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Association between serum 25-hydroxyvitamin D concentration and severity of first-diagnosed bullous pemphigoid in older adults

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ABSTRACT

Background: Higher vitamin D status has been associated with symptom improvement and decreased risk of various autoimmune disorders. Our objective was to determine whether higher serum 25-hydroxyvitamin D (25OHD) concentration correlated with less severe first-diagnosed bullous pemphigoid (BP) in older inpatients.
Methods: This cross-sectional study was performed from November 2012 to February 2014 among 30 consecutive older inpatients (21 women; mean ± SD, 83 ± 7 years; all Caucasian) with a *de novo* diagnosis of active BP recruited in the Department of Dermatology of Angers University Hospital, France. The severity of BP was graded clinically on the basis of i) the number of bullae during the first three days of hospitalization (grade 0–4, worse), and ii) the extent of the lesions (grade 0–5, worse).
Results: Sixteen participants had ≤ 5 bullae at the time of diagnosis, 8 had 6–20 bullae, 3 had 20–50 bullae, and 3 had > 50 bullae. The lesions were spread over 5 cutaneous areas in 5 participants (17%). The median 25OHD concentration was 23 [IQR, 16–42] nmol/L. Serum 25OHD concentration was inversely correlated with the bullae grade ($\rho = -0.38$, $p = 0.04$) and the lesion extension grade ($\rho = -0.50$, $p = 0.005$).
Conclusions: Higher serum 25OHD concentration correlated with less severe BP prior to initiation of treatment among our sample of older inpatients. This result suggests that vitamin D may be involved in the pathophysiology of BP and could serve as prognostic biomarker of BP.

1. Background

Vitamin D deficiency exhibits various non-skeletal effects, including those affecting the regulation of the immune system and self-tolerance (D'Aurizio, Villalta, Metus, Doretto, & Tozzoli, 2015). Higher vitamin D status has been associated with symptom improvement and decreased risk of autoimmune disorders such as lupus and multiple sclerosis (Ben-Zvi, Aranow, & Mackay, 2010; Munger, Levin, & Hollis, 2006). Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disease mainly affecting adults aged ≥70years. A few studies have focused on the link between vitamin D and BP, and have reported lower serum 25-hydroxyvitamin D (25OHD) concentrations amongst patients with BP (Marzano, Trevisan, & Eller-Vainicher, 2012; Sarre, Annweiler, Legrand, Martin, & Beauchet, 2016; Tukaj, Schmidt, & Recke, 2013). Given the clinical improvement observed with vitamin D in other autoimmune diseases, we hypothesized that serum 25OHD could have an effect on the severity of BP. Our aim was to determine whether higher serum 25OHD concentration correlated with less severe first-diagnosed BP in older inpatients.

2. Materials and methods

Thirty consecutive inpatients with a *de novo* diagnosis of active BP in the Department of Dermatology, University Hospital of Angers, France (47.3 °N), were enrolled in this cross-sectional study between November 2012 and February 2014. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). Written informed consent was obtained at enrolment. The local

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Ethics Committee approved the study (N°1635125).

Initially, patients were routinely referred for a skin disease to the Department of Dermatology, which is the locoregional referral centre, without any other specific admission criteria, and whether or not there was any suspicion of BP. The diagnosis of active BP was then raised on consensus clinical criteria (i.e., chronic bullous disease, age ≥ 70 years, no atrophic scars, no mucosal involvement, no predominant bullous lesions on the neck or head) (Vaillant, Bernard, & Joly, 1998), and subsequently confirmed by skin histology and direct immunofluorescence (Courville, Kupfer, & Gilbert, 2000). Inpatients with other bullous diseases and those having used vitamin D supplements within the preceding three months were not included in the analysis. The severity of BP was graded clinically on the basis of i) the number of bullae, and ii) the extent of the lesions. The mean number of bullae was estimated during the first three days of hospitalization, and graded as follows: Grade 1 for 0–5 bullae; Grade 2 for 6–20 bullae; Grade 3 for 21–50 bullae; and Grade 4 for > 50 bullae. The extent of the lesions was graded from 0 to 5 (most extensive) on the basis of the number of the following body parts affected by the disease: lower limbs, upper limbs, back, trunk, and pelvis.

Venous blood samples were collected before BP treatment for the measurement of serum 25OHD concentration by radioimmunoassay (DiaSorin Inc., Stillwater, MN). With this method, there is no lipid interference, which is often observed in other non-chromatographic assays of serum 25OHD concentrations. The intra- and interassay precision were 5,2% and 113% respectively (range 30–125 nmol/L in normal adults aged 20–60 years).

For descriptive analysis, continuous variables were reported using means ± standard deviations or median [interquartile interval], as appropriate. All statistical analyses were performed using R software (v3.2.5). Spearman's rank correlation was used to examine the relationship between serum 25OHD concentration and BP severity (i.e., bullae grade, and extent of lesions grade). p-values < 0.05 were considered significant. The distribution of 25OHD stratified by grade was illustrated in Fig. 1 using Side-by-Side Box-Whisker plots.

3. Results

Thirty consecutive BP cases were recruited (21 women and 9 men; mean, 83 ± 7 years; all Caucasian). The median 25OHD concentration was 23 [16–42] nmol/L. Sixteen participants had ≤ 5 bullae at the time of diagnosis, 8 had 6–20 bullae, 3 had 20–50 bullae, and 3 had > 50 bullae. The lesions were spread over 1 cutaneous area in 9 patients (30%), 2 areas in 10 patients (33%), 3 areas in 6 patients (20%), and 5 areas in 5 participants (17%). Serum 25OHD concentration was inversely correlated with the bullae ($\rho = -0.38$, $p = 0.04$) and lesion extension grades ($\rho = -0.50$, $p = 0.005$).

4. Discussion

Our results showed that higher serum 25OHD concentration correlated with less severe BP prior to initiation of treatment. There is growing epidemiological evidence regarding the beneficial effects of higher vitamin D status at the onset and during the progression of autoimmune disorders (Ben-Zvi et al., 2010; Munger et al., 2006), including BP. These effects have been reported in a few studies (Marzano et al., 2012; Marzano, Trevisan, & Cairoli, 2015; Tukaj et al., 2013) focusing specifically on the association between lower serum 25OHD concentrations and BP, with mixed results. While (Marzano et al. (2012), Vaillant et al. (1998) showed a significant association, Tukaj et al. (2013) reported no association. Surprisingly, the severity of BP has been little studied so far and, to our knowledge, only one previous study showed an inverse relationship between 25OHD concentration and disease severity measured with the Autoimmune Bullous Skin Disorder Intensity Score (Marzano et al., 2015). Despite the use of a score validated only in pemphigus (Pfütze, Niedermeier, Hertl, & Eming, 2007), this result was consistent with our study using instead two clinical scores appropriate to BP. These findings could be explained by the regulation of innate and adaptive immunity by vitamin D (D'Aurizio et al., 2015), both of which being involved in the pathogenesis of BP. Our results suggest that vitamin D may be involved in the pathophysiology of BP and could serve as prognostic biomarker of BP. Our results also suggest that enhancing vitamin D status in older adults might represent an efficient strategy to prevent the onset and progression of BP. However, the observational cross-sectional design of our study prevents any causal inference. Large prospective, preferentially interventional, studies are needed to corroborate and explain these results.

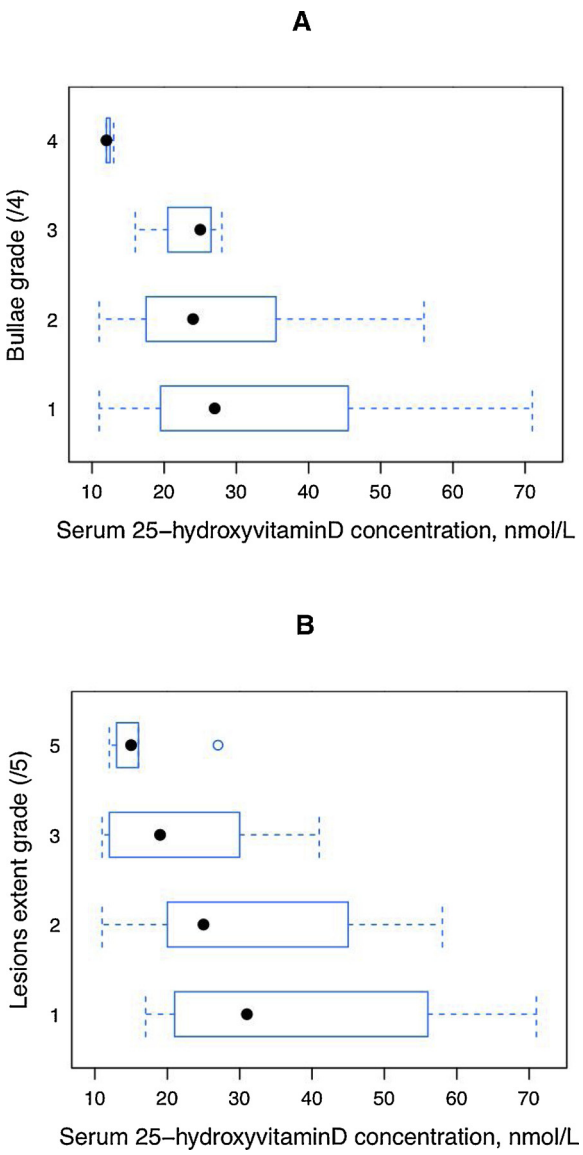

Fig. 1. Distribution of serum 25-hydroxyvitamin D concentration by severity of bullous pemphigoid assessed with (A) the bullae grade, and (B) the extent of lesions grade (n = 30).

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Competing interests

Dr. Sarre was supported by a grant from SVR. She has no relevant financial interest in this manuscript.

Pr. Annweiler serves as an editor for Maturitas, and for Gériatrie, Psychologie et Neuropsychiatrie du Vieillissement, and as an associate editor for the Journal of Nutrition Health and Aging, and for the Journal of Alzheimer's Disease. He has no relevant financial interest in this manuscript.

The other authors report no conflict of interest with this manuscript. They have no relevant financial interest in this manuscript.

Authors' contributions

MES had full access to the data in the study and takes responsibility for their integrity and the accuracy of the data analyses.

All authors contributed in gathering the data, and in the interpretation of the data. They revised and critically appraised the intellectual content of the manuscript, and approved the final version.

Ethics

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). Ethics approval was obtained from the local Ethics Committee (N°1635125). Written informed consent was obtained at enrolment according to protocols approved by the local Ethics Committee.

Data and material availability

Patient level data are freely available from the corresponding author at Cedric.Annweiler@chu-angers.fr. There is no personal identification risk within this anonymized raw data, which is available after notification and authorization of the competent authorities. Data requests may be sent to the following address: Centre Hospitalier Universitaire, Délégation à la recherche clinique et à l'innovation (DRCI), 4 rue Larrey, F-49933 Angers cedex 9 France.

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