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# Pemphigus and Osteoporosis

## A Case-Control Study

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**Objective:** To investigate the association between pemphigus and osteoporosis.

**Design:** Case-control study.

**Setting:** A large health care provider organization in Israel.

**Participants:** Patients with pemphigus older than 20 years (hereinafter, pemphigus patients) were compared with a sample of age- and sex-matched controls.

**Interventions:** Data retrieval from a large community-based medical database regarding health-related lifestyles, comorbidities, use of medications, bone mineral density scans, and drugs for osteoporosis.

**Main Outcome Measures:** The prevalence of osteoporosis in patients and controls, use of bone mineral density scans, and drugs for osteoporosis.

**Results:** The study included 255 pemphigus patients and 509 controls older than 20 years. Osteoporosis was diagnosed among 40.4% of pemphigus patients compared

with 6.5% of controls ( $P < .001$ ; odds ratio [OR], 9.77; 95% confidence interval [CI], 6.34-15.10). After controlling for confounders, including age, sex, and duration of glucocorticosteroid therapy and proton pump inhibitor therapy, the associations with osteoporosis persisted (OR, 4.27; 95% CI, 2.44-7.47;  $P < .001$ ). Similar results were obtained when using cumulative glucocorticosteroid dose. Only 73 pemphigus patients with osteoporosis (70.9%) had undergone a bone mineral density test within the past 10 years. While most pemphigus patients with osteoporosis purchased medications for osteoporosis, including calcium (95.1% of patients), cholecalciferol (89.3%), bisphosphonates (90.3%), or raloxifene (8.8%), the duration of therapy was short.

**Conclusions:** We found an association between pemphigus and osteoporosis, which persisted after controlling for glucocorticosteroid use. Monitoring and treatment of osteoporosis in pemphigus patients was suboptimal in this study.

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**P**EMPHIGUS, A RELATIVELY RARE autoimmune bullous disease involving the skin and mucous membranes, is associated with substantial morbidity and is potentially fatal. Basically it is considered to be an antibody-mediated disorder; however, the exact immunopathogenesis in pemphigus is not completely elucidated but probably involves both autoreactive B and T cells and inflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF), leading to acantolysis.<sup>1</sup>

### See Practice Gaps at end of article

Systemic corticosteroids are an established therapy for patients with pemphigus (hereinafter, pemphigus patients) but

entail clinically significant adverse effects, such as osteoporosis; weight gain; hypertension; unfavorable changes in cholesterol and triglyceride, glucose, and electrolyte levels; and an immune suppression leading to an increased risk of infections.

Glucocorticosteroid-induced osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing the individual to an increased risk for fractures. It is one of the most common and serious adverse effects for patients receiving corticosteroids. In addition to glucocorticosteroid therapy, other mechanisms may account for the marked osteoporosis seen in pemphigus patients, linked to its immune inflammatory pathogenesis, because studies published in recent years have revealed that excessive skeletal bone loss is associated with inflammatory and autoimmune diseases.<sup>2-4</sup>

We assessed the association between pemphigus and osteoporosis using the large medical database of Clalit Health Services (CHS), Tel Aviv, Israel.

## METHODS

For the current retrospective case-control study, data mining techniques using the CHS database were used. Clalit Health Services is the largest health care provider organization in Israel, serving a population of approximately 3 900 000 enrollees. A comprehensive computerized database with continuous real-time input from pharmaceutical, medical, and administrative computerized operating systems facilitates epidemiological studies, such as the current analysis.

Patients were defined as having pemphigus when a diagnosis of pemphigus was documented at least twice in the medical record by a CHS dermatologist. Further differentiation between superficial and deep variants of pemphigus was not available for our recording system.

The control group was randomly selected from the list of CHS enrollees, excluding patients with a diagnosis of pemphigus, and matched to cases regarding age and sex. Based on an estimated prevalence of osteoporosis of 7.5% in controls and an at least double (ie, 15.0%) prevalence of osteoporosis in pemphigus cases, we calculated that at least 236 pemphigus patients and 472 controls would be needed with a power of 80% and a significance level of 5% (calculations made using Stata statistical software, version 8; StataCorp LP, College Station, Texas). Therefore, we included all known pemphigus patients older than 20 years enrolled with CHS ( $n=255$ ) and controls in a ratio of 2:1 ( $n=509$ ).

Data available from the CHS database included age; sex; life-style habits, such as current smoking or alcohol abuse; chronic diagnoses, such as diabetes mellitus, hypertension, obesity, ischemic heart disease, and osteoporosis; as well as a large variety of diagnoses (109 different unique codes used within the database to identify chronic diseases). The diagnoses of chronic diseases, including osteoporosis, were taken from the CHS chronic diseases registry, which is based on use of medications, certain laboratory values thresholds, and data withdrawn from hospital and primary care physicians' reports. An osteoporosis code is registered in the database when a diagnosis of osteoporosis is made by a primary care physician or during hospitalization. The registry is validated by primary physician confirmation of registered diagnoses of chronic diseases. The validity of diagnoses in the register was previously estimated and found to be high for important chronic diagnoses.<sup>5</sup>

Data regarding glucocorticosteroid therapy, other medications known to be associated with an increased risk of osteoporosis, and drugs used to treat osteoporosis were available as of 1998 and extracted from the central pharmaceutical database. Data included duration of therapy in months for medications actually purchased at pharmacies. For the current study, we defined "chronic glucocorticosteroid therapy" as consumption of corticosteroids for more than 1 month over the past 10 years (1998-2008). Similarly, chronic medication use was defined for other medications, including proton pump inhibitors, anticoagulants, anticonvulsants, calcium supplements, cholecalciferol, bisphosphonates, and raloxiphen hydrochloride. Data regarding the total cumulative steroid dose were also retrieved. Various glucocorticoid preparations doses were translated to milligrams of prednisolone acetate using the defined daily dose of each preparation. Data regarding bone mineral density scans were also available from the database. The date of each scan was available, but the actual result of the scan was not.

The proportions of patients with osteoporosis were compared between patients with and without pemphigus by uni-

variate analyses, using  $\chi^2$  tests to compare categorical parameters between the groups. Because none of the continuous variables were normally distributed (based on the Kolmogorov-Smirnov test for normality), Mann-Whitney test was used for comparison of continuous variables. For cross-tabulations containing empty cells, the 95% confidence interval (CI) was calculated using the Cornfield method. The association between pemphigus and osteoporosis was stratified by age and sex and analyzed using the Mantel-Haenszel method. Logistic regression models were used to measure the association between pemphigus and osteoporosis in a multivariate analysis. In the multivariate models, covariates were selected for analysis if the univariate  $P$  value for the association between the potential confounder and osteoporosis was  $P < .10$ , and remained in the model if the multivariate  $P < .05$ . Statistical analysis was performed using SPSS software (version 15; SPSS Inc, Chicago, Illinois) and Stata software, version 8. The study was approved by the local institutional review board of the Soroka University Medical Center, Beersheba, Israel.

## RESULTS

The study included 255 pemphigus patients and 509 controls older than 20 years. Pemphigus patients had a similar age and sex distribution to controls (mean age, 63.5 vs 63.2 years;  $P=.70$ ; female sex, 61.6% vs 61.5%, respectively,  $P=.98$ ). Pemphigus patients were more likely to be diagnosed as having hypothyroidism and malignant diseases. They were also more likely to purchase medications associated with osteoporosis, including glucocorticosteroids, proton pump inhibitors, levothyroxine sodium, and methotrexate for more than 1 month (**Table 1**). The cumulative glucocorticosteroid dose was much higher among pemphigus patients (Table 1). No differences in the rates of patients who purchased other medications known to be associated with osteoporosis, including furosemide, coumarin anticoagulants, heparin sodium, and anticonvulsants were found (data not shown). Osteoporosis was diagnosed among 40.4% of cases compared with 6.5% of controls ( $P < .001$ ; odds ratio [OR], 9.77; 95% CI, 6.34-15.10).

A stratified analysis by age and sex (**Table 2**) revealed that the association between pemphigus and osteoporosis was more prominent in males than in females. In addition, the association was strongest among patients younger than 50 years, and its strength decreased with increasing age (Table 2).

After controlling for confounders, including age, sex, and duration of glucocorticosteroid and proton pump inhibitor therapy, the associations with osteoporosis persisted, although the strength of the association decreased (OR, 4.27; 95% CI, 2.44-7.47;  $P < .001$ ) (**Table 3**).

Levothyroxine, methotrexate, coumarin anticoagulants, and anticonvulsant therapy, as well as hypothyroidism and the presence of malignant disease, were not associated with osteoporosis in the multivariate analysis. When we replaced duration of glucocorticosteroid therapy with cumulative glucocorticosteroid dose, the OR for osteoporosis associated with pemphigus remained significant (OR, 5.73; 95% CI, 3.39-9.69, controlled for age, sex, duration of proton pump inhibitor therapy, and cumulative glucocorticosteroids dose; data not shown).

**Table 1. Demographic and Clinical Characteristics of the 764 Study Participants<sup>a</sup>**

Characteristic	Patients With Pemphigus (n=255)	Controls (n=509)	P Value
Age, mean, y	63.5	63.2	.70
Median (range)	66 (23-96)	65 (24-105)	
Female sex	157 (61.6)	313 (61.5)	.98
Hypothyroidism	31 (12.2)	33 (6.5)	.008
Malignant disease	41 (16.1)	47 (9.2)	.005
Glucocorticosteroid therapy, duration >1 mo	204 (80.0)	72 (14.1)	<.001
Duration of glucocorticosteroid therapy, mo			
Mean	30.3	1.4	<.001
Median (range)	20 (0-122)	0 (0-91)	
Cumulative glucocorticosteroid dose, g <sup>b</sup>			
Mean	370	5.5	<.001
Median (range)	170 (0-3670)	0 (0-1517)	
Proton pump inhibitor therapy, duration >1 mo	156 (61.2)	149 (29.3)	<.001
Duration of proton pump inhibitor therapy, mo			
Mean	2.5	2.5	<.001
Median (range)	4 (0-25)	0 (0-32)	
Levothyroxine therapy, duration >1 mo	38 (14.9)	39 (7.7)	.002
Duration of levothyroxine therapy, mo			
Mean (SD)	1.4	0.7	.001
Median (range)	0 (0-12)	0 (0-12)	
Methotrexate therapy, duration >1 mo	32 (12.5)	4 (0.8)	<.001
Duration of methotrexate therapy, mo			
Mean	1.1	0.1	<.001
Median (range)	0 (0-12)	0 (0-12)	
Osteoporosis	103 (40.4)	33 (6.5)	<.001

<sup>a</sup>Unless otherwise indicated, data are given as number (percentage).

<sup>b</sup>Given in grams of prednisolone acetate.

**Table 2. Osteoporosis and Pemphigus, Stratified by Age and Sex<sup>a</sup>**

Age Group, y	Males			Females		
	Patients With Pemphigus (n=98)	Control Group (n=196)	OR for Osteoporosis (95% CI)	Patients With Pemphigus (n=157)	Control Group (n=313)	OR for Osteoporosis (95% CI)
20-49	0	3 (18.8)	∞ (2.1-∞)	6 (17.1)	0	∞ (3.3-∞)
50-69	0	13 (35.1)	∞ (8.5-∞)	34 (54.8)	7 (5.3)	21.7 (8.7-54)
≥70	2 (2.2)	11 (24.4)	14.7 (3.1-70)	36 (60.0)	24 (20.7)	5.8 (2.9-11.5)
<b>Total</b>	<b>2 (1.0)</b>	<b>27 (27.6)</b>	<b>36.9 (8.5-160)</b>	<b>76 (48.4)</b>	<b>31 (9.9)</b>	<b>8.5 (5.2-13.9)</b>

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Data are given as number (percentage) unless otherwise indicated.

However, the fit of the statistical model was worse than that of the model presented in Table 3.

Among patients with osteoporosis, a bone mineral density scan had been performed within the past 10 years in 70.9% of pemphigus patients and 81.8% of controls ( $P=.22$ ) (Table 4). The proportion of patients undergoing a bone mineral density scan was lower in males than in females, although not significantly (males with pemphigus and osteoporosis, 66.7%; females, 72.4%;  $P=.34$ ; control males with osteoporosis, 50.0%; females, 83.9%;  $P=.58$ ). Among patients with osteoporosis who underwent a bone mineral density scan, 26.0% of pemphigus patients had intervals of more than 5 years between adjacent tests, a proportion similar to that of controls (29.6%;  $P=.72$ ).

Most pemphigus patients with osteoporosis had purchased medications for osteoporosis for more than

1 month; these included calcium (95.1%), cholecalciferol (89.3%), and specific antiresorptive medications (91.3%; bisphosphonates, 90.3%; raloxifene, 8.8%) (Table 4). Specific antiresorptive therapy (bisphosphonates for males or females, raloxifene for females only) was more often purchased by females than males, both among pemphigus patients (females, 94.7%; males, 81.5%;  $P=.04$ ) and controls (females, 90.3%; males, 50%;  $P=.23$ ). However, the mean duration of therapy was extremely short, from 2.6 months of raloxifene therapy to 16.3 months of calcium therapy.

#### COMMENT

In the present population-based, large case-control study, pemphigus was found to be associated with osteoporosis.

**Table 3. Logistic Regression for Osteoporosis in 764 Study Participants**

Variable	OR (95% CI)	P Value
Pemphigus	4.27 (2.44-7.47)	<.001
Age, per 10-y increase	1.46 (1.22-1.73)	<.001
Female sex	3.93 (2.28-6.77)	<.001
Duration of glucocorticosteroid therapy, per additional 6 mo	1.19 (1.12-1.27)	<.001
Duration of proton pump inhibitor therapy, per additional 6 mo	1.38 (1.12-1.71)	.002

Abbreviations: CI, confidence interval; OR, odds ratio.

sis, particularly in males and in younger patients. After controlling for glucocorticosteroid therapy, pemphigus patients were still more likely to be diagnosed as having osteoporosis.

Despite the seriousness of osteoporosis, there is only scarce documentation in the literature on morbidity or mortality rates attributed to osteoporosis in pemphigus patients. Older publications describing retrospective uncontrolled studies found osteoporosis to occur in about one-third of glucocorticosteroid-treated patients, leading to vertebral compression fractures in most of them,<sup>6</sup> while mortality rate attributed to glucocorticosteroid treatment due to all reasons, including osteoporosis, was reported to be 10%.<sup>7</sup>

Over the past decades, systemic glucocorticosteroids have been considered the mainstay of therapy for pemphigus, accounting for corticosteroid-induced osteoporosis, one of the most common and serious adverse effects in patients receiving long-term treatment for various immune-mediated diseases. Glucocorticosteroid-induced osteoporosis is characterized clinically by significant bone loss, which occurs in most patients, leading to fractures most commonly affecting the hip, spine, and wrist, in 30% to 50% of patients with long-term use.<sup>8-10</sup> Loss of bone mineral density is greatest in the first few months of corticosteroid use, even with doses as low as prednisolone acetate, 2.5 mg/d, and the risk of fractures increases rapidly from the onset of therapy.<sup>8</sup> The diagnosis of osteoporosis is made either by the occurrence of fragility fracture or by dual x-ray absorptiometry (DEXA scan), in which scores that are 2.5 or more standard deviations below the mean bone mineral density of healthy young adults are diagnostic for osteoporosis.<sup>11</sup>

Osteoclast-mediated bone loss has been observed and reported in various inflammatory and autoimmune diseases, such as rheumatoid arthritis,<sup>12-15</sup> diabetes mellitus, lupus erythematosus,<sup>10</sup> inflammatory bowel diseases in adults and children,<sup>16,17</sup> primary biliary cirrhosis,<sup>18</sup> periodontal disorders, chronic viral infection,<sup>19,20</sup> and, recently, psoriasis.<sup>21</sup> Glucocorticosteroid use has been addressed only in few studies, and only limited attempts have been made to isolate corticosteroid-induced osteoporosis from other risk factors for osteoporosis.

Pemphigus is a complex T-cell-dependent autoimmune disease (mainly of autoreactive T<sub>H</sub>2 cells), which also involves a proinflammatory array of cytokines of the innate immune system, such as TNF and IL-1 and IL-6 activated proteases, and the enhancement of acantholy-

**Table 4. Bone Mineral Density Monitoring and Medical Treatment of Osteoporosis Among Patients With Osteoporosis<sup>a</sup>**

Medication	Patients With Pemphigus (n=103)	Controls (n=33)	P Value
DEXA scan performed, 2000-2009	73 (70.9)	27 (81.8)	.22
Interval between scans <5 y among those with scans (n=100)	54 (74.0)	19 (70.4)	.72
Calcium therapy			
Duration >1 mo	98 (95.1)	27 (81.8)	.02
Duration, mean (SD), mo	16.3 (9.2)	8.4 (6.4)	<.001
Cholecalciferol therapy			
Duration >1 mo, No	92 (89.3)	27 (81.8)	.26
Duration, mean (SD), mo	10.0 (5.2)	7.4 (5.7)	.007
Antiresorptive therapy >1 mo, bisphosphonates or raloxiphen hydrochloride	94 (91.3)	29 (87.9)	.57
Bisphosphonates therapy			
Duration >1 mo	93 (90.3)	27 (81.8)	.19
Duration, mean (SD), mo	11.2 (4.9)	8.5 (4.9)	.02
Raloxiphen therapy			
Duration >1 mo	9 (8.8)	5 (15.2)	.29
Duration, mean (SD), mo	2.6 (12.0)	4.6 (13.9)	.53

Abbreviation: DEXA, dual x-ray absorptiometry.

<sup>a</sup>Unless otherwise indicated, data are given as number (percentage).

sis.<sup>22-27</sup> Thus, the marked association between osteoporosis and pemphigus may be explained at the molecular level by the immunopathogenic process and proinflammatory cells and cytokines shared by these 2 disorders leading to the net great enhanced bone resorption.

Updated general measures to reduce bone loss include use of the lowest effective dose and adequate calcium and vitamin D supplementation and the use of bone-sparing agents, based on results from large randomized controlled clinical trials that provide evidence that bone loss and fractures may be prevented.<sup>28</sup> Patients at high risk of osteoporosis, including those with postmenopausal status (especially with early menopause), older than 62 years, with a family history of osteoporosis, those who are underweight (body mass index, calculated as weight in kilograms divided by height in meters squared, <19), and those with a prior fragility fracture, are advised to start bone-protective therapy at the time of starting corticosteroids.<sup>29,30</sup> Low bone density, as measured by DEXA testing, is an imperfect predictor of fracture risk, identifying fewer than half the people at risk of osteoporotic fracture. Therefore, most updated data suggest the consideration of pharmacological treatment for all patients, men and women, who are at moderate risk for developing osteoporosis even without the documentation of marked osteoporosis.<sup>31</sup> Guidelines on osteoporosis screening and prevention recommend assessing the patient's individual risk of osteoporosis and fractures based on these risk factors, the dose, and the total duration of oral corticosteroids.

De novo or chronic users of prednisolone acetate, 2.5 mg (or equivalent doses of other preparations), for 3 months who are at high risk should begin treatment with oral bisphosphonates without the need for DEXA testing. All other patients who will require 3 months of cor-

ticosteroid therapy should be screened with DEXA scans of the hip and spine prior to starting therapy and every 6 to 12 months during their steroid regimen and should be treated with an oral bisphosphonate if their T scores are lower than  $-1.5$ .<sup>32-34</sup> Bisphosphonates (alendronate sodium, risedronate sodium) are the first-choice therapy for the prevention and treatment of corticosteroid-induced osteoporosis.<sup>31</sup>

In the present study, 27% of patients with osteoporosis had no documented DEXA scans in the past 10 years, and another 26% of those undergoing DEXA scans had intervals of more than 5 years between scans. Although large proportions of patients were treated with bisphosphonates or raloxiphen, the mean duration of purchasing these medications (and thus the potential treatment duration) was far from being satisfactory, indicating suboptimal compliance of patients with osteoporosis, both among pemphigus patients and among controls.

The finding that osteoporosis was more prominent in males and among patients younger than 50 years is probably connected with the older standard of prevention, which offers treatment only to high-risk individuals with known osteoporosis or with documented fractures. Osteoporosis is an underrecognized and undertreated problem in men.<sup>35</sup> This may reflect a true difference between males and females or a behavioral tendency on the part of physicians, since women are more likely to be evaluated and treated for their bone loss.

There are some limitations to the present study. We had no data on the severity of pemphigus or osteoporosis. Hormonal status was similarly unavailable. A potential detection bias of osteoporosis cannot be completely excluded (eg, pemphigus patients might have undergone more bone density scans). We had no data regarding the results of DEXA scans, which limited our ability to discern between patients with normal bone density and those with osteopenia (a slightly low degree of bone mineral density loss, 1-2.5 standard deviations below that of young healthy adults).

In conclusion, we observed a marked association between pemphigus and osteoporosis that persisted after controlling for the duration or cumulative dose of glucocorticosteroid therapy. Based on these findings, we consider that the association between pemphigus and osteoporosis, as seen in other autoimmune disorders, represents the inflammatory process that causes both pemphigus and osteoporosis. Compliance with current guidelines regarding the detection, prevention, and treatment of osteoporosis in pemphigus patients remains suboptimal. We recommend that in patients with pemphigus, osteoporosis should be evaluated, monitored, and treated early at the onset of the disease and glucocorticosteroid therapy.

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full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Wohl, Dreier, and Cohen. *Acquisition of data:* Wohl, Dreier, and Cohen. *Analysis and interpretation of data:* Wohl, Dreier, and Cohen. *Drafting of the manuscript:* Wohl, Dreier, and Cohen. *Critical revision of the manuscript for important intellectual content:* Wohl, Dreier, and Cohen. *Statistical analysis:* Dreier and Cohen. *Administrative, technical, and material support:* Dreier and Cohen. *Study supervision:* Wohl, Dreier, and Cohen. **Financial Disclosure:** None reported.

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## PRACTICE GAPS

# Underutilization of Prophylaxis for Osteoporosis

**M**ost general and medical dermatologists treat patients with autoimmune skin disease. Most of these dermatologists possess the knowledge that treatment of such patients with chronic glucocorticoids can lead to bone resorption and osteoporosis.<sup>1</sup> Yet, one gap, identified in the article by Wohl et al, is that the percentage of dermatologists who comply with the current guidelines for screening, prevention, and management of osteoporosis remains suboptimal. According to the study, over half of at-risk patients had undergone no DEXA scan in more than 5 years.

The article also identifies a potential knowledge gap that should alter dermatologists' approach to treating patients with autoimmune skin disease. The autoimmune skin disease process itself, at least in the case of patients with pemphigus, and not just the glucocorticoid therapy, contributes significantly to the increased rate of osteoporosis. This has practice gap implications, and suggests that DEXA scan screening and monitoring may be important in our patients with autoimmune skin diseases regardless of whether systemic steroid therapy is selected. In addition, osteoporosis is underrecognized and undertreated in men with autoimmune skin disease. Women are more likely to be evaluated and treated for their bone loss.

Closing the gap requires heightened efforts to teach and test dermatologists about the current osteoporosis guidelines. Education should build competency and performance of the dermatologist to either take an active role in the screening, prevention, and management or to take a more active role in the communication of need to those health care providers who do. Education should particularly highlight the gap in recognizing the risk and un-

dertreatment of osteoporosis in men with these skin conditions. Closing the gap will also likely require non-educational systems improvements, including electronic reminder systems to perform initial DEXA screenings when encountering patients with autoimmune disease diagnosis or glucocorticoid treatment, and reminder systems when repeated DEXA scans are due. Such electronic reminder systems are becoming mainstream in electronic health record systems for primary care chronic disease management, but they are not yet as well integrated into specialty care. Once these electronic reminder systems are available, dermatologists will need instruction in integrating them into their practice.

Barriers to change may include the specialist's discomfort in managing the drugs<sup>2</sup> or his or her view that screening or monitoring a patient's osteoporosis is outside the scope of dermatology, despite it being the skin disease or skin management that led to the osteoporosis risk.

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