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EDITORIAL

Vitamin D and systemic lupus erythematous

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Vitamin D classically mediated its cognate nuclear vitamin D receptor (VDR, one of the nuclear receptors [NRs]) functioning as a steroid hormone to regular transcription as well as epigenomic effects is mainly responsible for the regulation of calcium and phosphate metabolism and for maintaining a healthy mineralized skeleton.[1–3] Due to the wide expression of VDR and vitamin D metabolic enzymes in most tissues, serving as sensors of stimuli, mast regulators of downstream molecular events, and hubs governing complex gene regulatory networks, there are numerous genetic, molecular, cellular, and animal studies strongly suggesting that vitamin D signaling by regulating a wide array of genes may have many extra-skeletal effects, such as regulation of cell proliferation, immune and muscle function, skin differentiation, and reproduction, as well as vascular and metabolic properties.[1–3] From observational studies in human subjects, poor vitamin D function, such as low level of vitamin D, dysfunction of VDR, and interference of interaction between vitamin D and VDR is actively involved in many aspects of human physiology and pathology.[3–5] Additionally, reports from randomized controlled trials show the potential benefits of vitamin D supplementation on the reduction of incidence of many diseases,[6–8] although evidence is still in debate.[3,7,8] Therefore, any research focusing on the vitamin D3 and health/or disease is welcome. In the May issue of the Journal of the Chinese Medical Association, we are happy to learn the research addressing this type of problem (the correlation between vitamin D levels and the disease activity of childhood-onset systemic lupus erythematosus [SLE]).[9] Cheng et al[9] tried to investigate whether the correlation between vitamin D3 levels and the disease activity of children with SLE is present in Taiwan.

The authors recruited 31 children with SLE who were treated with either steroid and nonsteroid or combination regimens and found that vitamin D3 deficiency is common in children with SLE, and serum vitamin D3 levels negatively correlate to disease activity of SLE.[9] Of most importance, the authors found that the children treated with steroids had a statistically significantly lower serum level of vitamin D3 than those without.[9] The current study is interesting and worthy of discussion.

First, SLE, one of the chronic multisystem autoimmune diseases with extremely varied clinical manifestations and pathogenesis which is a result of complex interactions between genetic, epigenetic, immunoregulatory, ethnic, hormonal, and environmental factors is a female-predominant disease, suggesting sexual hormone may play an important role in the pathogenesis of SLE.[10,11] Although the authors have shown that the serum vitamin D3 levels were not statistically significantly different between boys and girls (23.6 ± 7.5 vs. 18.9 ± 7.9 ng/mL),[9] it is surprising to find that all boys have received steroid treatment. Since steroid treatment will significantly decrease the serum level of vitamin D3 (17.7 ± 5.9 vs. 29.8 ± 9.8 ng/mL, $p = 0.004$); additionally, the mean age of the subjects in the current study was 18 years of age, it is highly suspected that sexual hormones have been already worked in the subjects enrolled into the current study, suggesting the potential bias based on sexual hormone profiles may influence the measurement of vitamin D3 and subsequently affect the interpretation of the data in the current study. Furthermore, the absolute number of boys in their study was relatively small, to minimize the bias of influence by sexual hormones on the current study, we suggested that these five boys can be considered to be excluded in the current study,

Second, the SLE Disease Activity Index 2000 (SLEDAI-2K) is the most widely used SLE disease activity measure;[12,13] therefore, in Dr. Cheng's study, SLEDAI-2K was also applied to quantify the disease activity of SLE subjects.[9] However, some arguments are present in considering the accuracy and reproducibility of this score system (SLEDAI-2K), since the performance in detecting clinically meaningful changes in disease activity may be limited.[14] Each item of SLEDAI is scored dichotomically with the same numerical weight regardless of the severity of change observed.[12] Additionally, potentially severe lupus manifestations, such as hemolytic anemia, pneumonitis, types of rash, and systemic vasculitis are not scored in SLEDAI-2K;[12] therefore, another SLE disease activity score (SLE-DAS) has been developed and it is reported that SLE-DAS is an accurate and easy-to-use tool for defining SLE clinical remission state and disease activity categories.[14] Based on the accuracy and ease to use by SLE-DAS system to measure SLE disease activity,[14] we are wondering to know whether the results obtained from SLEDAI-2K or SLE-DAS are similar or not.

Third, regardless of whether the subjects are diagnosed with SLE or not, the National Health and Nutrition Examination Survey has confirmed the risks of steroid use associated with severe vitamin D deficiency;[15] additionally, a recent meta-analysis enrolling 472 studies with 746 564 participants showed the mean serum vitamin D concentration was 49.39 nmol/L with

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20.9% <25 nmol/L, 22.8% <30 nmol/L, 57.7% <50 nmol/L, and 76.9% <75 nmol/L, suggesting the high prevalence of vitamin D deficiency in Asia population.[16] However, in the real world clinical practice in Taiwan, it is surprising to find that near half of patients (48.4%, 15/31) did not receive any vitamin D supplementation therapy, even those patients (50%, 13/26) who are concomitantly treated with steroid in Cheng's study.[9] Some may argue that the need of vitamin D supplementation for these SLE subjects based on high controversies of the effect of vitamin D on the reduction of disease activity of SLE,[2,3,7,8] but there is no doubt that steroid use is a key determinant criteria to push all of them to receive "adequate vitamin D supplementation" based on the fact that steroid use is in the highest risk of vitamin D insufficiency.[15] The value of Cheng's study makes us fully understand that there is presence of many potentially clinical malpractices in the real world, including in Taiwan. We congratulate the success of Cheng's publication and hope their findings to awake more physicians, patients and healthy providers to provide more detailed and effective strategies and policies on this issue. Some clinical practices need updating, as shown in our previous concerns.[17]

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REFERENCES

1. Fletcher J, Bishop EL, Harrison SR, Swift A, Cooper SC, Dimeloe SK, et al. Autoimmune disease and interconnections with vitamin D. *Endocr Connect* 2022;**11**:e210554.
2. Charoenngam N. Vitamin D and rheumatic diseases: a review of clinical evidence. *Int J Mol Sci* 2021;**22**:10659.
3. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and extraskeletal actions of Vitamin D: current evidence and outstanding questions. *Endocr Rev* 2019;**40**:1109–51.
4. Yang SK, Liu N, Zhang WJ, Song N, Yang JP, Zhang H, et al. Impact of Vitamin D receptor gene polymorphism on systemic lupus erythematosus susceptibility: a pooled analysis. *Genet Test Mol Biomarkers* 2022;**26**:228–38.
5. Guan SY, Cai HY, Wang P, Lv TT, Liu LN, Mao YM, et al. Association between circulating 25-hydroxyvitamin D and systemic lupus erythematosus: a systematic review and meta-analysis. *Int J Rheum Dis* 2019;**22**:1803–13.
6. Hahn J, Cook NR, Alexander EK, Friedman S, Walter J, Bubes V, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* 2022;**376**:e066452.
7. Zheng R, Gonzalez A, Yue J, Wu X, Qiu M, Gui L, et al. Efficacy and safety of Vitamin D supplementation in patients with systemic lupus erythematosus: a meta-analysis of randomized controlled trials. *Am J Med Sci* 2019;**358**:104–14.
8. Charoenngam N. Vitamin D and rheumatic diseases: a review of clinical evidence. *Int J Mol Sci* 2021;**22**:10659.
9. Cheng KH, Tsai MC, Fu LS. The correlation between VitD3 levels and the disease activity of childhood-onset systemic lupus erythematosus. *J Chin Med Assoc* 2022;**85**:627–32.
10. Lu HW, Wang FY, Chang CK, Teng SW, Wang PH. Postpartum flare up of systemic lupus erythematosus: pulmonary diffused alveolar hemorrhage. *Taiwan J Obstet Gynecol* 2018;**57**:906–7.
11. Chang WH, Huang HY, Wang PH. The use of serum level of microRNA-485-5P in prediction of renal function in lupus nephritis patients. *J Chin Med Assoc* 2021;**84**:736.
12. Arshad A, Mahmood SBZ, Ayaz A, Al Karim Manji A, Ahuja AK. Association of vitamin D deficiency and disease activity in systemic lupus erythematosus patients: two-year follow-up study. *Arch Rheumatol* 2021;**36**:101–6.
13. Wang PH, Teng SW, Lee FK. Disease activity of pregnant women with systemic lupus erythematosus. *J Chin Med Assoc* 2015;**78**:193–4.
14. Jesus D, Larosa M, Henriques C, Matos A, Zen M, Tomé P, et al. Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS) enables accurate and user-friendly definitions of clinical remission and categories of disease activity. *Ann Rheum Dis* 2021;**80**:1568–74.
15. Chiruvolu NV, Safarpour Y, Sandhu VK. Vitamin D and lupus: are we doing enough? *J Community Hosp Intern Med Perspect* 2021;**11**:624–8.
16. Jiang Z, Pu R, Li N, Chen C, Li J, Dai W, et al. High prevalence of vitamin D deficiency in Asia: a systematic review and meta-analysis [Epub ahead of print. November 16, 2021]. *Crit Rev Food Sci Nutr*. 1-10.
17. Yang ST, Wang PH. Abandon ifosfamide-based regimen and use paclitaxel-carboplatin regimen for the treatment of uterine carcinosarcoma. *J Chin Med Assoc* 2022;**85**:649–50.