Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the hair follicles. The aim of this case-control study was to assess whether HS is associated with disturbances in trabecular bone score, bone mineral density, bone remodelling markers, and calcitropic hormones. A total of 81 patients and 79 controls of similar age and sex were included. Demographic, anthropometric, laboratory data, trabecular bone score, bone mineral density, serum 25-hydroxyvitamin D (25OHD), serum amino-terminal pro-peptide of type I collagen (PINP), and C-terminal telopeptide of type I collagen (CTX) concentrations were assessed in both groups. Patients with HS had lower serum 25OHD levels than controls, and approximately 62% of them had vitamin D deficiency. Serum PINP was increased and CTX was decreased in patients with HS. Fully adjusted trabecular bone score values were lower in patients with HS compared with controls. Adjusted lumbar bone mineral density was similar in HS and controls, whilst total hip bone mineral density was lower in patients with HS. There were no statistical differences regarding disease severity in terms of 25OHD, serum turnover markers, bone mineral density, or trabecular bone score values. This study shows that patients with HS have lower trabecular bone score and total hip bone mineral density values than population-based controls. In addition, the prevalence of vitamin D deficiency is high in subjects with HS.

Key words: hidradenitis suppurativa; metabolic bone diseases; bone density; 25-hydroxyvitamin D.

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Corr: Marcos A. González-López, Division of Dermatology, Hospital University Marqués de Valdecilla. Avda Valdecilla s/n, ES-39008 Santander, Spain. E-mail: marcosg@aedv.es

Hidradenitis suppurativa (HS) is a chronic, relapsing, inflammatory cutaneous disease that primarily affects the pilosebaceous unit (1). It is clinically characterized by painful nodules, abscesses, fistulae, and scarring in apocrine gland-bearing areas of the body (1, 2). HS affects approximately 1% of the general population of Western countries and is more common in women than in men (1). Although the etiopathogenesis of HS is not completely understood; genetic, endocrinological, and microbiological factors have been involved. In addition, obesity and smoking are well-defined risk factors for the development of HS (1). Recent research suggests that the formation of protuberances of follicular infundibulum (also known as tendrils) is a defining feature of HS. These tendrils lead to the formation of cysts, which rupture continuously, leading to an inflammatory response driven by the release of keratin debris into the dermis (3). Current knowledge indicates that a dysregulation of the immune response plays a major role in the pathophysiology of HS. In this regard, patients with HS have increased serum levels of several proinflammatory cytokines, including tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and -17 (4). Furthermore, macrophages, which are the main TNF-α-producing cells, are usually very abundant in the inflammatory infiltrate present in HS biopsies (5). Moreover, an increase in Th17 cells, which are characterized by the production of the proinflammatory cytokine IL-17, has been found in HS lesions (6). In addition, HS has been linked to other chronic inflammatory conditions, including inflammatory bowel disease, psoriasis, pyoderma gangrenosum, spondyloarthitis, and pyogenic arthritis (7, 8).

The effect of chronic inflammation on bone mineral metabolism is well-known. Nevertheless, the pathogenic mechanisms underlying the interplay between inflammation and bone disease are extraordinarily complex and may affect all phases of the bone remodelling process (9). Thus, even low-grade, subclinical inflammation can have deleterious effects on bone metabolism (10). In this respect, several studies have proved that bone mineral density (BMD) and microarchitecture are impaired in patients with several chronic inflammatory disorders,
including systemic sclerosis, rheumatoid arthritis (RA), and systemic lupus erythematosus (11–13).

Bone strength is determined by bone mass (density and volume), bone tissue quality (microarchitecture), and bone geometry (14). BMD can be estimated by dual X-ray absorptiometry (DXA), a simple, reproducible, low radiation-emitting technique that is commonly used in clinical practice for identifying osteoporosis and assessing the risk of fracture (15). Trabecular bone score (TBS) is an index that complements DXA by indirectly exploring bone microarchitecture. It evaluates pixel grey variations obtained from lumbar spine (LS) DXA images and has proven to be an independent predictor of bone fracture risk (16).

Taking these considerations into account, the aim of this study was to assess bone involvement in patients with HS compared with controls of similar age and sex. To the best of our knowledge, bone and mineral metabolism has not been investigated previously in patients with HS.

MATERIALS AND METHODS

Study design and participants

A prospective case-control study was conducted that included 81 patients with HS and 79 controls of similar age and sex. Patients were recruited between May 2014 and June 2019 from the dermatology outpatient clinic in a tertiary-care hospital that serves as a reference centre for a population of 350,000 inhabitants in Santander, northern Spain. The clinical diagnosis of HS was always established by an experienced dermatologist.

The control group includes subjects who were taking part in a prospective population-based cohort, the Camargo cohort, as well as hospital staff members who agreed to participate in the current study. The Camargo cohort was set up with postmenopausal women and men aged 50 years or older who attended a primary care centre in northern Spain for medical reasons or for their regular health examination, whichever occurred first. Full details of this cohort have been reported previously (17, 18).

Exclusion criteria included pregnancy, as well as the presence of medical conditions or therapies known to affect bone metabolism, such as primary hyperparathyroidism, hyperthyroidism, hypothyroidism, chronic renal failure, or treatment with bisphosphonates, testosterone, teriparatide, L-thyroxin, calcium, vitamin D supplements, or glucocorticoids. The study protocol was approved by the Clinical Research Ethics Committee of Cantabria (code 2019.039). Written informed consent was obtained from all participants.

Clinical and laboratory variables

Demographic data (age, sex, weight, height) was obtained from all participants. Height and weight were measured with participants wearing light underwear and no shoes. Body mass index (BMI) was defined as weight divided by squared height (kg/m²). Smoking status was recorded as current smoker, former smoker, or never smoker. Alcohol consumption was defined as >20 g of alcohol per day. Personal history of cardiovascular risk factors (diabetes mellitus, hypertension, and dyslipidaemia) was also collected. Metabolic syndrome was defined following National Cholesterol Education Program-Adult Treatment Panel III (NCEP/ATP III) criteria (19).

The severity of HS was evaluated using the HS-Physician Global Assessment (HS-PGA) and Hurley clinical staging (20, 21). Disease severity was classified as minimal-mild when HS-PGA<3 and as moderate-very severe when PGA≥3. In addition, the Inter-national Hidradenitis Suppurativa Severity Score System (IHS4) was calculated, considering IHS4<3 mild HS, 4–10 moderate HS, and ≥11 severe HS (22).

For each participant, fasting blood samples were collected between 09:00 h and 10:30 h in the morning. All subjects were asked to fast for at least 8 h before the samples were taken. Lipid profile, serum creatinine, glomerular filtration rate (GFR) according to the Modification of Diet in Renal Disease formula (MDRD), calcium, phosphate, glucose, and C-reactive protein (CRP) levels were measured by standard automated methods in an ADVIA 2400 Chemistry System autoanalyzer (Siemens, Germany). In addition, serum concentrations of 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (PTH), C-terminal telopeptide of type 1 collagen (CTX), and amino-terminal pro-peptide of type 1 collagen (PINP) were also determined by a fully automated Roche electrochemiluminescence system (Elecsys 2010, Roche Diagnostics, GmbH, Mannheim, Germany). The detection limit of serum 25OHD was 4 ng/ml, its intra-assay coefficient of variation (CV) was 5%, and its interassay CV was 7.5%. Vitamin D deficiency was defined as serum 25OHD levels < 20 ng/ml. Regarding intact PTH, the detection limit is 6 pg/ml, with a normal range of 15–65 pg/ml. Intra-assay and interassay CV are 3.4% and 5.9%, respectively. The PINP limit of detection is 5 ng/ml, its reference range is 15–78 ng/ml, and its intra-assay and interassay CV are 3.9% and 4.1%, respectively. Intra-assay and interassay CV for CTX are 4.2% and 4.7%, respectively, the detection limit is 0.01 ng/ml, and its reference range is 0.112–1.018 ng/ml.

Bone mineral density and trabecular bone score assessment

BMD was measured by DXA (Hologic® QDR 4500, Bedford, MA, USA) at the LS, femoral neck, and total hip. Results were expressed as g/cm². In vivo precision was 0.4–1.1% at the different sites. Quality control was performed according to the usual standards. Fat percentage was also determined by DXA.

TBS measurements were obtained from stored DXA images of the LS scans using TBS Insight® software v2.1 (Medimaps, Pessac, France). TBS was calculated based on the raw data acquired in the DXA scan, assessing the same vertebral bone on which the LS-BMD was measured (23). As a rule, the measurement of BMD in LS was performed in L1–L4, except in those cases in which the morphology of a vertebra advised its exclusion. All DXA and TBS measurements were performed by the same operator.

Statistical analysis

Data are presented as mean ± standard deviation (SD), median (interquartile range), and numbers and percentages, as appropriate. Correlation analysis was assessed with the Pearson or Spearman rho tests, as appropriate. Student t-test or Mann–Whitney U test were used to compare quantitative values and Pearson’s χ² test when comparing categorical variables. One-way analysis of variance (ANOVA) or Kruskal–Wallis tests with post-hoc Bonferroni comparisons were used, as appropriate, to assess the variables related to the IHS4 score. Multivariable linear general models, adjusted for potential confounders, were built to assess the differences in BMD, TBS, and calcitropic hormones and bone turnover markers between patients with HS and controls. All tests were 2-tailed and significance was set at p<0.05. Analyses were conducted using SPSS 28.0 statistical package (IBM Corporation, New York, USA).

RESULTS

A total of 81 patients with HS and 79 controls were recruited for the study. Their main demographic and laboratory characteristics are summarized in Table I. Twenty-eight patients (34.6%) were classified as having minimal to mild
Vitamin D and bone remodelling markers

Patients with HS had lower serum 25OHD levels than controls (18.9 vs 24.9 ng/ml; \( p = 0.001 \)). These differences remained significant once adjusted by age, sex, BMI, fat percentage, diabetes mellitus, estimated GFR, and serum CRP (\( p = 0.01 \) and \( p < 0.0001 \), respectively). Serum PINP/CTX ratio was 268.8 (188.0–408.4) in patients with HS vs 126.6 (103.4–174.0) in the control group (\( p < 0.0001 \)).

Overall, mean BMD and TBS values were lower in patients with HS than in controls, although they did not reach a significant difference when unadjusted data were compared (Table II). Nevertheless, in the multivariable linear general models adjusted by age, sex, BMI, smoking, diabetes, hypertension, estimated GFR, serum CRP, PINP/CTX ratio, 25OHD levels, and fat percentage (and lumbar BMD in the case of TBS), patients with HS had lower BMD at the femoral neck and total hip than the control group (\( p = 0.09 \) and \( p = 0.013 \), respectively).

No significant difference was found at the LS. Adjusted TBS values were also lower in patients with HS compared with the control group (\( p = 0.007 \)) (Table II). In addition, further adjustment for the current use of anti-TNF-α agents did not virtually change the TBS and total hip BMD results (\( p = 0.02 \) and \( p = 0.047 \), respectively), and the non-significant trend for a lower femoral neck BMD in patients with HS was maintained (Table II).

**Fig. 1** shows the distribution of TBS values in cases and controls, according to the criteria proposed by Mccloskey et al. (24). It is noteworthy that patients with HS...
had a higher percentage of degraded and partially degraded bone microarchitecture than the control group (p for trend = 0.045). Seventeen participants had TBS values consistent with degraded microarchitecture (12 patients with HS and 5 controls; p = 0.039).

**Hidradenitis suppurativa severity and bone metabolism**

To determine whether disease severity had an impact on BMD and TBS values, patients with HS were divided into 2 subgroups according to their HS-PGA score (<3 or ≥ 3). Serum 25OHD levels were slightly lower, albeit non-significant, in the group of patients with severe disease compared with those with mild-moderate HS (18.0 vs 20.8 ng/ml; p = 0.29). No differences were found in terms of vitamin D deficiency (serum 25OH levels < 20 ng/ml) between both groups (60.7% vs 62.3% in patients with PGA < 3 vs PGA ≥ 3, respectively; p = 0.89). No significant difference were found concerning bone remodelling markers according to HS severity, either in crude or in adjusted analyses.

Moreover, although TBS and BMD values at the 3 sites were lower in patients with HS-PGA scores ≥3 than those with values <3, no significant difference was found between both severity groups in crude or in adjusted linear models.

A similar pattern was observed regarding BMD, TBS, bone remodelling markers, and calcitropic hormones, when ISH4 was considered as a score for HS severity. Thus, mean 25OHD levels were 21.1 ng/ml in patients with mild disease, 19.3 ng/ml in those with moderate disease, and 15.6 ng/ml in those with severe disease (mild vs severe disease; p = 0.07). The corresponding figures for serum PTH levels were 27.2, 38.0, and 40.9 pg/ml (p = 0.023 and p = 0.025, for mild vs moderate and mild vs severe disease, respectively).

**DISCUSSION**

This study found that patients with HS have lower serum vitamin D as well as hip BMD and TBS values than controls of similar age and sex. This disturbance in bone metabolism could be associated with the main risk factors for HS: obesity and smoking. However, total hip BMD and TBS remained significantly lower in patients with HS after adjustment by BMI and tobacco use among other potential confounders. This suggests that HS might be an independent risk factor for bone disease. The mechanism underlying this association has not previously been elucidated, but might be related, at least in part, to the inflammatory nature of HS. This would be in line with previous research assessing TBS and BMD in patients with other inflammatory conditions, such as RA, psoriasis, and systemic lupus erythematosus (12, 25, 26). Thus, TBS has been assessed in several rheumatic diseases and values consistent with degraded microarchitecture have been related to disease activity in patients with ankylosing spondylitis, systemic sclerosis, and RA (13). Recently, lower TBS values have been reported in 97 patients with RA not on biologic therapy compared with 45 matched controls (27). Therefore, the concurrent presence of HS and chronic inflammatory arthritis could influence the TBS values. Although the incidence of inflammatory arthritis in patients with HS is low, the disease has been associated with an increased risk of developing mainly ankylosing spondylitis and RA (28). Nevertheless, in the current study, neither patients with HS nor controls had chronic inflammatory arthritis.

These results confirm that TBS values were lower in patients with HS, although the study did not find any correlation with the severity of the disease. Anti-TNF-α agents did not have a significant influence on TBS in our patients with HS. In this sense, Killinger et al. found that patients with active RA treated with biologic agents have increased TBS values compared with those on methotrexate, especially premenopausal women (29).

Decreased serum 25OHD levels in patients with HS are in keeping with previously published studies (30–33). Some have even found oral supplementation of vitamin D to be useful in the treatment of this condition (32, 33). This vitamin D deficiency could be related to the limited time they tend to spend outdoors, as well as to their lack of physical exercise. Another possible explanation is the genetic basis for this hypovitaminosis. In this regard, several mutations in genes related to vitamin D metabolism have been identified in patients with HS (34). Low vitamin D levels could trigger the development of HS via several mechanisms. Firstly, serum 25OHD plays a major role in epidermal proliferation and differentiation, which are altered in HS (35). In addition, it also plays an important role in skin immunity regulating the synthesis of antimicrobial peptides, which, in turn, impact the skin microbiome, frequently disturbed in patients with HS (35, 36). Finally, 25OHD also prevents the progression toward chronic inflammation by downregulating the expression of toll-like receptors in monocytes and could therefore act as a protective factor against HS and its associated proinflammatory state (37). Moreover, a trend was found toward an association between higher IHS4 scores and...
lower serum 25OHD and significantly higher PTH levels, indicating that these calcitropic hormones could play a role in the disturbance of bone metabolism in more severe stages of HS.

The underlying pathophysiology by which inflammation influences bone remodeling is complex and has not been completely clarified. One of the main mechanisms is probably the promotion of osteoclastogenesis and bone resorption in the setting of a proinflammatory environment (38, 39). In addition, increased levels of proinflammatory cytokines, such as TNF-α can block osteoblast differentiation and function and may even promote their apoptosis (38–40).

Regarding biochemical markers of bone metabolism, the current study shows that patients with HS have lower serum CTX and higher PINP values than controls. This is an unexpected result that could represent the effect of anti-TNF-α agents on bone turnover (41). It should be noted that 28 (34.6%) of our patients with HS were on TNF-α inhibitors. Thus, TNF-α blocking therapy has been linked to a significant increase in bone-specific alkaline phosphatase, a marker of bone formation, and decreased serum CTX levels after 3 years of treatment in patients with ankylosing spondylitis (42). Another study, which assessed the effect of infliximab (a TNF-α inhibitor) in patients with RA, revealed an increase in PINP and a reduction in CTX levels after 6 weeks of treatment (43). Moreover, this pattern of bone turnover markers has also been related to an effect of anti-TNF-α agents on the Wnt pathway and cathepsin K levels. In this sense, Gulyás et al. (44) found that, in patients with RA and ankylosing spondylitis, 1 year of treatment with TNF-α inhibitors significantly increased serum PINP and PINP/CTX ratio and decreased DKK-1 and cathepsin K levels. The overall effect was an increase in bone formation and a decrease in bone resorption, the same result as observed in the patients with HS in the current study.

The current study found that patients with HS on anti-TNF-α had increased concentrations of PINP and lower CTX levels than both HS subjects who were not on these drugs, and controls (data not shown). Low levels of serum CTX could be also associated with a greater proportion of smokers among patients with HS (45, 46). However, CTX remained significantly low even after adjustment for active smoking. Therefore, anti-TNF-α therapy may have underestimated the real impact of chronic inflammation of HS on bone turnover markers (40, 41). Nevertheless, TBS and total hip BMD values did not substantially change after adjusting for the current use of TNF-α blockers.

Finally, several adipokines are dysregulated in HS, even after adjustment for BMI. This imbalance could influence bone metabolism, although the role of these adipokines in patients with HS has not been assessed (47–49). Surprisingly, disease severity did not have a significant effect on bone turnover markers, BMD, or TBS. In this regard, previous studies have also failed to demonstrate an association between HS severity and serum adipokine levels disturbances, suggesting that even mild disease is sufficient to trigger systemic inflammation and impair bone homeostasis (47–49).

The current study is, to the best of our knowledge, the first to address bone metabolism in patients with HS. However, the study has some limitations. Firstly, due to its design, association, but no causality, can be inferred from the results. Secondly, the cases were recruited from a dermatology outpatient clinic of a tertiary-care centre. This probably implies that some of the less severe patients, who are usually not referred to the hospital, could be under-represented.

In summary, this study highlights the impact of HS on bone metabolism. Patients with HS have lower TBS and total hip BMD values than population-based controls of a similar age and sex. Furthermore, the results provide further evidence that the prevalence of vitamin D deficiency is high amongst patients with HS. These patients should be encouraged to avoid factors that can have a deleterious effect on bone metabolism, including tobacco use and overweight, both of which are particularly prevalent in this condition. Moreover, assessment of BMD and bone quality by DXA and TBS might be considered, at least in subjects with risk factors for osteoporosis.

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The authors have no conflicts of interest to declare.

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