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Risk of Osteoporosis Associated with Glucocorticoid Use in Pemphigus Vulgaris: Insights from a Retrospective Cohort Study

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ABSTRACT

Introduction: Pemphigus vulgaris (PV) is an autoimmune bullous disease affecting the skin and mucous membranes. Osteoporosis, a significant side effect of commonly used glucocorticoids in treatment, can adversely contribute to the existing morbidity.

Objectives: This study aimed to assess the impact of glucocorticoid therapy on bone mineral density in patients with PV.

Methods: Patients newly diagnosed with PV were included in this study. Femur and lumbar T-scores, serum calcium, vitamin D, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels were analyzed before and one year after therapy.

Results: Among 66 patients, the average time to diagnosis was 10.14 months, and the average daily dose of prednisone was 16.95 mg, with 63.6% of patients receiving medium doses. Our data showed no significant change in lumbar T-scores after one year of glucocorticoid treatment, but a significant decrease in femur density was observed. The decrease in femur T-scores was significant in the medium-dose group, while the lumbar T-scores decreased significantly in the high-dose group. There was no significant correlation between T-scores and sex, menopausal state, diagnosis time, or obesity. Additionally, vitamin D and LDH levels significantly increased after treatment, while changes in serum calcium and ALP levels were not significant.

Conclusion: Given the multiple factors that reduce bone mineral density in PV patients, the current strategies for glucocorticoid-induced osteoporosis prophylaxis in this group may need re-evaluation, with potential for additional recommendations to be included in pemphigus guidelines.

Introduction

Pemphigus vulgaris (PV) is an autoimmune bullous disease affecting the skin and mucous membranes. It is characterized by acantholysis resulting from antibodies against desmoglein 1 and desmoglein 3 [1,2]. Clinically, this typically presents as flaccid vesicles, bullae, or erosions on the skin and mucous membranes, with the oral mucosa being the primary site of onset [3]. Although its incidence worldwide is 2.83 per million person-years, it is a life-threatening disease [4]. While corticosteroids have been the first choice of treatment for many years, they have been ranked alongside rituximab in new guidelines due to the risk of morbidity and mortality [5,6]. Osteoporosis, a known side effect of corticosteroids, can occur due to senility, reduced mechanical stimulation/immobilization, bone and hormone metabolism disorders, inflammatory diseases, and malnutrition [7]. Various guidelines are being developed for the prophylaxis and treatment of corticosteroid-induced osteoporosis [8,9]. However, these guidelines are not disease-specific. Current PV guidelines include recommendations for calcium and vitamin D supplementation, screening for osteoporosis, and bisphosphonates in patients at risk [5]. The clinical impact of adhering to PV guidelines on bone mineral density needs to be investigated since there is a lack of studies on this topic.

Objectives

Our study aimed to retrospectively evaluate the bone mineral density changes in patients diagnosed with PV who were taking corticosteroids, receiving treatment and lifestyle modifications according to osteoporosis prevention measures within the first year.

Methods

Study Design

This retrospective study was conducted in dermatology inpatient and outpatient clinics between June 2019 and May 2024 in a training and research hospital in Ankara, Turkey. The study was approved by the hospital's ethics and scientific committee (approval date: 29.05.2024, decision number: 2-24-206).

Study Population

Newly diagnosed pemphigus vulgaris patients who were glucocorticoid-naive and whose diagnosis was confirmed by biopsy were included in our study. Patients with endocrinological, rheumatological, and inflammatory diseases, malignancies, having a history of antiepileptic or benzodiazepine usage, having diseases causing malnutrition, or with a history of gastrointestinal surgery were excluded. Patients who were not documented to have regularly taken daily calcium and vitamin D supplements or to adhere to daily lifestyle and diet recommendations or patients with incomplete documents were also excluded from the study. All patients were provided with a daily supplement of 1200 mg of calcium and 800 IU of vitamin D in accordance with current guidelines, along with dietary and exercise recommendations [8]. Additionally, further treatment options were discussed with the physical therapy and rehabilitation department when necessary.

Studied Variables

The charts of pemphigus vulgaris patients were reviewed from the medical records. Age, sex, body mass index (BMI), menopausal status of female patients, lumbar and femur T-scores, serum 25-hydroxyvitamin D (25(OH)D), serum calcium corrected for serum albumin (reference interval 8.4-10.2 mg/dL), serum total alkaline phosphatase (ALP) (reference interval 53–128 UI/L), and serum lactate dehydrogenase (reference interval 120-246 U/L) levels before and one year after treatment were obtained from the data system. Additionally, the cumulative and daily prednisone doses were also evaluated. The average daily glucocorticoid dose was classified as low (≤ 7.5 mg/day), medium (> 7.5 mg/day but ≤ 30 mg/day), or high (> 30 mg/day) [10]. Bone mineral density (BMD) was measured by Dual-energy X-ray Absorptiometry (DXA) (GE Healthcare, Madison WI, USA) at lumbar spine and femoral neck and expressed as standard deviation (SD) units in relation to the reference healthy population of the same age (Z-score) and of the young adults (T-score). Osteopenia was defined as a T-score between -1.0 and -2.5 and osteoporosis as a T-score of -2.5 and less. Serum 25 (OH)D levels were measured by competitive immunoassay (Atellica IM, Siemens Healthineers, Forchheim, Germany) (reference interval: 30–100 µg/L).

Statistical Analysis

The data were analyzed using SPSS version 26.0 for Windows (IBM SPSS Statistics, Armonk, NY). Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean and standard deviation. For normal distributions, continuous variables were compared using independent samples t-test and paired sample t-test. For non-parametric distributions, Mann-Whitney U test was used. A p-value of 0.05 was considered the threshold for statistical significance.

Results

A total of 73 patients were included in this study, with 66 patients evaluated due to exclusion criteria. Of the 66 patients (39 females, 27 males), the mean age of females

Table 1. Characteristics of the Study Population.

Variable	Total (N=66) Mean (SD)	Male (N=27) Mean (SD)	Female (N=39) Mean (SD)	P-value
Age (years)	53.83 (16.15)	54.8 (14.9)	53.15 (17.06)	0.685
BMI (mg/m^2)	27.61 (5.06)	26.7 (3.72)	28.2 (5.79)	0.228
Time before diagnosis (months)	10.14 (13.89)	10.78 (12.7)	9.69 (14.7)	0.758
Cumulative prednisone dose (mg)	6190.08 (3598.4)	6828.8 (4030.1)	5747.88 (3247.4)	0.233
Daily prednisone dose (mg)	16.95 (16.10)	20.78 (10.84)	17.76 (9.53)	0.236

Abbreviations: BMI = body mass index; SD = standard deviation.

Table 2. Comparison of T-scores and Laboratory Values Before and After Treatment.

Variable	Before Treatment Mean ± SD	After Treatment Mean ± SD	P-value
Lumbar T-score	–0.91 ± 1.56	–1.06 ± 1.44	0.102
Femur T-score	–0.64 ± 1.10	–0.87 ± 1.09	0.001
ALP	69.90 ± 26.22	68.83 ± 22.87	0.724
Calcium	9.43 ± 0.48	9.41 ± 0.48	0.819
Vitamin D	34.64 ± 15.62	39.49 ± 19.40	0.018
LDH	203.03 ± 41.79	232.01 ± 59.54	<0.001

Abbreviations: ALP = alkaline phosphatase; LDH = lactate dehydrogenase; SD = standard deviation.

was 53.15 ± 17.06 and of males was 54.8 ± 14.9 years. The age of these patients ranged from 18 to 83 years, with a mean of 53.83 ± 16.15 years. The mean BMI was 27.61 ± 5.06. According to BMI, 66.7% (N=44) were overweight and obese, while 33.3% (N=22) were of normal weight. Among the female patients, 45.5% (N=30) were postmenopausal. The average time to diagnosis was 10.14 ± 13.89 months, and the daily dose of prednisone was 16.95 ± 16.10 mg. When categorized according to daily prednisone doses, 18.2% (N=12) were on low, 63.6% (N=42) were on medium, and 18.2% (N=12) were on high doses. The mean cumulative prednisone dose was 6190.08 ± 3598.4 mg (Table 1). Our results show that the lumbar T-scores did not differ before and after one year of glucocorticoid treatment (P=0.102). In contrast, there was a significant decrease in femur density (P=0.001). After one year of glucocorticoid therapy, the changes in mean serum calcium and serum ALP levels were not significant (P=0.819, P=0.724, respectively). A significant increase in 25 (OH)D levels (P=0.018) and in LDH levels (P<0.001) were observed after treatment compared to pre-treatment levels (Table 2). There was no significant correlation between T-scores and sex, diagnosis time, or obesity (Table 3). Although femur and lumbar T-scores were low both before and after treatment in the menopausal group, the difference was not significant (Table 4). Vitamin D values of non-menopausal patients increased significantly compared to menopausal patients (P=0.044). When analyzing glucocorticoid dose categories, a significant decrease in femur T-scores was observed in patients receiving moderate doses, while a significant decrease in lumbar T-scores was found in the high-dose group (P=0.000 and P=0.018, respectively). No significant decrease in T-scores was observed in the low-dose group (Table 5).

Conclusions

This study describes the change in bone mineral density status in a population of 66 PV patients treated with glucocorticoids. Although corticosteroids have been prioritized with rituximab in the treatment of moderate-to-severe pemphigus vulgaris in recent years, they are still among the chronically used medications [5]. Previous studies have shown that osteoporosis, one of the well-known side effects of systemic glucocorticoids, is increased in PV patients compared to healthy volunteers even before treatment [11]. This difference could not be confirmed in our case series since our study lacked a control group. Similar to our study, Marzano et al. found that PV patients have lower serum calcium and vitamin D levels compared to controls before treatment. Along with this result, they suggested that low vitamin D might play a role in the pathogenesis of pemphigus vulgaris [12,13]. Although the absence of a significant decrease in calcium and vitamin D levels post-treatment suggests that prophylaxis may be adequate, low vitamin D levels before treatment, malnutrition,

Table 3. Comparison of Bone Mineral Density Values Before and After Treatment According to Sex and Body Mass Index.

Variable	Sex Mean ± SD			Body Mass Index Mean ± SD		
	Male	Female	P-value	≥30 mg/m^2	<30 mg/m^2	P-value
Femur T-score						
Before	-0.67±0.93	-0.61±1.22	0.824	-0.43±1.06	-0.74±1.12	0.293
After	-0.70±1.06	-0.98±1.12	0.318	-0.81±0.89	-0.89±1.19	0.785
Lumbar T-score						
Before	-0.79±1.41	-1.00±1.67	0.603	-0.77±1.53	-0.99±1.59	0.598
After	-0.82±1.21	-1.23±1.57	0.256	-1.1±1.39	-1.05±1.48	0.896
ALP						
Before	69.07±25.56	70.48±26.99	0.832	77.81±35.25	65.9±19.61	0.153
After	69.85±22.66	68.12±23.29	0.765	70.63±24.31	67.93±22.35	0.654
Calcium						
Before	9.45±0.38	9.41±0.55	0.792	9.4±0.31	9.44±0.56	0.792
After	9.41±0.39	9.41±0.55	0.975	9.38±0.51	9.43±0.47	0.735
Vitamin D						
Before	41.74±15.12	29.72±14.16	0.002	35.13±14.33	34.39±16.38	0.858
After	46.89±21.48	34.36±16.20	0.014	38.65±18.41	39.91±20.08	0.807
LDH						
Before	202.51±38.86	203.38±44.20	0.935	206.86±41.29	201.11±42.38	0.602
After	218.96±41.83	241.05±68.28	0.109	235.31±56.67	230.36±61.50	0.753

Abbreviations: ALP = alkaline phosphatase; LDH = lactate dehydrogenase; SD = standard deviation.

Table 4. Comparison of Bone Mineral Density Values Before and After Treatment According to Menopausal State.

Variable	Menopausal State Mean ± SD		
	Menopausal	Non-Menopausal	P-value
Femur T-score			
Before	-0.66±1.30	-0.61±0.93	0.869
After	-0.97±1.25	-0.78±0.96	0.493
Lumbar T-score			
Before	-1.17±1.76	-0.70±1.36	0.224
After	-1.25±1.74	0.91±1.13	0.370
ALP			
Before	71.76±24.88	68.36±27.55	0.603
After	70.23±25.24	67.66±20.99	0.653
Calcium			
Before	9.37±0.51	9.48±0.46	0.353
After	9.40±0.51	9.42±0.47	0.823
Vitamin D			
Before	30.54±14.91	38.06±15.58	0.051
After	34.25±17.15	43.85±20.31	0.044
LDH			
Before	207.60±41.58	199.22±42.17	0.422
After	246.86±68.01	219.63±49.04	0.064

Abbreviations: ALP = alkaline phosphatase; LDH = lactate dehydrogenase; SD = standard deviation.

Table 5. Comparison of T-scores Before and After Treatment According to Dose Categories.

	Before Treatment Mean (SD)	After Treatment Mean (SD)	P-value
Low Dose			
Femur T-score	-0.49 (0.89)	-0.4 (1.11)	0.571
Lumbar T-score	-0.63 (1.25)	-0.6 (1.47)	0.908
Medium dose			
Femur T-score	-0.8 (1.13)	-1.02 (1.09)	0.000
Lumbar T-score	-1.26 (1.5)	-1.24 (1.47)	0.785
High dose			
Femur T-score	-0.2 (1.15)	-0.79 (1.02)	0.018
Lumbar T-score	-0.01 (1.73)	-0.89 (1.29)	0.059

Abbreviation: SD = standard deviation.

and pre-existing inflammation may contribute to the significant decrease in femur T-scores in PV patients and that there may be a need to initiate additional anti-resorptive treatments earlier [12,14,15]. Additionally, glucocorticoids directly affect osteoclasts and osteoblasts, reducing bone mineral density, which negatively contributes to the current condition of bone mineral density [16-18]. This study has potential limitations. First, the retrospective design of our study limited our ability to clearly evaluate the presence of malnutrition in the patients. The compliance with physical activity and dietary follow-up could not be monitored. Second, the lack of control group limits establishing causal relationships and comparing outcomes with alternative treatment strategies. Third, since disease severity was not included in the study, its relationship with bone mineral density could not be determined. Van Staa et al. demonstrated that the risk of

both hip and vertebral fractures was significantly higher in patients receiving moderate-to-high daily doses of glucocorticoids (7.5 mg and above) compared to those on low doses (below 2.5 mg) [19]. Although fracture incidence was not included in our study, previous studies have shown that low BMD is a crucial determinant of fragility fractures, and DXA measurements of BMD are strong predictors of fracture risk in individuals [20-22]. Patients with a BMI < 30 kg/m² had lower femur and lumbar T-scores before treatment compared to those with a BMI > 30 kg/m². After treatment, the BMD scores decreased in both groups, with no significant difference between them. Previous studies have shown that a low body mass index causes osteoporosis and a decrease in BMD [23]. Excess estrogen production in the adipose tissue and additional load carried by the bone, which contributes to microtrauma, and genetic variations may contribute to the positive impact of obesity on BMD [18, 24].

For years, various guidelines have been published to reduce and prevent the risk of osteoporosis in patients with long-term corticosteroid use. These guidelines are generally not disease-specific and cover most conditions. Considering the variety of factors that reduce bone mineral density in PV, the prophylaxis provided to this patient group may need to be re-evaluated, and additional recommendations may need to be included in pemphigus guidelines.

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