exist in the inflammatory and physiological changes triggered by exercise in athletes.

One of the major triggers for bronchoconstriction in a vulnerable subject is water loss during periods of high ventilation. Strenuous exercise creates a hyperosmolar environment by introducing dry air into the airway with compensatory water loss, leading to transient osmotic changes in the airway surface. This hyperosmolar environment leads to mast cell degranulation and eosinophil activation with consequent release of inflammatory mediators, including leukotrienes. This process triggers bronchoconstriction and inflammation of the airway, as well as stimulation of sensory nerves and release of neurokinin and mucins [31]. Prior studies in animal models and human cells have reported sex differences in mast cell functionality and suggested a potential regulation by sex hormones [32][33][34][35][36]. Mast cells expressing estrogen, progesterone, and androgen receptors have also been identified in the human upper airway and nasal polyps, indicating that this may be a major route for the involvement of sex hormones in exercise-induced airway inflammation [37][38]. Similarly, studies have suggested a relationship between mast cell-derived mediators, sex hormones, and the development of asthma and allergic lung disease [39]. The biosynthesis of leukotrienes and other pro-inflammatory eicosanoids and prostaglandins by mast cells is also sex-biased and has been shown to be mediated by androgens [40][41][42]. At the neural level, sex differences in neurokinins and their receptors have been reported in adults [43][44], and sex hormones have been shown to regulate neurokinin-dependent activation of airway smooth muscle in allergic asthma [45][46][47]. Together, these studies illustrate the complexity of mechanisms involved in EIB in males and females and suggest a potential regulation by sex steroids at the immune and neural level.

Compared to the general population, elite athletes have a higher prevalence of EIB that varies with the intensity of exercise and the environment [31]. Increased bronchial responsiveness and asthma are strongly associated with atopic disposition and its severity in elite athletes [48], and atopic diseases are overall more common in athletes [49]. Our analysis of the literature revealed that 23% of the athlete population studied presented with EIB. Interestingly, the severity and prevalence of EIB was even higher (30.3%) in studies that reported sex differences. Our data also concur with prior research reporting a greater prevalence of EIB in high-performance athletes than in the general population. These studies suggested that prolonged inhalation of cold, dry air, and airborne pollutants are some of the factors influencing the high prevalence of EIB in athletes [14]. Other studies have reported a prevalence of EIB between 30–70% among elite or Olympic-level athletes [19][50], as opposed to 5–20% in the general population [31][51]. While EIB is frequently documented with asthma and reflects insufficient control of underlying asthma, few

epidemiological studies of EIB have categorized participants by asthma status. Thus, the true prevalence of EIB within the non-asthmatic general population has not been fully established, preventing researchers from evaluating and quantifying sex and/or gender differences as well. In this regard, a sex disparity in EIB and airway hyperresponsiveness (AHR) has been reported in young adults, with lower rates of mild AHR in males vs. females but higher rates of moderate AHR and atopy in males [52]. In the United States, 56.3% of asthma cases are attributable to atopy, a percentage that is greater among males than females [12][53]. Repeated and strong exposure to pollen and other allergens causes bronchial and upper respiratory symptoms in athletes, although very few studies have investigated the occurrence of atopic status in athletes [54]. Our analysis revealed that male sex and atopic status are potential risk factors for EIB in athletes. We also identified a 2:1 ratio of atopic EIB in male vs. female athletes. However, female athletes were overall underrepresented in studies assessing EIB, as is the case for studies in many lung diseases [55].

Estimating the prevalence of EIB has also been problematic due to the lack of a gold standard for diagnosis. Since 2016, a joint task force (JTF) including the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma, and Immunology [54] has recommended that the diagnosis of EIB should rely on performing a standardized bronchoprovocation challenge (exercise or a surrogate), because the presentation of EIB will vary with the type of challenge and the conditions under which the challenge is performed. In our review of the literature, we found that 43% of the selected papers used an exercise challenge alone as a diagnostic tool, whereas 14.2% used it in combination with a bronchial provocation test, such as mannitol or methacholine. While we do not know the exact conditions in which these tests were performed, there is a possibility that a sex bias exists in their ability to serve as EIB diagnostic tools. In this regard, 9% of the studies included used self-reporting data via questionnaires. The JTF recommends that a diagnosis of EIB is confirmed by demonstration of airway reversibility or challenge in association with a history consistent with EIB because self-reported symptoms are not always accurate [54][56].

Our study has several limitations. First, while we took measures to minimize bias, there is a risk of bias assessment associated with the protocols used to retrieve and select the literature, including selective reporting of findings in abstracts, and variations in the nomenclature and definitions used in studies [57]. Furthermore, the analysis conducted in this report showed an overall higher rate of self-reporting EIB asthma-like symptoms in females than males, indicating that the sex differences observed in atopic EIB in athletes may be even more striking due to the underreporting of symptoms by male athletes. Moreover, none of the studies accounted for the menstrual phase of female participants, nor for oral contraceptive use at the time they were surveyed. This represents a limitation since hormonal status has been shown to potentially alter self-reported asthma-like symptoms in women [55][58]. Another limitation of the current analysis is that the protocols for determining the presence and magnitude of EIB were not consistent among the studies included. While there are no reports comparing the accuracy of these methods in diagnosing EIB in males and females, it is possible that variations in EIB prevalence across studies are a result of variability in these measurements' validity. Our analysis also incorporated data from studies enrolling both professional and recreational athletes who exercised at a specific frequency and intensity, according to our inclusion criteria. While sports medicine experts still have not reached a consensus on a defined nomenclature to describe training intensity, regularity, and/or competitiveness level in

athletes and non-athletes [59], it is possible that combining all regular exercisers in our analysis led to missing potential differences in EIB/atopy prevalence in men and women who are professional athletes vs. recreational exercisers.

Recent studies have yielded significant advances in our understanding of how intrinsic and extrinsic factors can impact airway function in athletes. Extrinsic factors include environmental exposure to temperature, humidity, aeroallergens, irritants, and pollution. Intrinsic factors include atopy, allergic rhinitis, asthma, body mass index, and airway anatomy. These factors can affect both the athlete's quality of life and athletic performance, but also contribute to sex differences in exercise physiology and EIB [60]. In this regard, the menstrual cycle phase is an important determinant of EIB severity in female athletes with mild atopic asthma [61]. An estimated 33–52% of females with asthma report a premenstrual worsening of asthma symptoms, and an additional 22% report asthma that is worse during menses [61]. However, the temporal correlation between asthma symptoms and steroid levels does not provide a simple answer as to whether estrogen and/or progesterone improve or worsen asthma. Female sex steroid hormones could affect exercise capacity and performance through numerous psychologic mechanisms, including substrate metabolism, cardiorespiratory function, and thermoregulation [62][63][64][65]. Thus, hormone level changes may lead to either improved or decreased performance at various times throughout the menstrual cycle [66][67]. It is also possible that the reduction in estrogen levels and other menstrual cycle disturbances that occur with exercise is associated with the lower prevalence of atopic EIB observed in female athletes [26][68]. Overall, the relationship between exercise and the menstrual cycle is an important variable to consider when analyzing sex differences in EIB and atopy. Future research studies in animal models and human subjects should assess the factors predisposing athletes to develop concurrent atopy and EIB, as well as the mechanisms underlying different outcomes in males vs. females. Overall, more research that accounts for sex as a biological variable and incorporates anatomical and/or physiological factors (e.g., lung volumes, hormone fluctuations) is needed to better understand sex-specific mechanisms of EIB, and potentially develop sex-specific therapeutics to prevent and treat EIB and other pulmonary conditions [69].

3. Conclusions

In conclusion, we show here that a relationship exists between male sex and atopic status in the course of EIB in athletes. Understanding sex differences in EIB and atopy in athletes could lead to the development of better-personalized training and disease management plans for athletes with these underlying conditions.

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