

Editorial

Selenium and asthma: a complex relationship

Descriptive studies in humans investigating the relationship between selenium (Se) status and asthma have presented inconsistent results. The concept of low Se status as a potential risk factor for increased prevalence or severity of asthma is based on the role that Se, through its incorporation into selenoproteins, plays as a potent antioxidant capable of augmenting the oxidative stress that accompanies asthma. However, Se intake also exerts a significant influence over immune responses. Thus, the dual effects of Se status on controlling oxidative stress in the lungs and regulating T helper 2 responses that drive allergic asthma, as well as which selenoproteins are key to regulating these processes, must be considered when attempting to decipher the relationship between this essential nutrient and complex allergic diseases such as asthma.

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Dietary selenium (Se) is an essential antioxidant important for many aspects of human health (1). Because asthma involves increased levels of oxidative stress, Se intake has been hypothesized to play a role in the development and/or severity of this complex disease. However, descriptive studies in humans have produced conflicting results with some finding an association between low Se status and asthma (2–5), and others failing to confirm this association (6–8). Dietary Se has even been found to be positively associated with severity of bronchial responsiveness (9). The research effort to decipher the role of Se and other factors involved in asthma was strengthened in 2005 with the establishment of the Global Allergy and Asthma European Network (GA²LEN) project (10). While well-designed studies conducted under GA²LEN and similar projects may sometimes generate negative data, this does not diminish their importance. In fact, such data may emphasize the need for new research directions to elucidate factors contributing to complex diseases like asthma. This seems to be the case with the study conducted by Burney et al. in the current issue of *Allergy* (11). This multi-regional study involves the analysis of plasma Se levels and asthma prevalence/severity from no less than 14 centers in Europe. The data convincingly demonstrate that Se status is not significantly associated with asthma levels in the study subjects. Does this mean that dietary Se intake does not influence the onset or severity of asthma? Hardly, but it does emphasize the complexity of the relationship between dietary Se and asthma. It also

highlights the need for researchers to identify the next step in analyzing the effects of Se intake and asthma in human populations. That is, the lack of a consistent correlation may signal the need to move away from case-control studies that attempt to assess Se status as a risk factor for asthma prevalence or severity and move toward more complicated analyses. To help guide the nature and extent of new human studies, basic science investigations will be relied upon for uncovering the relationships between dietary Se, individual selenoproteins, oxidative stress, allergies, inflammation and immune responses.

Selenium exerts most, if not all, of its biological functions through its incorporation into selenoproteins as the amino acid, selenocysteine. As noted, studies involving Se and asthma are conducted on the basis that Se acts through antioxidant selenoproteins that reduce oxidative stress in the lungs, as well as the organism in general, to reduce the burden of asthma-associated airway inflammation. Studies have focused mainly on glutathione peroxidase (GPX), the best-known member of the selenoprotein family, in carrying out antioxidant functions of Se. There are, in fact, five human GPX selenoenzymes: GPX1–4 and 6. In addition to the GPX enzymes, other selenoproteins to which antioxidant or redox properties have been attributed include thioredoxin reductase-1, -2 and -3 as well as selenoproteins H, P, R and W (12–15). A total of 25 selenoproteins have been identified in humans, 24 of which exist as selenoproteins in rodents (16). Functions have yet to be identified for more than half of these proteins. Perhaps the most

important challenge facing Se biology researchers is determining what it is that these different selenoproteins are doing and in what tissues they are doing it. Once we identify functions for more members of the selenoproteome, we can then better understand the influence of dietary Se levels upon complex diseases like asthma.

Underlying the complicated relationship between Se and asthma is the fact that, while Se affects oxidative stress, Se also exerts a significant influence over the robustness of immune responses. In other words, increasing Se intake may help reduce oxidative stress in the lungs, but it may also boost immune responses to allergens by increasing T helper (Th) responses. Importantly, the effects of increasing Se intake depends on the initial Se status of an individual – increasing from moderately low to adequate levels of Se is quite different than increasing from adequate to high levels of Se. This was demonstrated in a study recently published by our laboratory addressing Se intake and the development of allergic asthma using an established mouse model of allergic airway inflammation (17). Our results showed that Se intake did not affect development of allergic asthma in a simple dose–response manner. Using this model, we found that the Th2 responses, inflammatory infiltration and airway hyperreactivity were lowest in the low Se group, suggesting an immune-compromised situation that resulted in lower allergic asthma. Maintaining mice at adequate Se levels (medium Se group) resulted in stronger responses and more severe allergic asthma, but increasing Se intake (high Se group) slightly reduced the responses to airway allergen challenge

compared with the medium Se group. This biphasic response may help explain the inconsistency in epidemiological studies measuring associations between Se intake and asthma in humans (Fig. 1). Increasing Se intake from moderately low to adequate levels may actually boost the immune responses that drive allergic asthma. Increasing Se intake further using Se supplementation may slightly lower Th2 immune responses adding to the protective, antioxidant effects in the airways and result in an overall reduction in asthma. Another explanation of the slightly reduced asthma in the high Se group may be that Se supplementation diverts immune responses away from Th2-type responses and toward Th1-type responses, which is a hypothesis currently under investigation in our laboratory. Importantly, this mouse model is useful for identifying factors contributing to the development of allergic asthma, but is less helpful for elucidating the aetiology of nonallergic asthma.

Whether the processes regulating airway inflammation in mice are similar to those found to regulate human asthma remains to be seen. Of course, development of allergic asthma in humans does not occur in a controlled manner as it does in the mouse model of the disease (e.g. consistent dosage and schedule for sensitizations/challenges, pathogen-free environment, genetically similar subjects, etc.). Moreover, human Se status may change over time, making it impossible to determine the Se status of the individual at the time of the first crucial allergen exposures. Indeed, it may be during the first exposures that Se status has the most influence over development of

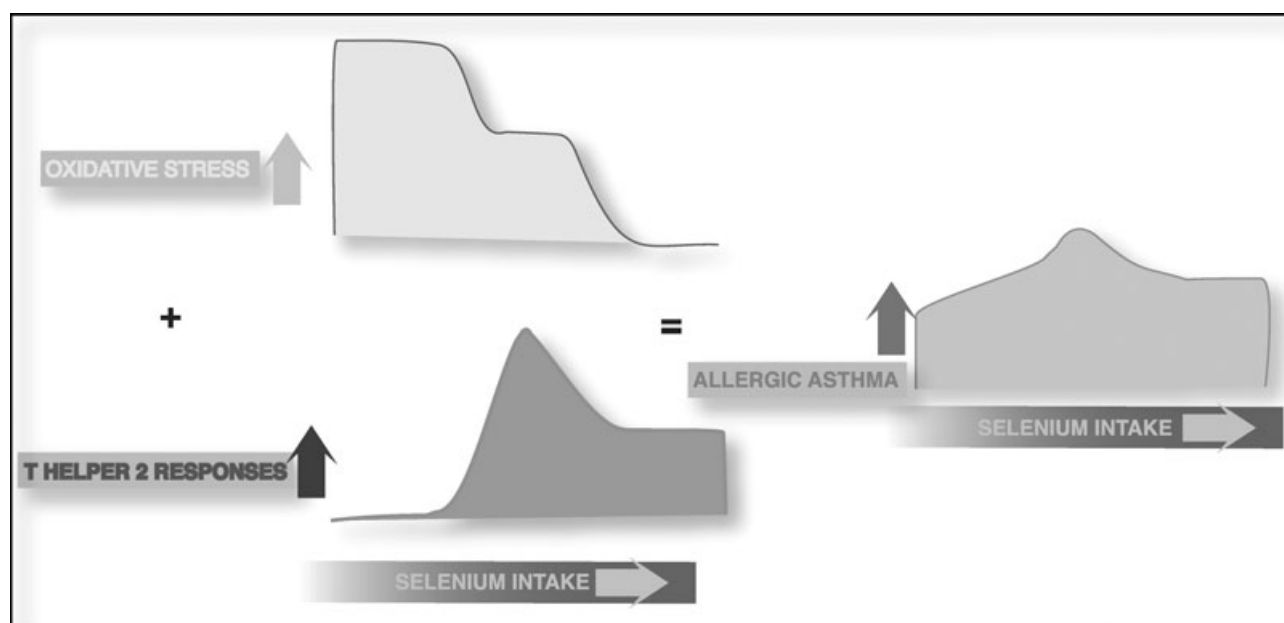


Figure 1. The effects of Se levels on both oxidative stress and immune responses contribute to the overall influence of Se intake on asthma development and severity. This may help explain inconsistencies in finding correlations between Se status and asthma in case–control studies.

an allergic asthma response. In this sense, measuring an individual's Se status long after allergen sensitivity has been established may actually be misleading if the status has changed since the individual's first crucial allergen exposures.

With the mouse model results in mind, human studies involving Se status and asthma may be viewed from a slightly different perspective. For example, studies in which no association was found between Se intake and allergic asthma may be re-analysed by dividing the subjects into low, medium and high Se groups or, alternatively, into Se status quartiles. The severity of allergic asthma may then be assessed in terms of different Se groups. If lower allergic asthma is found in Se deficient subjects compared with medium Se subjects, it would suggest that Se deficiency actually lowers susceptibility to allergic asthma. Furthermore, if

individuals in the high Se group have lower levels of allergic asthma compared with the medium Se group, this may suggest that lowering oxidative stress in the lungs overcompensates for any immune boosting effect of increased Se.

Overall, it is important to exercise caution in interpreting the results of case-control studies showing no significant association between Se intake and asthma. It may be that the multifactorial nature of asthma, particularly allergic asthma, does not allow detection of significant influence of dietary Se on its incidence, prevalence or severity. On the other hand, a better understanding of the function of individual selenoproteins as well as the effect of Se on both airway oxidative stress and Th2 immune responses may lead to future clinical studies that help define the relationship between Se intake and asthma.

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