Vitamin D: Shining A Light on Clinical and Sex Specific Effects in Multiple Sclerosis?

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Editorial

Multiple sclerosis (MS) is a chronic neurological disorder resulting from an interaction between genetic and environmental components. Among a wealth of potential environmental risk factors, hypovitaminosis D is one of the most promising candidates in terms of clinical implications and prospects for disease prevention.[1-3] A protective effect for vitamin D supplementation has long been proposed following observations showing the prevalence of MS is inversely related to sunlight exposure. More stronger evidence comes from prospective studies showing that low vitamin D levels prior to disease onset is associated with increased MS risk. During the last decade, serial population based studies have shown a sharp increase in the prevalence and incidence of MS in the Iranian population, especially in women.[4] Hypovitaminosis D is a world-wide concern, especially in Iran; with a number of other predisposing factors, e.g., spread of urbanization; indoor living; special clothing; changes in diet; and widespread use of sun screens. The high prevalence of hypovitaminosis D among women, youngsters and high school students, especially girls, has been found by recent local studies in our population.[5,6] In the literature, hypovitaminosis D could partially account for the sharp increase in the prevalence of MS in the Iranian population.

25-Hydroxyvitamin D, According to some recent epidemiological studies in our Iranian population, such an interaction between estrogen and vitamin D has been postulated to be the origin of increased female preponderance of MS over the last decade.[7,8] Although estrogen and vitamin D may synergistically reduce the disease development and severity, other elusive points need to be considered as well. Firstly, there is the issue of reverse causality for this study. It may be that female patients are more likely than men to stay indoors as they get disabled providing the inverse relationship between serum vitamin D and disability. We await the results of adequately powered randomized controlled trials assessing the effects of vitamin D on MS clinical outcome. The study may also be subject to confounding. Filippi *et al*.[9] have indicated that increasing serum vitamin A (another fat-soluble vitamin) reduces MRI activity and disease severity. Interestingly, the vitamin A levels differed significantly between genders, with higher values found in men. It may be

that other unmeasured metabolites can explain the findings seen in the study. As highlighted in a paper published in this issue of the International Journal of Preventive Medicine, an inverse relationship between serum 25(OH) D_3 and disability has been observed. Interestingly, this association was observed only in female patients, suggesting that vitamin D may have a clinical impact, but specifically only in females. The female preponderance of MS has always been an enigma, but could point to the role of sex hormones in the development and progression of the disease. There are several lines of evidence supporting a synergistic effect of 17-β estradiol and 25(OH) D3; on one hand, vitamin D3 stimulates 17-β estradiol synthesis and activity of several promoters of the aromatase gene and consequent conversion of androgen to estrogen in glial cells; and on the other hand, 17-β estradiol promotes expression of the vitamin D3 receptor and its function in the central nervous system.[10,11] Such gender differences in the metabolism of vitamin D3 and its interaction with estrogen production, supports the notion that vitamin D supplementation may have a stronger protective effect in women, especially in youngsters.[12] Such a hypothesis, might be supported by clinical conditions associated with high levels of estrogen, e.g. pregnancy and ovulation, which are reported to be accompanied by clinical remission of MS.[13] Moreover, a history of administration of combined oral contraceptives or having given birth is associated with a higher mean age of onset of the disease, perhaps suggesting that estrogens may prevent or delay disease onset.[14] Future experimental studies should consider a number of factors concurrently to understand, which ones have important influences on the disease severity and course; this in turn will provide further strategies for disease treatment and prevention.

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