Sex Hormones and Asthma

A potential causal association between changes in sex hormones and asthma incidence or severity has long been supported by several well-known epidemiological observations; for example, asthma is more prevalent and severe in male children, yet after childhood, women are more commonly affected throughout adulthood (1). Perimenstrual worsening has been reported to occur in 20–40% of patients with severe or difficult-to-control asthma, particularly among obese females (2). On the basis of this information, suppressing sex hormone fluctuations through hormonal replacement therapy (HRT) would indeed make logical sense to reduce asthma incidence or potentially improve asthma outcomes; however, this has not been consistently shown, and in fact, some longitudinal studies have shown that HRT actually increased the odds of developing this disease (3, 4). Several factors such as the type and timing of HRT, the type study design, and individual characteristics (obese vs. nonobese) may potentially explain the variability in response to this treatment. It may also imply, however, that we do not fully understand how variations in sex hormone levels affect asthma, and therefore, we do not know in whom and when HRT could be useful.

To this effect, in this issue of the *Journal*, Han and colleagues (pp. 158–166) present the first large population-representative study evaluating the association between serum estradiol and serum free testosterone levels with self-referred current asthma diagnosis in men and women participating in the National Health and Nutrition Examination Survey (5). This cross-sectional analysis of 7,615 (3,953 men and 3,662 women) adults shows that women with higher serum testosterone levels have between 30% and 44% lower odds of current asthma when compared with the women with the lowest testosterone levels. Given the significant interaction found between obesity and sex hormones on asthma, the authors showed in the fully adjusted model that in obese women, higher serum estradiol and serum free testosterone were, respectively, associated with a 40% and a 40–50% reduction in the odds of current asthma. The associations in men were less impressive, as only the highest serum estradiol quartile, relative to the lowest, was associated with reduced asthma odds in nonobese subjects.

Whereas prior large-scale epidemiological studies have attributed changes in asthma-related outcomes to sex hormones only by proxy (i.e., puberty or menstrual period), the results from this study, by directly measuring serum levels, significantly strengthen causality. Further, the association with testosterone, which had been largely overlooked in many prior asthma studies, potentially adds new insights into the pathophysiology of sex hormones and airway diseases. A mechanistic link between testosterone and asthma is supported by studies showing that it is positively associated with lung function in both male and female children with asthma, and by the fact that inhaled dehydroepiandrosterone-3-sulfate (an androgen derivative) had been shown to improve short-term control in patients with moderate to severe asthma (6, 7). Also, in experimental models, testosterone has been shown to lessen airway smooth muscle contraction and to decrease lung innate type 2 cell numbers and lessen allergen-induced IL-5 and IL-13 expression in innate type 2 cells (8–10).

The interaction between serum testosterone levels and body mass index on asthma is certainly intriguing and could potentially play a role in understanding late-onset asthma in women, which after the age of 45 years becomes the predominant phenotype, particularly among those who are also obese (10). One could easily speculate that losing the protective androgenic effect with aging (11) could potentially explain why late-onset asthma is more common in older women, particularly in conjunction with other risk factors such as obesity and/or metabolic syndrome. The potential causal role of estradiol levels in asthma is more difficult to understand, given the inconsistencies in epidemiological and experimental studies. It is also possible that the estradiol associations with asthma found in this study are explained by unmeasured confounding.

In summary, this study represents a major advancement in the epidemiology of asthma and sex hormones and should spearhead further longitudinal and intervention studies related to primary asthma prevention. However, given its cross-sectional nature and the use of a self-referred asthma case definition, these findings should be interpreted with some caution. ■

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Shades of Gray Matter in Severe Traumatic Brain Injury

Traumatic brain injury (TBI) is a critical public health problem throughout the world. As the leading global cause of death in persons under the age of 40 years, trauma classically affects young, healthy individuals, but it is also one of the main causes of death across all ages and locations, ranging from low- to high-income countries. In higher-income countries, as a result of improved life expectancy and increased mobility in the elderly, the incidence of TBI in individuals over the age of 65 years is rising exponentially (1). The epidemiologic patterns of severe TBI are in fact shifting toward a more balanced bimodal distribution. The management of older patients with severe TBI presents a significant challenge owing to their complex health status, including aspects such as chronic medical conditions, polypharmacy, and premorbid disabilities. Although the predominant mechanism of injury is falling from a height (2), the anticoagulant agents and platelet aggregation inhibitors that are often prescribed to these patients predispose them to a greater risk of bleeding and the development of subdural hematomas and hemorrhagic contusions (3). Furthermore, differences in the medical and surgical management of older patients with severe TBI compared with younger patients with the same brain injuries have been observed (4). More importantly, overall, older patients are more likely to die from their brain injuries than any other age group (1).

Given this changing epidemiology and lack of informative data on longer-term functional outcomes in older patients, the study by Maiden and colleagues (pp. 167–177) published in this issue of the *Journal* is an important and timely addition to our evolving knowledge in this domain (5). This registry-based cohort study, which included data from older adults (≥65 yr old) with severe TBI who had been admitted to hospitals in Victoria, Australia, showed a very high mortality rate and incidence of unfavorable neurologic outcomes. At 6 months, 85% of the patients (456/536) had died, 9% were dependent on others to live (Glasgow outcome score extended [GOSe] 2–4), and 6% were functionally independent (GOSe 5–8). A particular strength of the study by Maiden and colleagues is the inclusion of outcome assessments for up to 2 years, which had been collected as part of the comprehensive state trauma registry. Importantly, the proportion of patients in each functional status category did not change from 6 months up to 24 months after injury. These results are comparable to those obtained by Haller and colleagues in a study in which they examined the trajectory of disability (GOSe) after severe TBI (6). They observed no functional improvement in a subgroup of older patients (>65 yr) at 3–12 months after hospital discharge and also found no significant improvement in quality of life using the physical and mental components of the Short Form-12 Health Survey.

The majority of patients who are admitted to a hospital after a severe TBI die after a decision for withdrawal of life-sustaining therapy (WLST) is made (7–9). Such decisions appear to be variable across centers and are often made in the very early phase of acute care despite clinicians' limited ability to determine a long-term prognosis after a severe TBI (8, 10). These observations have generated concern within the neurological critical care community that a decision for very early WLST may not always be well informed. The very high in-hospital mortality rate (93% in the non-ICU admission cohort), the short lengths of stay, and the low rate of transfer to neurosurgical centers in the current study by Maiden and colleagues suggest that a large proportion of the patients experienced early limitation of interventions or WLST (5). Considering the historically very high mortality rate among elderly patients, there may be a tendency to withdraw or withhold life-sustaining therapies at an earlier stage in this age group owing to a perceived overly poor prognosis, resulting in a higher likelihood of self-fulfilling prophecies and potentially excess mortality (11, 12). In the case of young, otherwise healthy individuals, level-of-care decisions involving surrogate decision-makers are mainly guided by the neuroprognostic implications of the TBI; however, in elderly patients with a severe TBI, previous health conditions, existing disabilities, and quality of life must also be considered. Yes, there is

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