Journal Pre-proof

Diffuse idiopathic skeletal hyperostosis (DISH) and trabecular bone score (TBS) in postmenopausal women: the Camargo Cohort

Stefanie F. Pini , Emilio Pariente , José M. Olmos , Marta Martín-Millán , Raquel Pascua , Victor M. Martínez-Taboada , José L. Hernández

PII: S0049-0172(23)00059-8
DOI: https://doi.org/10.1016/j.semarthrit.2023.152217
Reference: YSARH 152217

To appear in: *Seminars in Arthritis & Rheumatism*

Please cite this article as: Stefanie F. Pini , Emilio Pariente , José M. Olmos , Marta Martín-Millán , Raquel Pascua , Victor M. Martínez-Taboada , José L. Hernández , Diffuse idiopathic skeletal hyperostosis (DISH) and trabecular bone score (TBS) in postmenopausal women: the Camargo Cohort, *Seminars in Arthritis & Rheumatism* (2023), doi: https://doi.org/10.1016/j.semarthrit.2023.152217

Highlights

- Postmenopausal women with DISH have a partially degraded trabecular structure measured by TBS.
- TBS values showed a gradual decrease as the disease progressed.
- Women with DISH had lower TBS values despite having a higher lumbar spine BMD.
- A prevalence of vertebral fractures of almost double was found in DISH comparing to NDISH women.

Diffuse idiopathic skeletal hyperostosis (DISH) and trabecular bone score (TBS) in postmenopausal women: the Camargo Cohort

Stefanie F. Pini[a,#], Emilio Pariente[b,#,*] emilio.pariente@scsalud.es, parienteej@unican.es, 0000-0003-0035-3298, José M. Olmos[c], Marta Martín-Millán[c], Raquel Pascua[d], Victor M. Martínez-Taboada[e], José L. Hernández[c]

[a]Hospital at Home Department, Hospital Universitario Marqués de Valdecilla, Instituto de Investigación Valdecilla (IDIVAL), Santander, Cantabria, Spain

[b]Camargo Interior Primary Care Center, Servicio Cántabro de Salud, Depto. de Medicina y Psiquiatría, Universidad de Cantabria, Instituto de Investigación Valdecilla (IDIVAL), Santander, Cantabria, Spain

[c]Internal Medicine Department. Bone Metabolism Unit, Hospital Universitario Marqués de Valdecilla, Depto. de Medicina y Psiquiatría, Universidad de Cantabria, Instituto de Investigación Valdecilla (IDIVAL), Santander, Cantabria, Spain

[d]Instituto de Investigación Valdecilla (IDIVAL), Santander, Cantabria, Spain

[e]Rheumatology Division, Hospital Universitario Marqués de Valdecilla, Depto. de Medicina y Psiquiatría, Universidad de Cantabria, Instituto de Investigación Valdecilla (IDIVAL), Santander, Cantabria, Spain

[*]Correspondence to: Emilio Pariente (MD, PhD), "Camargo Interior" Primary Care Center, Associate Professor, University of Cantabria, Avda Bilbao, s/n. 39600-Muriedas, Cantabria, Spain, Tel: +34 942 254 499

[#]Drs. Stefanie Pini and Emilio Pariente contributed equally and shared the first authorship.

Abstract

Objectives: The potential relationship between diffuse idiopathic skeletal hyperostosis (DISH) and bone microstructure has not been studied in women. We aimed to assess the association between the trabecular bone score (TBS) and DISH in postmenopausal women, as well as the role of other parameters related to bone metabolism, such as bone mineral density (BMD), calciotropic hormones, and bone remodeling markers.

Methods: Cross-sectional study, nested in a prospective population-based cohort (Camargo cohort). Clinical covariates, DISH, TBS, vitamin D, parathormone, BMD and serum bone turnover markers, were analyzed.

Results: We have included 1545 postmenopausal women (mean age, 62±9 years). Those with DISH (n=152; 8.2%) were older and had a significantly higher prevalence of obesity, metabolic syndrome,

hypertension, and type 2 diabetes mellitus (p<0.05). Moreover, they had lower TBS values (p=0.0001) despite having a higher lumbar spine BMD (p<0.0001) and a higher prevalence of vertebral fractures than women without DISH (28.6% vs. 15.1%; p=0.002). When analyzing DISH through Schlapbach grades, women without DISH had a median TBS value consistent with a normal trabecular structure while the values for women with DISH from grades 1 to 3 were consistent with a partially degraded trabecular structure. Women with vertebral fractures and DISH had a mean TBS corresponding to a degraded trabecular structure (1.219±0.1). After adjusting for confounders, the estimated TBS means were 1.272 (1.253-1.290) in the DISH group, and 1.334 (1.328-1.339) in the NDISH group (p<0.0001).

Conclusion: An association between DISH and TBS has been shown in postmenopausal women, in which hyperostosis has been significantly and consistently related to trabecular degradation and, therefore, to deterioration in bone quality after adjusting for confounding variables.

Keywords

Diffuse idiopathic skeletal hyperostosis; Trabecular bone score; Bone turnover markers; Bone metabolic diseases; Vertebral fracture.

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) was first described by Forestier and Rotes-Querol in 1950. [1]. It is a disorder characterized by the ossification of ligaments, tendons, and joint capsules with a special predilection for the axial skeleton, especially the anterior vertebral ligament (AVL), also known as anterior longitudinal ligament of the thoracic spine [2,3]. The disease mainly affects individuals older than 40 years and it is more common in men than in women, with a 2:1 ratio [2, 4, 5]. Its prevalence ranges from 2% to more than 20% showing ethnic and geographic variations [6-8].

Although its etiopathogenesis is unknown, different genetic, mechanical, and metabolic factors have been involved [9, 10]. Thus, the environment of the ligaments and entheses would be influenced by different mediators, either increasing the transformation of different cells or decreasing different inhibitors of bone formation [11-13].

DISH is usually defined by the Resnick and Niwayama criteria: AVL ossifications of at least 4 contiguous vertebral bodies, relative preservation of the intervertebral disk space in the affected segment without signs of degenerative disk changes, and the absence of apophyseal joint degeneration or sacroiliac inflammatory changes [14, 15]. However, there is a current debate regarding the radiological diagnosis of this entity since these changes contemplate a highly evolved and established stage of the disease and do not reflect its progressive nature [16-18].

DISH has also been associated with a variety of metabolic factors that, in turn, increase the risk of cardiovascular morbidity [10, 19]. Thus, associations have been found between DISH and obesity, a higher body mass index (BMI), a greater abdominal circumference, elevated blood glucose levels, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and metabolic syndrome [5, 10, 19, 20].

Although DISH is usually an asymptomatic disorder, patients may present with joint pain, limited axial mobility, dysphagia, and airway obstruction. In addition, these patients have an increased susceptibility to vertebral fractures due to a decrease in the biomechanical properties of bone. In this sense, several studies have suggested that these vertebral fractures tend to be more unstable and frequently associated with a high risk of neurological complications and mortality [21-24]. Paradoxically, high bone mineral density (BMD) values have been reported in patients with DISH, which would imply a lower risk of fracture. Nevertheless, some investigators have suggested that this may be an overestimate, due to the effect of ligamentous ossification and other factors that may contribute to fracture risk, regardless of BMD [25-27]. One of them could be the trabecular microarchitecture which can be indirectly assessed by the trabecular bone score (TBS), a surrogate parameter of bone strength [28-30]. TBS is not affected by bone ossifications, and it measures the texture of an image that correlates with the determination of trabecular structure [31]. A low TBS value reflects a weak architecture, with impaired bone quality and a high propensity to fracture [32]. A previous study by our working group showed that men older than 50 years with DISH have a significantly decreased TBS compared to men without DISH and that DISH was associated with a deterioration of the trabecular microstructure after adjusting for confounders [33] However, an assessment of trabecular microstructure using TBS has not been performed in women with DISH, to our knowledge.

Based on these considerations, this study aimed to know the potential relationship between TBS and DISH in postmenopausal women. A secondary objective has been to ascertain the behavior of other parameters related to bone metabolism, such as BMD and bone remodeling markers.

Participants and Methods

Study design

The study population consisted of all postmenopausal women included in a well-defined prospective population-based cohort, the Camargo Cohort, whose details have been previously published [34]. Briefly, the Camargo Cohort began in 2006 intending to know the incidence and prevalence of metabolic bone diseases in the general population. Its participants are postmenopausal women and men ≥50 years, who attended a Primary Care center in northern Spain for medical reasons or for their regular health examination, whichever occurred first.

At baseline, patients were asked to complete a questionnaire on bone metabolism and general diseases, current or past medication use, and risk factors for osteoporosis and fragility fractures. Moreover, blood samples were obtained, and all the participants underwent lateral thoracic and lumbar spine radiographs and dual-energy X-ray absorptiometry (DXA). Participants whose initial assessment revealed the presence of diseases or treatments that may affect bone metabolism were excluded from the present study. The Camargo Cohort study was approved by the Clinical Research Ethics Committee of Cantabria (Internal Code 2016.003). All participants gave written informed consent.

Clinical and laboratory variables

Weight (in kg), height (in meters), and abdominal perimeter (in cm) were obtained with the subjects wearing underwear and without shoes. Body mass index (BMI) was measured in kg/m2, considering obesity when BMI ≥30 kg/m^2. Physical activity was categorized as sedentary (sitting in a chair most of the time, short walks outside the house), light (shopping, domestic work), or moderate-intense (daily -or most days- exercise or intense work). Smoking was evaluated as non-smoker or smoker. Alcohol intake was defined as a daily consumption >20 g. Diagnoses of hypertension, ischemic heart disease, stroke and chronic renal failure were extracted from the medical records in Primary Care and were based on clinical guidelines and international standards. The diagnosis of T2DM was made if the basal plasma glucose was ≥126 mg/dL in two blood tests or if the subject received specific treatment for T2DM.

Blood samples were obtained from an antecubital vein in the morning after a requested 12-hour overnight fast. Serum concentrations of calcium, phosphorus, albumin and total alkaline phosphatase were obtained by automated methods in an ADVIA® 2400 Chemistry System autoanalyzer (Siemens, Germany). Serum concentrations of 25-hydroxyvitamin D (25-OHD), intact parathyroid hormone (iPTH), amino-terminal pro-peptide of type 1 collagen (P1NP), and C-terminal telopeptide of type 1 collagen (CTX) were determined by an automated method of electrochemiluminescence (Elecsys® 2010, Roche Diagnostics, GmbH, Mannheim, Germany). The detection limits for iPTH, P1NP, and CTX were 6 pg/ml, 5 ng/ml, and 0.01 ng/ml, and the normality ranges were 15-65 pg/ml, 15-78 ng/ml and 0.069-0.760 ng/ml, respectively. The glomerular filtration rate (GFR) was estimated according to the CKD-EPI formula and expressed in ml/min/1.73 m². Metabolic syndrome was defined according to the NCEP-ATPIII criteria [35].

DXA and TBS data

BMD was measured by DXA, with a Hologic® QDR-4500 device, at the lumbar spine, femoral neck, and total hip. The in-vivo precision was 0.4-1.5% in the different locations, and the results were

expressed in gr/cm². TBS measurements were carried out from the DXA images in the lumbar spine (L1-L4) with the TBS iNsight software (TBS iNsight® v2.1, Medimaps, Mérignac, France). All measurements were made by the same operator. According to the current consensus [36], the following cut-off points have been used: TBS values >1.310 have been considered normal; between 1.230 and 1.310 have been considered to correspond to a partially degraded trabecular structure and TBS values <1.230 to a degraded structure.

DISH and vertebral fracture assessment

Two independent trained researchers, blinded to clinical data, evaluated DISH and vertebral fractures. DISH was diagnosed according to the Resnick and Niwayama criteria [15] and the grade of vertebral fractures was assessed by the semiquantitative method of Genant [37].

Additionally, the Schlapbach graded scale was applied to the radiographs to analyze the relationship between intermediate stages of DISH [38]. This scale consists of 4 levels, starting from an absence of ossification that corresponds to grade 0, the presence of an intervertebral bone bridge that corresponds to grade 1, the presence of 2 intervertebral bone bridges that corresponds to grade 2 and grade 3 (3 intervertebral bone bridges), which is equivalent to Resnick-Niwayama criterion 1. In their original work, the authors reported kappa values ranging from 0.80 to 0.90 using the graded scale, with no significant differences in grading reliability between two rheumatologists and one radiologist [38]. In a previous phase, and attempting to minimize potential bias, the investigator designed to perform the radiological evaluation of DISH received specific training from a specialist in bone radiology and developed a study focused on the reliability of this scale. We found weighted kappa values (95% CI) of 0.89 (0.84-0.94), 0.85 (0.79-0.91), and 0.87 (0.82-0.92) for rater 1, rater 2, and rater 3, respectively (p=0.58). As for interobserver agreement, these values for the rater pairs were 0.87 (0.82-0.93), 0.84 (0.77-0.91), and 0.81 (0.72-0.90), for pairs 1, 2, and 3, respectively [39].

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) or median [interquartile range], and categorical variables, in percentage. Student-t-test, Mann-Whitney U test, median test, and ANOVA were used to compare quantitative variables and Pearson's chi-squared test in the case of categorical variables. The relationships between variables were initially analysed through bivariate correlations using Pearson or Spearman coefficients and then, univariable general linear regression models. The risk was expressed as prevalence odds ratio (OR) with 95% confidence interval (95%CI). Confounding adjustments were made by stratification, and linear regression and ANCOVA models were built to model the relationship between DISH and TBS, including variables (age, years since menopause, smoking, hypertension, T2DM, metabolic syndrome, lumbar BMD, vertebral fracture,

glomerular filtration rate, serum alkaline phosphatase, iPTH and 25OHD) that showed significant differences between the DISH and non-DISH (NDISH) groups. 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 1942 postmenopausal women were recruited. Of them, 397 were excluded due to incomplete data or because they had diseases or were on treatments that affect bone metabolism. Thus, 1545 women with a mean age of 62±9 years (range, 44-94 years), were finally included in the study. Of them, 126 (8.2%) were diagnosed with DISH according to Resnick's criteria. Following the Schlapbach scale a DISH prevalence of 5.8% (n=90) for grade one and 2.1% (n=32) for grade 2 was found. DISH was most frequently found at the thoracic spine (91.3%) and thoracolumbar spine (8.7%). Estimated TBS mean (95% CI) of women without DISH (NDISH), with thoracolumbar DISH, and with thoracic DISH, after adjusting for age, was 1.336 (1.32-1.34), 1.312 (1.28-1.36), and 1.289 (1.27-1.30), respectively ($p=0.0001$ for the difference between NDISH and thoracic DISH).

An increasing prevalence of DISH was observed according to age tertiles (24%, 32%, and 55.6%, respectively; $p=0.0001$). Women with DISH had significantly lower TBS values than women without across all age tertiles ($p=0.0001$).

The main characteristics of women with and without DISH are summarized in Table 1. Specifically, women with DISH were older and had higher abdominal circumference and BMI. They also had a significantly higher prevalence of obesity, metabolic syndrome, hypertension, and T2DM ($p<0.05$). Basal glycemia was higher, although the difference did not reach significance (100 [21] vs. 94 [16] mg/dL; $p=0.52$).

Regarding bone metabolism parameters (Table 2), women with DISH had lower serum 25OHD and CTX concentrations and higher iPTH levels than women without. When analysing the group of women with DISH and low serum CTX levels we found that these patients had a higher prevalence of T2DM (22% vs. 9.5%; $p=0.002$) and higher basal glycemic levels (94 [24] vs. 90 [16] mg/dL; $p=0.005$).

In addition, they had lower TBS values ($p=0.0001$) despite having a higher lumbar spine BMD ($p<0.0001$). Noteworthy, they also had a higher prevalence of vertebral fractures ($p=0.01$) than women without DISH. Concerning BMD, a negative correlation of BMD with age was observed in both groups (DISH: $r=-0.2$; $p=0.03$ and non-DISH: $r=-0.13$; $p=0.0001$). Women with DISH presented significantly higher lumbar BMD values compared to those without ($p=0.0001$).

In terms of risk, the presence of DISH was related to reduced TBS values, with a crude OR = 3.9 (95%CI 2.6-5.6; p=0.001). Moreover, when participants were stratified according to the TBS categories proposed by McCloskey et al. [36], more than 60% of women with DISH had an abnormal TBS, and 42.1% had TBS values consistent with a degraded trabecular structure. These data contrasted with women without DISH whom 62.6% presented a normal trabecular structure (p=0.0001).

When analyzing Schlapbach grades, significant differences were also found regarding the TBS values (p=0.0001). Thus, while women without DISH had a median TBS consistent with a normal trabecular structure, women with DISH from grades 1 to 3 (equivalent to Resnick's criteria) had median TBS values consistent with a partially degraded trabecular structure, and progressively decrease as the Schlapbach grades increase (Figure 1).

The percentage of vertebral fractures was significantly higher in DISH than in NDISH women (28.6% vs. 15.1%; p=0.002). Figure 2 shows the prevalence of vertebral fractures according to the Schlapbach graded scale. The most common location of single vertebral fracture in women with DISH was T7 (22.2% of all single fractures), followed by T12 (14% of all single fractures). Up to 15 women with DISH (42%) had multiple vertebral fractures. As shown in Figure 3, in an additional analysis of the relationship between DISH, TBS, and vertebral fracture, we observed that all women with vertebral fractures had lower TBS. However, women with vertebral fractures and DISH had a mean TBS value of 1.219±0.1, corresponding to a degraded trabecular structure. This value was significantly lower than in those with vertebral fractures but NDISH (1.268±0.1; p=0.03).

Figure 4 depicts several features of the relationship between DISH and T2DM. First, both conditions separately (T2DM+ DISH- subjects, and T2DM- DISH+ individuals) showed TBS values in the range of partially degraded trabecular structure, with non-significant differences between them (p=0.64 and p=0.63, according to age). Secondly, when both entities were present, TBS decreased to the lowest values (1.234 and 1.208). Finally, compared to DISH- subjects, those DISH+ exhibited significant lowered TBS irrespective of age and T2DM (p=0.0001 for all differences).

In the linear regression model, DISH was a significant predictor of TBS with a β value=0.15 (p=0.001), after adjusting for confounding variables (age, years since menopause, smoking, physical activity, metabolic syndrome, lumbar BMD, prevalent vertebral fracture, glomerular filtration rate, serum alkaline phosphatase, 25OHD, and iPTH levels). The relationship between DISH and TBS was also modeled with a general linear model (ANCOVA), with DISH as the independent variable. After adjusting for age, years since menopause, smoking, hypertension, diabetes mellitus, metabolic syndrome, lumbar BMD, vertebral fracture, glomerular filtration rate, serum alkaline phosphatase, iPTH, and 25OHD levels, the

estimated TBS means were 1.272 (1.253-1.290) in the DISH group, and 1.334 (1.328-1.339) in the NDISH group ($p<0.0001$).

Discussion

To our knowledge, this is the first study that assesses the relationship between DISH and bone quality measured by the TBS, in a well-defined cohort of postmenopausal women. We found that there is an inverse relationship between DISH and TBS, independent of age, T2DM, metabolic syndrome, lumbar BMD, and other confounding variables. This finding could represent a biologically plausible explanation, among others, of the propensity for vertebral fracture independent of BMD, observed in patients with DISH.

The prevalence of DISH found in our study is similar to that previously described, although it is known that it has significant variability [8,40]. The clinical characteristics observed in women affected by DISH are consistent with what has been published on this disease, specifically the mean age and the higher prevalence of metabolic syndrome and some of its components [9,10,19,41]. In this sense, our results highlight the association of DISH and several metabolic disorders and factors such as T2DM, obesity, increased BMI, and abdominal circumference, which, in turn, would contribute to the higher frequency of metabolic syndrome observed.

DISH and TBS

TBS is considered a predictor of bone strength and has proven to be a useful tool for assessing the risk of fractures and osteoporotic fractures [31, 42-44]. Our results show that TBS values are significantly decreased in women with DISH and the average TBS was consistent with a partially degraded trabecular structure [36]. These TBS values persisted significantly decreased after adjusting for a wide set of potential confounding variables, which included hypertension, T2DM, metabolic syndrome and bone metabolism variables, and suggesting that DISH is an independent variable for trabecular degradation.

When analyzing the median TBS values stratified by Schlapbach grades, we observed that as the radiological involvement worsens, TBS significantly decreases. Even from a grade 1, the median TBS was consistent with a partially degraded trabecular microstructure. Therefore, it is tempting to speculate that DISH, even from the initial phases of the disease, might be harmful to the bone trabecular structure in post-menopausal women. In this sense, there is a consensus on the importance of establishing new diagnostic criteria that include earlier stages of the disorder and that incorporate clinical and radiological manifestations in areas other than the spine, such as peripheral joints and entheses [45]. Thus, there is scarce information on the pathogenesis of the initial phases of DISH and the beginning of

the ossification process, although systemic inflammation has been proposed as a factor for the initiation of DISH [46-49]. In our study, the TBS worsening since the initial stages of the disease and the values of TBS corresponding to a partially degraded trabecular structure, suggest that TBS could be a valuable tool for the assessment of the trabecular microstructure in postmenopausal women with DISH, even in the early stages of the disease.

Another aspect of interest is whether the segment affected by the hyperostosis and the location of the trabecular damage are related. Noteworthy that DISH was most frequently observed in the thoracic spine and TBS was measured in the lumbar spine (L1-L4). Further analysis has shown that after controlling for age, the estimated TBS mean in women with exclusively thoracic DISH was significantly lower than those without DISH. Considering that in both cases the beam did not capture hyperostosis and having annulled the effect of age, the difference in the TBS score demonstrated that in thoracic DISH the trabecular bone of the lumbar vertebrae was also affected, and providing evidence of a general worsening of the trabecular structure along the spine.

DISH, BMD, and bone remodeling markers

Our results showed that lumbar BMD was significantly increased in postmenopausal women with DISH compared to those without. These results corroborate the traditional observation that DISH is associated with an increased BMD measured by DXA at the lumbar level and that DISH-related lumbar ossifications should be considered when interpreting BMD measurements to predict the risk of fracture since it can mask pre-existing osteoporosis or poorer bone quality, which ultimately predisposes to a higher risk of fractures [21,26,50,51]. On the contrary, TBS is a marker not affected by the presence of hyperostosis. We have observed that lumbar BMD was higher in DISH than in NDISH participants, while TBS was significantly lower. This confirms the usefulness of TBS, added to BMD, in the assessment and stratification of risk for vertebral fracture in postmenopausal women with DISH.

Regarding BMT, there is no established pattern in patients with DISH, and their clinical utility and pre-analytical variability make their interpretation difficult, with non-significant variations recorded in these patients [50, 52, 53]. In our study, postmenopausal women with DISH presented significantly lower CTX values while the markers of bone formation, such as alkaline phosphatase and P1NP did not show significant differences These figures are similar to those observed in postmenopausal women in the general population, and although the variations could probably be due to the changes related to the menopause status [54] than to the effect of DISH itself, this finding could be also explained, at least in part, by the close relationship between DISH and impaired glucose metabolism. Thus, T2DM is associated with low bone turnover and decreased circulating bone remodeling markers, and there is

evidence that glucotoxicity, through different mechanisms, is involved [55]. As a matter of fact, in our study, the group of women with DISH and low serum CTX levels showed a higher prevalence of T2DM and higher basal glycemic levels, supporting the potential role of glucotoxicity in this disorder.

Concerning the relationships between DISH and T2DM, after adjusting for age, both conditions separately showed an impact on TBS that did not differ significantly. However, when they coexisted, the TBS fell within the range of degraded trabecular structure and the lowest values were recorded, pointing to a synergistic effect. The association of both diseases could explain the abovementioned low serum CTX that we found in women with DISH. Although T2DM was a potent confounding variable, TBS values associated with DISH persisted significantly low after adjustment. The multivariable analysis confirmed that DISH is a consistent predictor of low TBS, regardless of T2DM.

DISH, TBS, and vertebral fracture

It is known that patients with DISH have an increased risk of VF. As other studies have shown, the pathogenesis of VF in subjects with DISH is favored by the presence of a rigid column and they are usually seen in vertebrae close to where DISH is [21]. The affected segments are fused by ossification of the AVL, and the biomechanical alteration leads to a rigid and immobilized spine, unable to distribute energy if a traumatism occurs. For this reason, fractures in patients with DISH are often displaced even with a minor traumatic mechanism and entail an increased morbimortality. In addition, studies have suggested that VF in DISH is often more unstable and is often associated with an increased risk of deficits and neurological complications and a higher mortality rate [23,24].

We found an increased prevalence of VF, nearly double, in postmenopausal women with DISH than in those without. Moreover, TBS values in women with DISH and VF were consistent with a degraded trabecular microstructure. Therefore, TBS could be an additional tool for risk prediction of VF in this entity [56].

Although speculative, a chronic low-grade inflammation associated with DISH, as suggested by Mader et al [47], could explain several findings of the study, such as the close connections between DISH and components of the metabolic syndrome, the decreased TBS (measured at the lumbar spine) in cases of exclusively thoracic DISH, as well as some laboratory alterations observed in DISH subjects (in particular, a lower plasma albumin level and a decreased 25OHD level), usually observed in inflammatory environments. In line, the results of a recent work of our group aimed at early DISH [57] support the inflammatory theory and provide some evidence that the onset of ossification and trabecular deterioration coincide in a low-grade systemic inflammatory setting. In this rationale, DISH

could be a continuous process of bone production/bone loss, rather than a classical disorder of the bone formation process.

Limitations and strengths

Our study presents the limitations inherent to its cross-sectional design, which allows for investigating association but not definitive criteria for a causal relationship. In addition, postmenopausal women that participated in this study were Caucasian and, therefore, the results may not be extrapolated to other populations or ethnicities. Nevertheless, its main strength is that it provides an analysis, to our knowledge not previously performed, of TBS values in DISH, both with the established Resnick-Niwayama criteria and with a graded scale, carried out in a large and well-characterized prospective cohort of postmenopausal women.

Conclusions

An association between DISH and TBS, not previously described, has been shown in postmenopausal women, in which hyperostosis, after adjusting for confounding variables, has been significantly and consistently related to trabecular degradation and, therefore, to deterioration in bone quality.

In addition, TBS values showed a gradual decrease from the initial phases with worsening as the disease progressed according to the Schlapbach scale. The result in established DISH has been a TBS corresponding to a partially degraded trabecular microstructure.

Certain findings of the study seem to point to a low-grade inflammatory setting associated with DISH, which is currently under debate.

Longitudinal studies are warranted to establish the utility of the TBS as a tool for risk prediction of VF in postmenopausal women with DISH.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

SP: Conceptualization. Data curation. Formal analysis. Writing - original draft.
EP: Methodology. Formal analysis. Writing - original draft.
JMO: Investigation. Resources. Supervision.
MM: Data curation. Writing - original draft.
RP: Data curation. Validation.

VMT: Methodology. Writing - review & editing.
JLH: Conceptualization. Formal analysis. Writing - review & editing.
All authors read and approved the final manuscript.

Funding

Supported by a grant from Instituto de Salud Carlos III (PI21/00532) that could be co-funded by European Union FEDER funds.

Ethical approval

The Camargo Cohort study was approved by the Clinical Research Ethics Committee of Cantabria (Internal Code 2016.003).

Competing interests

The authors declare that they do not have any competing interests regarding this paper.

Acknowledgements

The authors would like to express their gratitude to all the participants from the Camargo Cohort.

Table 1. Baseline clinical characteristics of participants according to DISH status.

Variable	DISH (N=126)	NDISH (N=1419)	*p*
Age, *years*	66.8±9	61.5±9	0.0001
BMI *(Kg/m²)*	30.9 [8]	27.6 [6]	0.0001
Abdominal perimeter, *cm*	104 [17]	93 [19]	0.0001
Obesity, *n (%)*	73 (59)	473 (33)	0.0001
Diabetes mellitus, *n (%)*	21 (17)	133 (9)	0.01
Hypertension, *n (%)*	78 (62)	547 (39)	0.0001
Dyslipidemia, *n (%)*	35 (28)	395 (28)	0.99
Glomerular filtration rate, *ml/min/1.73 m²*	72.4±23	71.4±17	0.58
Metabolic syndrome, *n (%)*	63 (55)	447 (36)	0.0001

BMI: body mass index; NDISH: Non-DISH.

Quantitative variables are expressed as median [interquartilic range].

Table 2. Bone metabolism parameters according to DISH status.

Variable	DISH (N=126)	NDISH (N=1419)	*p*
Calcium, *mg/dl*	9.5 [0.7]	9.6 [0.4]	0.99
Albumin, *g/dl*	4.3 [0.4]	4.4 [0.4]	0.01
Phosphate, *mg/dl*	3.4 [0.6]	3.5 [0.6]	0.14
Alkaline phosphatase, *U/L*	73 [25]	71 [26]	0.74
25OHD, *ng/ml*	20.8 [10]	21.8 [11]	0.01
iPTH, *pg/ml*	57.8 [28]	49.8 [23]	0.03
P1NP, *ng/ml*	43.7 [25]	45.5 [27]	0.08
CTX, *ng/ml*	0.332 [0.24]	0.361 [0.26]	0.03
Lumbar BMD, *gr/cm²*	0.960±0.134	0.912±0.142	0.0001
Femur neck BDM, *gr/cm²*	0.739±0.119	0.719±0.134	0.11
Total hip BDM, *gr/cm²*	0.873±0.129	0.849±0.125	0.05
Trabecular bone score	1.255±0.13	1.335±0.12	0.0001

BMD: bone mineral density; 25OHD: 25-hydroxyvitamin D; iPTH: intact parathyroid hormone; PINP: amino-terminal pro-peptide of type 1 collagen; CTX: C-terminal telopeptide of type 1 collagen; NDISH: Non-DISH.

Quantitative variables are expressed as median [interquartilic range].

Figure 1. Median TBS values in women with DISH according to the Schlapbach graded scale.

Figure 2. Prevalence of vertebral fractures in the study groups.

Figure 3. TBS values according to the presence or absence of vertebral fractures in DISH and NDISH postmenopausal women.

Figure 4. TBS values associated with DISH and T2DM.

Figure 1

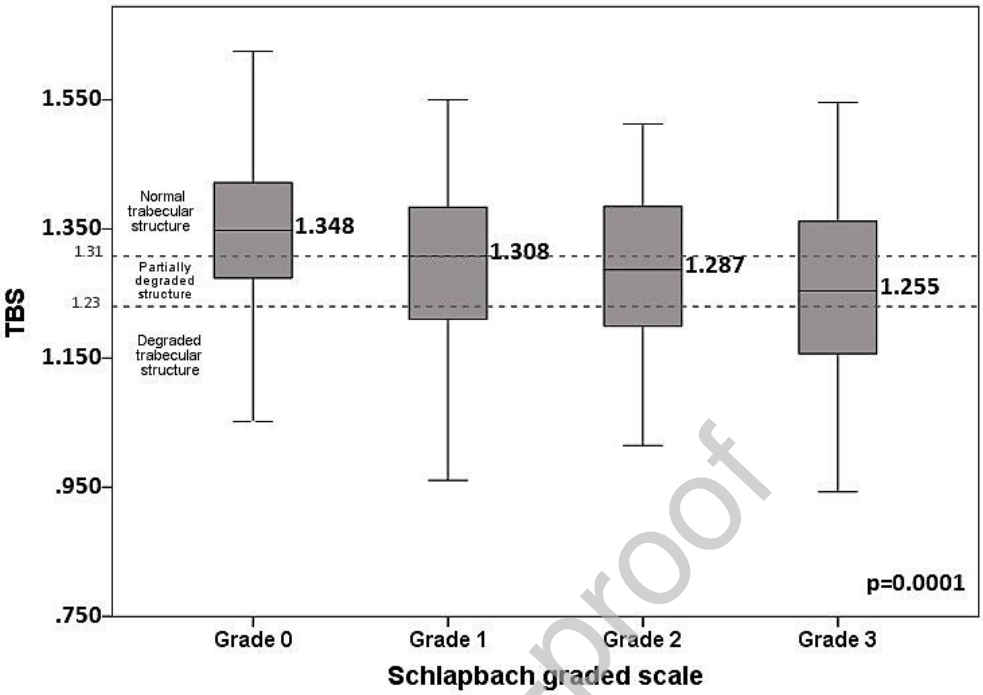


Figure 2

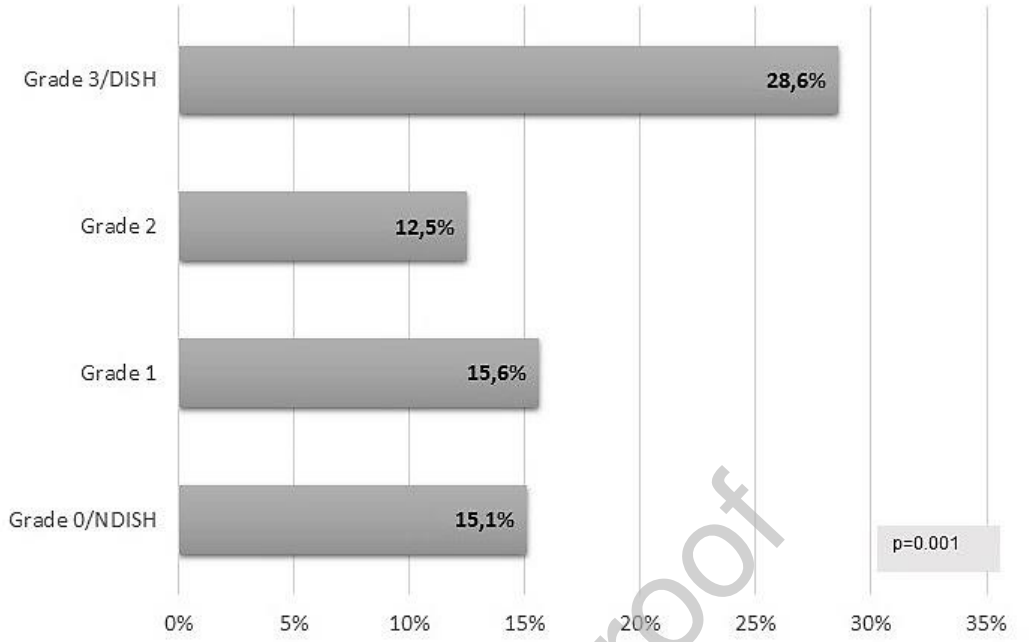


Figure 3

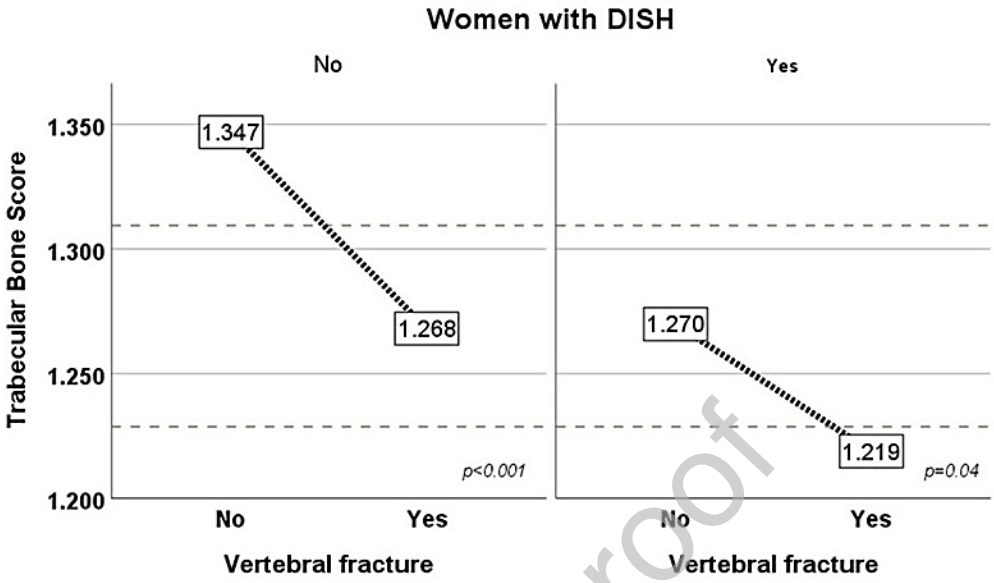
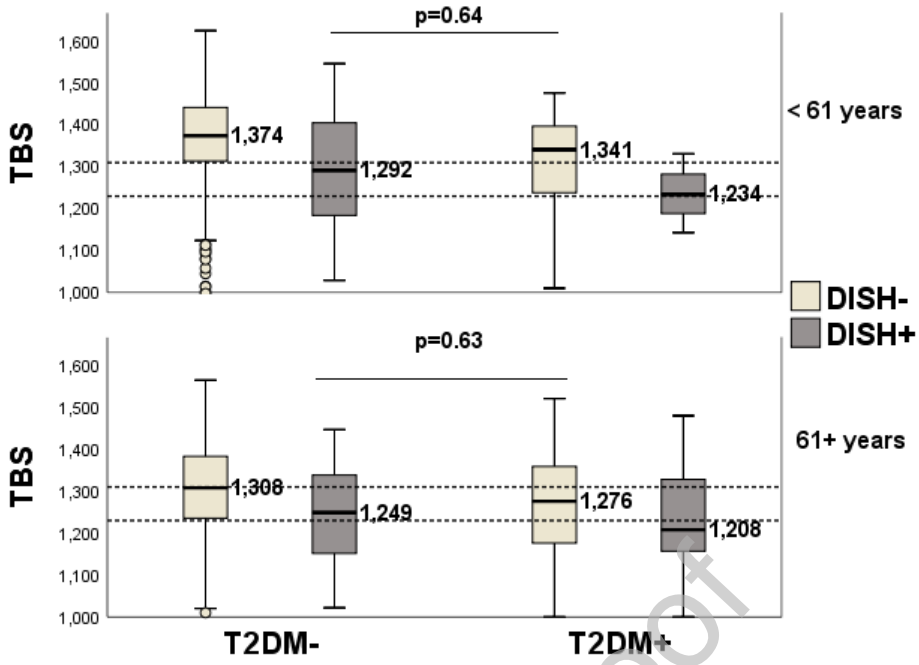


Figure 4



T2DM: Type 2-diabetes mellitus; TBS: Trabecular bone score.
Dashed lines at Y axis values of 1.230 and 1.310 define TBS ranges of degraded trabecular structure (<1.230), partially degraded trabecular structure (1.230-1.310) and normal trabecular structure (>1.310)

References

1. Forestier J, Rotes-Querol J. Senile ankylosing hyperostosis of the spine. Ann Rheum Dis. 1950;9:321-330. doi: 10.1136/ard.9.4.321.
2. Utsinger PD. Diffuse idiopathic skeletal hyperostosis. Clin Rheum Dis. 1985;11:325-29.
3. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier's disease with extraspinal manifestations. Radiology. 1975;115:513–24. doi: 10.1148/15.3.513.
4. Mazières B. Hiperostosis vertebral anquilosante (enfermedad de Forestier). EMC-Aparato Locomotor. 2014;47:1-11. doi: 10.1016/S1286-935X(14)66943-4.
5. Julkunen H, Heinonen OP, Knekt P, Maatela J. The epidemiology of hyperostosis of the spine together with its symptoms and related mortality in a general population. Scand J Rheumatol. 1975;4:23-7. doi: 10.1080/03009747509095610.
6. Vaishya R, Vijay V, Nwagbara IC, Agarwal AK. Diffuse idiopathic skeletal hyperostosis (DISH): A common but less known cause of back pain. J Clin Orthop Trauma. 2017;8:191-6. doi: 10.1016/j.jcot.2016.11.006.
7. Kim SK, Choi BR, Kim CG, Chung SH, Choe JY, Joo KB, et al. The prevalence of diffuse idiopathic skeletal hyperostosis in Korea. J Rheumatol. 2004;31:2032-5.

8. Westerveld LA, Quarles Van Ufford HME, Verlaan JJ, Oner FC. The prevalence of diffuse idiopathic skeletal hyperostosis in an outpatient population in the Netherlands. J Rheumatol. 2008;35:1635-8.
9. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: Clinical features and pathogenic mechanisms. Nat Rev Rheumatol. 2013;9:741-50. doi: 10.1038/nrrheum.2013.165.
10. Pillai S, Littlejohn G. Metabolic factors in diffuse idiopathic skeletal hyperostosis: A review of clinical data. Open Rheumatol J. 2014;8:116-28. doi: 10.2174/1874312901408010116.
11. Li H, Jiang LS, Dai LY. Hormones and growth factors in the pathogenesis of spinal ligament ossification. Eur Spine J. 2007;16:1075-84. doi: 10.1007/s00586-007-0356-4.
12. Niu CC, Lin SS, Yuan LJ, Chen LH, Yang CY, Chung AN, et al. Correlation of blood bone turnover biomarkers and Wnt signaling antagonists with AS, DISH, OPLL, and OYL. BMC Musculoskelet Disord. 2017;18:61. doi: 10.1186/s12891-017-1425-4.
13. Senolt L, Hulejova H, Krystufkova O, Forejtova S, Andres Cerezo L, Gatterova J, et al. Low circulating Dickkopf-1 and its link with severity of spinal involvement in diffuse idiopathic skeletal hyperostosis. Ann Rheum Dis. 2012;71:71-4. doi: 10.1136/annrheumdis-2011-200357.
14. Resnick D, Shapiro RF, Wiesner KB, Niwayama G, Utsinger PD, Shaul SR. Diffuse idiopathic skeletal hyperostosis (DISH) [ankylosing hyperostosis of Forestier and Rotes-Querol]. Semin Arthritis Rheum. 1978;7:153-87. doi: 10.1016/0049-0172(78)90036-7.
15. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in DISH. Radiology. 1976;119:559-68. doi: 10.1148/119.3.559.
16. Kuperus JS, de Gendt EEA, Oner FC, de Jong PA, Buckens SCFM, van der Merwe AE, et al. Classification criteria for diffuse idiopathic skeletal hyperostosis: a lack of consensus. Rheumatology (Oxford). 2017;56:1123-34. doi: 10.1093/rheumatology/kex056.
17. Mader R, Verlaan JJ, Eshed I, Bruges-Armas J, Puttini PS, Atzeni F, et al. Diffuse idiopathic skeletal hyperostosis (DISH): where we are now and where to go next. RMD Open. 2017;3:e000472. doi: 10.1136/rmdopen-2017-000472.
18. Mader R, Buskila D, Verlaan JJ, Atzeni F, Olivieri I, Pappone N, et al. Developing new classification criteria for diffuse idiopathic skeletal hyperostosis: back to square one. Rheumatology (Oxford). 2013;52:326-30. doi: 10.1093/rheumatology/kes257.
19. Mader R, Novofestovski I, Adawi M, Lavi I. Metabolic Syndrome and Cardiovascular Risk in Patients with Diffuse Idiopathic Skeletal Hyperostosis. Semin Arthritis Rheum. 2009;38:361–5. doi: 10.1016/j.semarthrit.2008.01.010.
20. Pariente E, Sgaramella GA, Olmos JM, Pini SF, Landeras R, Hernández JL. Relación entre hiperostosis esquelética idiopática difusa, calcificación de la aorta abdominal y las alteraciones

metabólicas asociadas: datos de la Cohorte Camargo. Med Clin (Barc). 2017;149:196-202. doi: 10.1016/j.medcli.2017.01.030.

21. Diederichs G, Engelken F, Marshall LM, Peters K, Black DM, Issever AS, et al. Osteoporotic Fractures in Men Research Group. Diffuse idiopathic skeletal hyperostosis (DISH): relation to vertebral fractures and bone density. Osteoporos Int. 2011;22:1789-97. doi: 10.1007/s00198-010-1409-9.
22. Westerveld LA, van Bemmel JC, Dhert WJA, Oner FC, Verlaan JJ. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. Spine J. 2014;14:729-40. doi: 10.1016/j.spinee.2013.06.038.
23. Caron T, Bransford R, Nguyen Q, Agel J, Chapman J, Bellabarba C. Spine fractures in patients with ankylosing spinal disorders. Spine (Phila Pa 1976). 2010;35:458-64. doi: 10.1097/BRS.0b013e3181cc764f.
24. Westerveld LA, Verlaan JJ, Oner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J. 2009;18:145-56. doi: 10.1007/s00586-008-0764-0.
25. Westerveld LA, Verlaan JJ, Lam MG, Scholten WP, Bleys RL, Dhert WJ, et al. The influence of diffuse idiopathic skeletal hyperostosis on bone mineral density measurements of the spine. Rheumatology (Oxford). 2009;48:1133-36. doi: 10.1093/rheumatology/kep177.
26. Schwartz JB, Rackson M. Diffuse idiopathic skeletal hyperostosis causes artificially elevated lumbar bone mineral density measured by dual X-ray absorptiometry. J Clin Densitom. 2001;4:385-88. doi: 10.1385/jcd:4:4:385.
27. Kuperus JS, Samsour L, Buckens CF, Oner FC, de Jong PA, Verlaan JJ. Bone mineral density changes over time in diffuse idiopathic skeletal hyperostosis of the thoracic spine. Bone. 2018;112:90-6. doi: 10.1016/j.bone.2018.04.005.
28. Albrand G, Munoz F, Sornay-Rendu E, DuBoeuf F, Delmas PD. Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: the OFELY study. Bone. 2003;32:78-85. doi: 10.1016/s8756-3282(02)00919-5.
29. Rubin CD. Emerging concepts in osteoporosis and bone strength. Curr Med Res Opin. 2005;21:1049-56. doi: 10.1185/030079905X50525.
30. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res. 2014;29:518-30. doi: 10.1002/jbmr.2176.
31. Olmos JM, González-Macías J. The trabecular bone index: a new tool for assessing osteoporosis. Rev Clin Esp (Barc). 2018;218:135-136. doi: 10.1016/j.rce.2018.01.007.

32. Harvey NC, Glüer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone. 2015;78:216-24. doi: 10.1016/j.bone.2015.05.016.
33. Pini SF, Sgaramella GA, Pariente-Rodrigo E, Ramos-Barrón MC, Olmos-Martínez JM, Hernández-Hernández JL. Trabecular bone score and bone turnover markers in men with DISH: Data from the Camargo Cohort study. Semin Arthritis Rheum. 2020;50:1521-1524. doi: 10.1016/j.semarthrit.2020.01.008.
34. Olmos JM, Hernández JL, Martínez J, Pariente E, Llorca J, González-Macías J. Bone turnover markers in Spanish adult men. The Camargo cohort study. Clin Chim Acta. 2010;411:1511-5. doi: 10.1016/j.cca.2010.06.010.
35. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome - A new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23:469-80. doi: 10.1111/j.1464-5491.2006.01858.x.
36. McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. J Bone Miner Res. 2016;31:940-8. doi: 10.1002/jbmr.2734.
37. Genant HK, Wu CY, Van Kuijk MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137-1148. doi: 10.1002/jbmr.5650080915.
38. Schlapbach P, Beyeler C, Gerber NJ, van der Linden S, Bürgi U, Fuchs WA, et al. Diffuse idiopathic skeletal hyperostosis (DISH) of the spine: a cause of back pain? A controlled study. Br J Rheumatol. 1989;28:299-303. doi: 10.1093/rheumatology/28.4.299.
39. Pini SF, Acosta V, Tobalina M, Pariente E, Rueda J, Olmos JM, et al. Interobserver agreement using Schlapbach graded scale for diffuse idiopathic skeletal hyperostosis (DISH): can we reduce the cut-off point of vertebral affection? Clin Rheumatol. 2019;38:1155-1162. doi: 10.1007/s10067-018-4398-2.
40. Weinfeld RM, Olson PN, Maki DD, Griffiths HJ. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large American Midwest metropolitan hospital populations. Skeletal Radiol 1997;26:222–5. doi: 10.1007/s002560050225.
41. Julkunen H, Heinonen OP, Pyörälä K. Hyperostosis of the spine in an adult population. Its relation to hyperglycaemia and obesity. Ann Rheum Dis. 1971;30:605-12. doi: 10.1136/ard.30.6.605.
42. McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. Adjusting fracture probability by trabecular bone score. Calcif Tissue Int. 2015;96:500-9. doi: 10.1007/s00223-015-9980-x.

43. Martineau P, Leslie WD. Trabecular bone score (TBS): Method and applications. Bone. 2017;104:66-72. doi: 10.1016/j.bone.2017.01.035.
44. Redondo L, Puigoriol E, Rodríguez JR, Peris P, Kanterewicz E. Usefulness of the Trabecular Bone Score for assessing the risk of osteoporotic fracture. Rev Clin Esp (Barc). 2018;218:121-127. doi: 10.1016/j.rce.2017.12.005.
45. Mader R. Diffuse idiopathic skeletal hyperostosis: time for a change. J Rheumatol. 2008;35:377-9.
46. Bieber A, Masala IF, Mader R, Atzeni F. Differences between diffuse idiopathic skeletal hyperostosis and spondyloarthritis. Immunotherapy. 2020;12:749-56. doi: 10.2217/imt-2020-0045.
47. Mader R, Pappone N, Baraliakos X, Eshed I, Sarzi-Puttini P, Atzeni F, et al. Diffuse Idiopathic Skeletal Hyperostosis (DISH) and a Possible Inflammatory Component. Curr Rheumatol Rep. 2021;23:6. doi: 10.1007/s11926-020-00972-x.
48. Harlianto NI, Westerink J, Foppen W, Hol ME, Wittenberg R, van der Veen PH, et al; on behalf of the UCC-SMART-Study Group. Visceral Adipose Tissue and Different Measures of Adiposity in Different Severities of Diffuse Idiopathic Skeletal Hyperostosis. J Pers Med. 2021;11:663. doi: 10.3390/jpm11070663.
49. Pappone N, Ambrosino P, Di Minno MND, Iervolino S. Is diffuse idiopathic skeletal hyperostosis a disease or a syndrome? Rheumatology (Oxford). 2017;56:1635-36. doi: 10.1093/rheumatology/kew451.
50. Uehara M, Takahashi J, Ikegami S, Tokida R, Nishimura H, Sakai N, et al. Differences in Bone Mineral Density and Bone Turnover Markers Between Subjects with and without Diffuse Idiopathic Skeletal Hyperostosis. Spine (Phila Pa 1976). 2020;45:1677-81. doi: 10.1097/BRS.0000000000003689.
51. Kolta S, Briot K, Fechtenbaum J, Paternotte S, Armbrecht G, Felsenberg D, et al. TBS result is not affected by lumbar spine osteoarthritis. Osteoporos Int. 2014;25:1759-64. doi: 10.1007/s00198-014-2685-6.
52. Greenblatt MB, Tsai JN, Wein MN. Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. Clin Chem. 2017;63:464-474. doi: 10.1373/clinchem.2016.259085.
53. Horie S, Sawaji Y, Endo K, Suzuki H, Matsuoka Y, Nishimura H, et al. Factors associated with bone metabolism in patients with cervical ossification of the posterior longitudinal ligament accompanied with diffuse idiopathic skeletal hyperostosis. SICOT J. 2018;4:7. doi: 10.1051/sicotj/2017061.

54. Martínez J, Olmos JM, Hernández JL, Pinedo G, Llorca J, Obregón E, et al. Bone turnover markers in Spanish postmenopausal women: the Camargo cohort study. Clin Chim Acta. 2009;409:70-4. doi: 10.1016/j.cca.2009.08.020.
55. Starup-Linde J, Lykkeboe S,Handberg A, Vestergaard P, Høyem P, Fleischer J, Hansen TK, Poulsen PL, Laugesen E. Glucose variability and low bone turnover in people with type 2 diabetes. Bone. 2021;153:116159. doi: 10.1016/j.bone.2021.116159.
56. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res. 2011;26:2762-9. doi: 10.1002/jbmr.499.
57. Pariente E, Pini SF, Olmos JM, Fierro P, Landeras R, Ramos C, et al. Early stages of diffuse idiopathic skeletal hyperostosis (DISH) and chronic inflammation: the Camargo Cohort Study. Clin Rheumatol. 2023 Mar 18. doi: 10.1007/s10067-023-06574-z.