Osteoporosis in Patients with Pemphigus Vulgaris before Steroid Therapy

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Abstract- Pemphigus Vulgaris (PV) is often complicated by osteoporosis. Although corticosteroid therapy undoubtedly plays a causative role, inflammation associated with PV may also contribute to osteoporosis. This study was designed to determine the prevalence of osteoporosis in patients with PV before corticosteroid therapy and to compare these findings with those reported previously in healthy volunteers. Newly diagnosed patients with PV, who had not received systemic corticosteroids, were enrolled. Bone mineral density (BMD) was measured both in the lumbar spine (L1-L4) and hip region. Data were compared with those of a healthy Iranian population. The association between the disease duration and severity and BMD was evaluated. A total of 50 patients (27 women) with a mean age of 42.6±14.5 years were enrolled. Osteoporosis was seen in 7 (14%) patients, 3 (11.1%) women, 4 (17.4%) men, and in both genders it was more common when compared to the population of healthy Iranians (8.2% in women and 4.9% in men). Osteopenia was found in 26 (52%) patients, 13 women and 13 men. Although both osteopenia and osteoporosis were more common in severe disease, neither the duration nor the severity of PV showed a statistically significant association with osteopenia or osteoporosis. The presence of a higher than expected rate of osteoporosis in patients with PV argues for osteoporosis screening and efforts aimed at prevention and early initiation of treatment to prevent unnecessary morbidity.

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Introduction

Pemphigus vulgaris (PV) is a rare but serious and potentially life-threatening autoimmune disorder of the skin and mucous membranes. It is characterized by circulating and tissue-bound auto antibodies against desmoglein 3 and/or 1 leading to the destruction of desmosomes, acantholysis, and eventually the formation of epidermal or mucosal blisters.

Inflammation has an essential role in the immunopathogenesis of PV. Auto-reactive B- and T-cells, as well as inflammatory cytokines, are probably involved in the pathogenesis of pemphigus. Various pro-inflammatory cytokines including IL-6, IL-8, IFN-γ, IL-1α, and TNF-α is known to amplify cell signals that mediate acantholysis (1). Several studies have shown that pro-inflammatory cytokines can reduce bone mineral density in autoimmune disorders such as rheumatoid arthritis, scleroderma and dermatomyositis (2-14).

Systemic glucocorticoids are the mainstay of therapy for pemphigus and almost all the patients require long-term treatment with relatively high doses of steroids. However, it is well established that in the majority of patients morbidity from pemphigus is related to the side effects of steroid therapy (15-19). Osteoporosis is a serious and common complication of systemic corticosteroid therapy.

Reviewing the literature, authors only found one retrospective study about the occurrence of osteoporosis in patients with pemphigus (20). Wohl *et al*., reported a higher prevalence of osteoporosis in patients with pemphigus. Although the authors treated their patients with steroids, a higher prevalence of osteoporosis was detected in patients with pemphigus even after controlling for the potential confounding effect of corticosteroid therapy. This study was designed to determine the prevalence of osteoporosis in patients with

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PV before corticosteroid therapy and to compare these findings with those reported previously in healthy volunteers.

Materials and Methods

This was a cross-sectional study performed on newly diagnosed patients referred to the Autoimmune Bullous Disease Research Center, Razi hospital, Tehran University of Medical Sciences, a referral dermatology center providing services to major parts of Iran. Inclusion criteria included: (1) diagnosis of PV based on the typical clinical, histopathological, and direct immunofluorescence findings, (2) not being treated with prednisolone or immunosuppressive drugs previously. The exclusion criteria included: (1) taking any other drugs that may affect bone density; (2) current or past history of other diseases that may affect bone density; (3) age under 15 years; (4) pregnancy; (5) not giving consent to participate in the study.

A detailed past medical history including demographic data and disease duration was obtained. Complete physical examination and routine laboratory tests (complete blood counts, erythrocyte sedimentation rate, serum calcium, phosphorus and alkaline phosphatase) were performed.

Bone mineral density (BMD) was determined on the lumbar spine, femoral neck and total hip for all patients using dual energy x-ray absorptiometry (DXA) method by Hologic QDR-4500W machine.

Patients were classified to three groups based on disease severity: Mild, mouth erosions < 3 and /or cutaneous lesions < 5; Moderate, mouth erosions 3 to 10 and/or desquamative gingivitis and/or cutaneous lesions 5 to 20; Severe, mouth erosions > 10 and/or severe and confluent erosions and/or generalized desquamative gingivitis and/or cutaneous lesions > 20 and/or confluent areas of skin erosions.

According to the World Health Organization (WHO), osteoporosis is defined as a BMD (either in lumbar spine, neck of femoris, or total hip) greater than or equal to 2.5 standard deviations (SD) below the peak BMD of gender- and ethnicity-matched healthy young adults (T-score ≤ 2.5 SD). Osteopenia is defined as a BMD T-score between –1 to – 2.5 SD. 21

Data analysis was performed with SPSS ver.15 software. Standard deviation (SD) was calculated for means, and the comparisons were performed by chi square, paired T-test and ANOVA test for rates, means and groups, respectively. P value of less than 0.05 was considered statistically significant.

This study was approved by the Tehran University of Medical Sciences Ethics Committee, and informed consent was obtained from all participants.

Results

During a 9-month period, from August 2008 to March 2009, 50 patients with PV were enrolled into the study. They included 23 men (46%) and 27 women (54%) with an average age of 42.5 ± 14.5 years and a mean disease duration of 20.5 ± 19.9 weeks (median= 12 weeks).

None of the patients had mild disease, while 18 (36%) had moderate, and 32 (64%) had severe disease. No significant difference was found in the severity of PV between the genders.

Seven patients (14%) had osteoporosis, 26 patients (52%) had osteopenia, and 17 patients (34%) had normal bone density.

There was no statistically significant difference between men and women regarding the frequency of either osteoporosis or osteopenia (P>0.05). Osteoporosis was observed in 4 men (17.4%) and 3 women (11.1%) while osteopenia was found in 13 men (56.5%) and 13 women (48.1%).

Frequency of osteoporosis increased with age. It was observed in 42.9% of the patients older than 60 years, 12.5% of those between 40 to 60 years, and 7.4% of the patients younger than 40 years. This difference was statistically significant (P=0.04).

Regarding the severity of PV, 18 patients showed moderate, and 32 patients showed severe disease. Although the frequency of both osteoporosis and osteopenia were higher in patients with severe form than those with moderate disease, the differences were not statistically significant (P>0.05). The prevalence of osteoporosis and osteopenia was 19% and 53%, respectively, in those with severe disease, and 5% and 50%, respectively, in patients with moderate disease (Table 1).

Duration of the disease was more than 12 weeks in 31 (62%) patients. In this group of patients, osteoporosis was observed in 9.6% and osteopenia in 54.8%. Among patients whose duration of the disease were less than 12 weeks (19 patients), 21% were osteoporotic, and 47.3% were osteopenic (Table I).

We found no significant correlation between duration of the disease and the prevalence of neither osteoporosis nor osteopenia (P>0.05).

Table 1. Frequency of osteopenia and osteoporosis based on severity and duration of disease in 50 pemphigus patients

	Normal (n/%)	Osteopenia (n/%)	Osteoporosis (n/%)	Total
Disease severity				
Moderate disease	8(45%)	9(50%)	1(5%)	18
Severe disease	9(28%)	17(53%)	6(19%)	32
Disease duration				
< 12 weeks	6(32%)	9(47%)	4(21%)	19
≥ 12 weeks	11(35%)	17(55%)	3(10%)	31

Discussion

Bone loss has been reported in various inflammatory and autoimmune diseases such as rheumatoid arthritis (2-5), systemic lupus erythematosus (22), inflammatory bowel diseases (23-24), primary biliary cirrhosis (25), chronic active hepatitis (26), HIV infection (27), and recently in psoriasis (28). As an autoimmune-mediated disease, pemphigus may also result in the reduction of bone mineral density regardless of being treated with corticosteroids. A number of cytokines involved in the immunopathogenesis of pemphigus are known to affect bone metabolism and mediate development of osteoporosis (8-14).

In a case-control study, Wohl *et al*., have reported that osteoporosis is associated with pemphigus (20). However, the mean duration of the disease was 30 months, and most patients were treated with glucocorticoids with a mean cumulative dose of 370 grams. While corticosteroids may have a substantial effect on the development of osteoporosis, the authors found a statistically significant association between pemphigus and osteoporosis even after controlling for the steroid therapy as a confounding factor (OR: 4.27).

In this study, we assessed the effect of pemphigus per se on BMD in newly diagnosed untreated patients. 14% of patients with pemphigus were osteoporotic before starting the treatment. This was markedly higher than the rate of osteoporosis in the normal Iranian population reported by Akbarian *et al*., (29) Osteoporosis was present in 17.4% of men and 11.1% of women with pemphigus, while in healthy controls these rates were 4.9% and 8.2%, respectively. Additionally, since current patients were younger than the healthy individuals reported by Akbarian *et al*., (29), pemphigus may even induce a more remarkable effect in the induction of osteoporosis. Although not statistically significant, a surprising finding in this study was a higher rate of osteoporosis in men compared to women.This finding was consistent with the findings of Wohl *et al*., (20) These data suggest that men with pemphigus are more susceptible to osteoporosis. We have no explanation for the difference in genders, and as the severity of disease was not different in two genders, it cannot be explained by disease severity.

Current study showed a higher prevalence of osteoporosis in older patients. This was in contrast with the Wohl *et al*., study (20) where the rate of osteoporosis was higher in those younger than 50 years.

In present study, a higher rate of osteoporosis was observed in patients with more severe disease. A possible explanation for this finding is that in patients with more severe disease, higher serum concentration of pro-inflammatory cytokines such as IL-6 and TNF-α may induce larger amounts of bone resorption through increased osteoclastic activity.

The authors also hypothesized that longer exposure to inflammatory cytokines may lead to an increased reduction in BMD in patients with pemphigus. To evaluate this hypothesis, the rate of osteoporosis/ osteopenia in untreated patients with disease duration more than 12 weeks were compared with those in an earlier phase of the disease (Table 1). Even though patients with longer disease duration had a lower rate of osteoporosis, the difference was not statistically significant. This could be due to the relatively few number of patients. Another reason may be that 12 weeks cutoff was not enough to reveal the difference between the effects of factors that promote osteoporosis. Further studies with relatively larger sample sizes and patients with longer duration of the disease are required to evaluate this difference. However, mucosal and cutaneous lesions of pemphigus are generally painful and most patients consult physician within a short time following initiation of their clinical manifestations making it difficult to enroll untreated pemphigus patients with relatively long duration of the disease. Another limitation of the current study was the lack of a control group (29). For better comparing, we presented BMD of patients with pemphigus and normal population in various age

groups (Tables 2 and 3).

In conclusion, there is a higher rate of osteoporosis in the newly diagnosed, untreated patients with PV in comparison with healthy individuals that suggests role of the inflammatory process of the disease in reduction of bone mineral density. Thus, the authors recommend that patients with PV undergo routine bone densitometry before starting the treatment with corticosteroid. To reduce morbidity and mortality of pemphigus, it is also recommended to consider appropriate strategies for prevention and treatment of osteoporosis from the first visit.

Table 2. BMD comparison between female patients with pemphigus and normal population

Age group	Number of patients	Mean BMD in women with pemphigus (lumbar)	Mean BMD in normal Iranian women (lumbar)	Mean BMD in women with pemphigus (femoral)	Mean BMD in normal Iranian women (femoral)
16-20	0	----------	0.829	----------	0.794
21-25	3	0.8746	0.935	0.7146	0.863
26-30	5	0.9788	0.996	0.8142	0.908
31-35	0	---------	1.019	----------	0.931
36-40	10	0.9973	1.013	0.8192	0.936
41-45	3	0.8646	0.944	0.8256	0.925
46-50	1	0.825	0.944	0.702	0.903
51-55	0	---------	0.896	----------	0.871
56-60	2	0.8275	0.849	0.709	0.833
61-65	0	--------	0.811	----------	0.793
66-70	2	0.7565	0.791	0.6555	0.752
71-75	1	0.789	0.795	0.754	0.714

Table 3. BMD comparison between male patients with pemphigus and normal population

Age group	Number of patients	Mean BMD in men with pemphigus (lumbar)	Mean BMD in normal Iranian men (lumbar)	Mean BMD in men with pemphigus (femoral)	Mean BMD in normal Iranian men (femoral)
16-20	1	0.872	0.763	0.782	0.873
21-25	3	0.9823	0.864	0.925	0.950
26-30	0	--	0.931	--	0.997
31-35	1	0.933	0.970	0.86	1.018
36-40	4	0.9382	0.986	0.8885	1.020
41-45	3	0.9746	0.984	0.8063	1.007
46-50	1	0.937	0.971	0.77	0.984
51-55	3	0.954	0.951	0.8453	0.957
56-60	3	0.899	0.931	0.745	0.931
61-65	2	0.8495	0.916	0.6705	0.910
66-70	1	0.832	0.911	0.753	0.900
71-75	1	0.602	0.923	0.628	0.906

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