Assessment of the Necessity of Osteoporosis Treatment for Patients with Low Bone Density in Diffuse Idiopathic Skeletal Hyperostosis

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Abstract:

Introduction: Although patients with diffuse idiopathic skeletal hyperostosis (DISH) do not have low bone density, it is a risk factor for spine fractures associated with DISH. We investigated the characteristics and bone metabolism markers of patients with DISH having low bone density to assess whether osteoporosis medication is necessary to prevent fractures.

Methods: A cross-sectional study was conducted between April 1, 2008, and March 31, 2019. The 86 patients included were divided into two groups according to their T-scores—one group had low bone density and DISH, and the other group did not. Group A (T-score ≤−1) and B (T-score >−1) data were adjusted for confounding factors and compared for differences in age, body weight, maximum number of vertebral bodies with bony bridges between adjacent vertebrae (max VB), and previous history (hypertension, malignant tumors, diabetes mellitus, cardiac diseases, chronic renal failure, and spinal fractures). In Group A, multiple linear regression was used to investigate relationships among max VB, femur bone mineral density (BMD), total type I procollagen N-terminal propeptide (P1NP), and tartrate-resistant acid phosphatase 5b (TRACP-5b).

Results: Group A had 36, and Group B had 50 male patients with DISH. Patients in Group B were heavier than those in Group A. The mean femur BMD in Group A was age-appropriate, and that in Group B was higher than the age-appropriate femur BMD. The mean values of P1NP and TRACP-5b were within the normal range. Max VB was positively correlated with total P1NP in Group A. Total P1NP was significantly and positively correlated with TRACP-5b.

Conclusions: The DISH group with a T-score of ≤−1 was age-appropriate. The group with a T-score of >−1 had higher BMD because of their higher body weight. The group with a T-score of ≤−1 had good bone metabolism and did not require aggressive osteoporosis treatment.

Keywords:
Bone mineral density, Diffuse idiopathic skeletal hyperostosis, Proximal femur, Type I procollagen N-terminal propeptide

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a relatively common clinical presentation characterized by abnormal bony bridges between adjacent vertebral bodies around the spinal joints and the peripheral or appendicular skeleton⁷. The lever arm formed bony bridges that link intervertebral bodies, which increases the risk of fracture after minor trauma in patients with DISH⁷. Spinal fractures often cause irreversible spinal cord injury or death with increasing age⁵,⁶. In spinal fractures associated with DISH, the lever arm is a factor in the fracture, but to date, no drugs have been developed that can inhibit bone cross-linking. Furthermore, results from several studies suggest that bone mineral density (BMD) is comparable or higher in patients with DISH than in those without DISH and healthy subjects⁶,¹⁰. By contrast, low BMD increases the risk of spinal fractures in DISH⁹. Another study, which utilized quantitative evaluation with computed tomography (CT) to examine the connection between fractures and BMD in males with DISH, found that BMD was 25% lower in patients with DISH and concomitant fractures than in those with DISH but without
vertebral fractures\(^{15}\). Hence, in low BMD patients with DISH, it is important to understand bone metabolism and whether osteoporosis treatment is needed for fracture prevention. In the present study, the low bone density population with DISH was investigated for characteristics and bone metabolism.

**Materials and Methods**

**Study design**

This was a cross-sectional study conducted between April 1, 2008, and March 31, 2019. Among patients who visited the Department of Orthopedic Surgery at Shizuoka City Shimizu Hospital, BMD was evaluated via dual-energy X-ray absorptiometry (GE Medical Systems Lunar, GE Healthcare, Chicago, IL, USA) in 197 male patients, and scans of the thoracic and lumbar vertebrae and pelvis were acquired via CT (Discovery CT 750HD, GE Healthcare, Chicago, IL, USA) in 183 male patients. A total of 166 male patients without a history of hyperparathyroidism or rheumatism, steroid usage, and pharmacological treatment for osteoporosis were identified through the review of medical records, in-person interviews performed during examinations, and telephone interviews. Among these 166 patients, 120 were diagnosed with DISH according to Resnick’s criteria\(^{14}\). After the exclusion of patients with sacroiliac joint ankylosis based on pelvic CT scans, there were 93 patients with DISH. Of these, 43 patients had a T-score of ≤−1. In the present study, 36 patients with available data on clinical data and bone metabolism markers comprised Group A and 50 patients with a T-score of >−1 comprised Group B (Fig. 1). Bone metabolic markers were evaluated in patients in Group A.

The study’s protocol was reviewed and approved by the Institutional Review Board of the Shizuoka City Shimizu Hospital (approval number: 44, Date: December 7, 2018), and informed consent was obtained from all individual participants included in the study. All procedures were conducted according to the Declaration of Helsinki.

**Data collection**

The medical records were used to collect data on the following parameters: age; body weight; maximum number of vertebral bodies with bony bridges between adjacent vertebrae (max VB); levels of calcium, phosphate, tartrate-resistant acid phosphatase 5b (TRACP-5b), total type I procollagen N-terminal propeptide (P1NP), and 1,25-dihydroxyvitamin D\(_3\) (1,25(OH)\(_2\)D\(_3\)); estimated glomerular filtration rate (eGFR); proximal femur BMD (including the neck, head, Ward’s triangle, and greater trochanter); and information on preexisting diseases and smoking at initial admission. Bone metabolic markers in patients with fractures were collected within 7 days from the date of injury. max VB was calculated using measurements between the thoracic vertebra and sacrum and on the basis of consultation among three orthopedic surgeons. Medical conditions, including the presence of hypertension, malignant tumors, diabetes mellit-
Table 1. Characteristics of T-score≤−1 and T-score>−1 Group with DISH before Adjustment for Confounding Factors.

|                          | T-score≤−1 | T-score>−1 | P value | Reference interval |
|--------------------------|------------|------------|---------|--------------------|
| Number                   | 36         | 50         |         |                    |
| Age (years)              | 82.6±8     | 75.9±8.3   | <0.05*  |                    |
| Body weight (kg)         | 57.6±8.5   | 66±10.9    | <0.01** |                    |
| max VB                   | 8.9±4      | 5.4±4.7    | n.s.    | 0–18               |
| Proximal femur BMD (g/cm²) | 0.7±0.1    | 1±0.1      | <0.01** |                    |
| T-score                  | −2±0.9     | 0.6±0.9    | <0.01** |                    |
| Z-score                  | −0.02±1.3  | 3.1±2      | <0.01** |                    |
| Total P1NP (μg/L)        | 73.4±38.1  | n.d.       | n.d.    | 18.1–74            |
| TRACP-5b (mU/dL)         | 542.8±165.1| n.d.       | n.d.    | 170–590            |
| 1,25(OH)2D3 (pg/mL)      | 54.8±26.1  | n.d.       | n.d.    | 20–60              |
| Ca (mg/dL)               | 9±0.5      | n.d.       | n.d.    | 8.4–10.2           |
| P (mg/dL)                | 3.3±0.5    | n.d.       | n.d.    | 2.5–4.5            |
| eGFR (mL/min/1.73 m²)    | 59±25.1    | n.d.       | n.d.    |                    |
| Hypertension             | 25         | 31         | n.s.    |                    |
| DM                       | 6          | 15         | n.s.    |                    |
| Malignant tumor          | 8          | 6          | n.s.    |                    |
| Cardiac diseases         | 8          | 7          | n.s.    |                    |
| CRF                      | 2          | 3          | n.s.    |                    |
| Spinal fractures         | 14         | 1          | <0.01** |                    |
| Smoking at initial admission | 10        | 16         | n.s.    |                    |

*p<0.05, **p<0.01

1,25(OH)2D3, 1,25-dihydroxyvitamin D3; BMD, bone mineral density; Ca, calcium; CRF, chronic renal failure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; max VB, maximum number of vertebral bodies with bony bridges between adjacent vertebrae; n.s., not significant; P, phosphate; P1NP, total type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b.

Data evaluation

Before adjustment for confounding factors, age, body weight, max VB, BMD-related parameters, and rates of pre-existing diseases were compared between Groups A and B. Additionally, age, body weight, eGFR, preexisting conditions, smoking at initial admission, and presence of spinal fractures were adjusted as confounding factors for regression analysis. After adjustment for confounding factors, age and body weight were compared between Groups A and B. In Group A, dichotomized by T-score≤−2.5 (osteoporosis group) and −2.5<T-score≤−1 (osteopenia group) or dichotomized by a history of fracture and no history of fracture, age, body weight, max VB, levels of Ca, P, TRACP-5b, total P1NP, and 1,25(OH)2D3 were compared. Finally, correlation analyses were performed after adjustment for confounding factors. Specifically, the correlation of max VB with proximal femur BMD and levels of total P1NP, TRACP-5b, 1,25(OH)2D3, calcium, and phosphate were examined. Additionally, the correlation of total P1NP with TRACP-5b, 1,25(OH)2D3, calcium, and phosphate were examined after adjustment for confounding factors.

Statistical analysis

All data were presented as means (±standard deviations) or numbers, and SPSS Statistics version 26 (IBM, Armonk, NY, USA) and the statistical software R-4.0.3 (Index of/src/base/R-4 (r-project.org)) were used for all statistical analyses. Nonparametric analysis of variance with the Mann-Whitney U and chi-square tests were used to compare between Groups A and B, osteoporosis and osteopenia groups, and history of fracture or no history of fracture group. Regression analysis and multiple linear regression analysis were used to evaluate correlations among parameters. P-values of <0.05 were considered to indicate statistical significance.

Results

Table 1 shows the characteristics of 36 patients (Group A: T-score≤−1) and 50 patients (Group B: T-score>−1) in DISH. Briefly, before adjustment, Group A was significantly older and had a significantly lower body weight and experienced more spinal fracture than Group B. After the adjustment for confounding factors, the comparison of the patients with DISH between the two groups revealed that the body weight was lower in Group A than in Group B (Table 2). By contrast, age was not significantly different between the
Table 2. Comparison of Weight between T-score≤−1 and T-score>−1 Group in DISH after Adjustment for Confounding Factors.

|                        | Beta  | 95% CI low | 95% CI high | P value |
|------------------------|-------|------------|-------------|---------|
| T score≤−1 group in DISH | −6.94 | −12.5      | −1.42       | <0.01** |
| max VB                 | 0.055 | −0.6       | 0.71        | 0.867   |
| Hypertension           | −1.47 | −6.45      | 3.51        | 0.558   |
| Malignant tumors       | 1.73  | −4.62      | 8.07        | 0.59    |
| DM                     | −1.17 | −6.6       | 4.25        | 0.667   |
| CRF                    | 2.31  | −7.63      | 12.3        | 0.645   |
| Cardiac diseases       | −4.85 | −11.2      | 1.5         | 0.132   |
| Spinal fractures       | −5.27 | −13        | 2.44        | 0.178   |
| Smoking at initial admission | −1.94 | −7.28    | 3.39        | 0.47    |

*P<0.05, **P<0.01
CI, confidence interval; CRF, chronic renal failure; DM, diabetes mellitus; max VB, maximum number of vertebral bodies with bony bridges between adjacent vertebrae

Table 3. Comparison with Osteoporosis and Osteopenia Patients with DISH.

|                        | Osteoporosis group (T-score≤−2.5) | Osteopenia group (−2.5<T-score≤−1) | P value | Reference interval |
|------------------------|-----------------------------------|----------------------------------|---------|-------------------|
| Number                 | 8                                 | 28                               |         |                   |
| Age                    | 84.1±7.6                          | 82.3±8.1                         | n.s.    |                   |
| Body weight (kg)       | 54.2±8.6                          | 58.6±8.2                         | n.s.    |                   |
| max VB                 | 10.8±1.6                          | 8.3±4.3                          | <0.05*  | 0–18              |
| Proximal femur BMD (g/cm²) | 0.5±0.05                          | 0.75±0.06                        | <0.01** |                   |
| T-score                | −3.3±0.3                          | 0.3±1.2                          | <0.01** |                   |
| Z-score                | −1.3±0.9                          | 0.3±1.2                          | <0.01** |                   |
| Total P1NP (μg/L)      | 99.8±38.4                         | 65.8±34.6                        | <0.05*  | 18.1–74           |
| TRACP-5b (mU/dL)       | 571.8±170.6                       | 534.6±162.7                      | n.s.    | 170–590           |
| 1,25(OH)2D3 (pg/mL)    | 34.7±9.9                          | 60±26.5                          | <0.01** | 20–60             |
| Ca (mg/dL)             | 8.8±0.5                           | 9±0.5                            | n.s.    | 8.4–10.2          |
| P (mg/dL)              | 3.5±0.5                           | 3.3±0.5                          | n.s.    | 2.5–4.5           |

*P<0.05, **P<0.01
1,25(OH)2D3, 1,25-dihydroxyvitamin D3; BMD, bone mineral density; Ca, calcium; max VB, maximum number of vertebral bodies with bony bridges between adjacent vertebrae; n.s., not significant; P, phosphate; P1NP, total type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b

Discussion

Patients with DISH in this study were approximately 80 years old, and because of their advanced age and age-related changes, their bone density decreased. In the results comparing the two groups, dichotomized by T-score, patients in Group B were significantly heavier than those in Group A, although the study population was limited to males and those with rare diseases that affect BMD were excluded before adjustment and the data were further adjusted for confounding factors that affect BMD. There have been several reports on the relationship between body weight and bone density, and generally, the heavier the body weight, the greater the bone density. Also, reportedly, DISH patients are heavier partly because of metabolic abnormalities such as the presence of type II diabetes. Growth hormone, insulin, or insulin-like growth factor was present in DISH, and they target the chondrocytes and mesenchymal cells in the
uncalcified portion of the enthesis; proliferation of these cell types results in new bone formation\(^\text{18}\). One of the reasons for the inconsistent results in the past reports of high or no change in bone density in DISH is that weight is not included as a confounding factor\(^\text{9-11}\). In this study, the mean Z-score for Group A was 0.02, which is appropriate for age, whereas the mean for Group B was 3.1, which is high. There has been little debate regarding whether a group of DISH patients with T-score\(^{\leq-1}\) need osteoporosis treatment just because they are age-appropriate. When the osteopenia and osteoporosis groups were compared, only eight patients had osteoporosis and most of them had osteopenia\(^\text{19}\). This difference in BMD between the two groups was attributable to the difference in max VB, as reported in a previous paper. The osteopenia group had a higher BMD because of a smaller max VB, and the osteoporosis group had a smaller BMD because of a larger max VB.

Nonetheless, given that DISH patients with lower bone density have a higher risk of fracture, understanding the bone metabolism in DISH may help to determine whether osteoporosis treatment is necessary.

There are several reports on bone metabolism markers in DISH, but there is still no consensus\(^\text{10,20,21}\). In discussing bone metabolism in DISH, factors that affect bone metabolism markers must be excluded. The assumption is that confounding factors affecting bone metabolic markers should be eliminated. Age, renal function, history of hyperparathyroidism, rheumatism, and history of steroid and osteoporosis medication use have been reported as factors affecting P1NP and TRACP-5b\(^\text{22-24}\). Thus, in the present study, we excluded patients fulfilling these criteria on the basis of the review of medical records and subsequent telephone interviews. Bone metabolic markers have also been reported to fluctuate after fracture, not increasing until 1 week after fracture but re-

### Table 4. Comparison with Spinal Fracture Group and No Spinal Fracture Group in Group A.

|                           | Spinal fracture group | No spinal fracture group | P value | Reference interval |
|---------------------------|-----------------------|--------------------------|---------|-------------------|
| Number                    | 14                    | 22                       |         |                   |
| Age                       | 81.8±8.6              | 84±6.7                   | n.s.    |                   |
| Body weight (kg)          | 59.3±8.6              | 55±7.4                   | n.s.    |                   |
| max VB                    | 7.2±3.5               | 11.4±3.4                 | <0.05*  | 0–18              |
| Proximal femur BMD (g/cm²) | 0.7±0.1               | 0.68±0.13                | n.s.    |                   |
| T-score                   | −1.9±0.9              | −2±0.9                   | n.s.    |                   |
| Z-score                   | −0.3±0.7              | 0.5±1.7                  | n.s.    |                   |
| Total P1NP (µg/L)         | 71.2±42.1             | 76.9±30.6                | <0.05*  | 18.1–74           |
| TRACP-5b (mU/dL)          | 535.1±140.2           | 555±197.6                | n.s.    | 170–590           |
| 1,25(OH)\(_2\)D\(_3\) (pg/mL) | 59.3±25.9            | 48.4±25.2                | <0.01** | 20–60             |
| Ca (mg/dL)                | 9±0.5                 | 9±0.4                    | n.s.    | 8.4–10.2          |
| P (mg/dL)                 | 3.4±0.5               | 3.3±0.5                  | n.s.    | 2.5–4.5           |

*P<0.05, **P<0.01

1,25(OH)\(_2\)D\(_3\), 1,25-dihydroxyvitamin D\(_3\); BMD, bone mineral density; Ca, calcium; max VB, maximum number of vertebral bodies with bony bridges between adjacent vertebrae; n.s., not significant; P, phosphate; P1NP, total type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b

### Table 5. Correlation of max VB with Bone Metabolic Markers after Adjusting for Confounding Factors.

|                          | Beta  | 95% CI low | 95% CI high | P value |
|--------------------------|-------|------------|-------------|---------|
| P1NP                     | 4.2   | 0.22       | 8.2         | <0.05*  |
| Age                      | 1.1   | −0.7       | 2.9         | 0.2     |
| Weight                   | 0.26  | −1.5       | 2           | 0.8     |
| eGFR                     | −0.06 | −0.57      | 0.45        | 0.8     |
| Hypertension             | −10   | −38        | 18          | 0.5     |
| Malignant tumors         | −12   | −43        | 20          | 0.4     |
| DM                       | 11    | −23        | 45          | 0.5     |
| Cardiac diseases         | 14    | −16        | 45          | 0.3     |
| Spinal fractures          | −19   | −50        | 11          | 0.2     |
| Smoking at initial admission | 23     | −11        | 57          | 0.2     |

*P<0.05, **P<0.01

CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; max VB, maximum number of vertebral bodies with bony bridges between adjacent vertebrae; P1NP, total type I procollagen N-terminal propeptide
Cross-links may affect osteoblastic performance. Thus, we believe that any effects of changes in bone metabolic markers after fracture on the results were minimal for two reasons. First, the samples were collected before the elevation of bone metabolic markers was considered to be a confounding factor in our analyses. The mean value of P1NP in Group A was slightly higher up to 1 year thereafter. Information on bone metabolic markers was collected during the initial examination of patients with DISH within 7 days from the date of fracture, indicating that these data were collected during the inflammatory phase of fracture healing. We believe that any effects of changes in bone metabolic markers after fracture on the results were minimal for two reasons. First, the samples were collected before the elevation of bone metabolism markers. Second, the presence of spinal fractures was considered to be a confounding factor in our analyses. The mean value of P1NP in Group A was slightly high, but the individual values varied. This made it difficult to interpret DISH in terms of bone metabolism. One of the reasons may be that DISH is defined as a single population including mesenchymal and osteoblastic progenitor cells, have been proposed for ectopic ossification. From these clinical and basic studies, one hypothesis is that the number of bony cross-links may affect osteoblastic performance. Thus, we thought that max VB could be an index for bone formation, and this index was adopted in this study. In the result, multiple linear regression analysis revealed that max VB was significantly correlated with P1NP, suggesting that high max VB might indicate a stronger degree of ossification. The mean value of TRACP-5b was also within the normal range, and there was no excessive bone resorption. Although TRACP-5b did not correlate with max VB, P1NP was also in turn correlated with increased TRACP-5b levels, indicating compensatory bone resorption occurs with bone formation and good bone metabolic turnover. There was no significant difference in femur BMD when compared between groups with and without a history of spinal fracture, and max VB was significantly greater in the fracture group, indicating that lever arm instead of low BMD is the main cause of fracture risk in DISH. Thus, the use of osteoporosis drugs for fracture prevention should be used with full consideration of their disadvantages. The use of bone resorption inhibitors, such as bisphosphonate, in patients who do not have excessively high bone resorption markers may not be appropriate given the risk of atypical femoral fractures. Increasing bone density by increasing bone formation is one way to do this; nevertheless, Hamano et al. reported that the intermittent administration of teriparatide in tyy mice had a strong effect on the trabecular bone; the treatment not only increased the amount of trabecular bone but also improved the trabecular structure. By contrast, because of its potent osteogenic effect, teriparatide might augment osteogenic lesions, such as ectopic ossification and spinal ankylosis. Thus, we did not feel the need for administering aggressive osteoporosis treatment to patients with DISH.

The retrospective study design and small sample size are major limitations of the present study. Only bedridden patients were barred from activity, which was not thoroughly investigated. The effect of the number of second and third longest continuous vertebral bone bridges was not considered. Additionally, this study does not represent all patients with DISH because it was conducted in the normal course of care and bone metabolism markers were measured in patients with osteopenia or osteoporosis with T-score <−1. Thus, prospective studies with larger sample sizes should be performed to corroborate the findings of the present study. BMD of DISH patients was divided into two groups according to their T-scores, and the DISH group with T-score <−1 was age-appropriate. Conversely, the group with T-score >1 tended to have higher BMD than their age, which was because of their higher body weight. Although low bone density is a risk factor for spine fracture, the T-scores−1 group has good bone metabolism and may not require aggressive osteoporosis treatment.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

| Table 6. Correlation of P1NP with Bone Metabolic Markers after Adjustment for Confounding Factors. |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| | TRACP-5b | 1,25(OH)2D3 |
| | Beta | 95% CI low | 95% CI high | P value | Beta | 95% CI low | 95% CI high | P value |
| P1NP | 2.2 | 0.65 | 3.8 | <0.01** | −0.25 | −0.52 | 0.01 | 0.06 |
| Age | −0.55 | −8.3 | 7.2 | 0.9 | 0.81 | −0.48 | 2.1 | 0.2 |
| Weight | −7.3 | −15 | 0.04 | 0.051 | 0.36 | −0.87 | 1.6 | 0.5 |
| eGFR | −0.05 | −2.2 | 2.1 | >0.9 | 0.01 | −0.4 | 0.42 | >0.9 |
| Hypertension | −36 | −155 | 82 | 0.5 | −12 | −33 | 9.5 | 0.3 |
| Malignant tumors | −48 | −179 | 84 | 0.5 | 16 | −6.6 | 38 | 0.2 |
| DM | 84 | −59 | 227 | 0.2 | −8.2 | −32 | 16 | 0.5 |
| Cardiac diseases | −46 | −175 | 83 | 0.5 | −8.1 | −30 | 14 | 0.5 |
| Spinal fractures | −6.8 | −119 | 105 | >0.9 | −7.3 | −27 | 12 | 0.4 |
| Smoking at initial admission | −104 | −245 | 37 | 0.14 | −20 | −45 | 5.2 | 0.11 |

*P<0.05, ** P<0.01

1,25(OH)2D3, 1,25-dihydroxyvitamin D3; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; P1NP, total type I pro-collagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b.
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Ethical Approval: This study was approved by the Institutional Review Board of Shimizu Hospital, Shizuoka City (Approval number: 44; Date: November 7, 2018). All procedures were conducted according to the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants included in the study.

References
1. 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(2):145-56.
2. Hendrix RW, Melany M, Miller F, et al. Fracture of the spine in patients with ankylosing spondylitis due to diffuse skeletal hyperostosis: clinical and imaging findings. AJR Am J Roentgenol. 1994;162(4):899-904.
3. Young JS, Cheshire JE, Pierce JA, et al. Cervical ankylosis with acute spinal cord injury. Paraplegia. 1977;15(2):133-46.
4. Caron T, Bransford R, Nguyen Q, et al. Spine fractures in patients with ankylosing spondylitis. Spine. 2010;35(11):e458-64.
5. Furukawa M, Okuyama K, Kawano Y, et al. Femur bone mineral density and pentosidine level distinguish ankylosing spinal disorder patients with and without sacroiliac ankylosis. Spine Surg Relat Res. 2020;4(4):333-40.
6. Sohn S, Chung CK, Han I, et al. Increased bone mineral density in cervical or thoracic diffuse idiopathic skeletal hyperostosis (DISH): a case-control study. J Clin Densitom. 2018;21(1):68-74.
7. Westerveld LA, Verlaan JJ, Lam MG, et al. The influence of diffuse idiopathic skeletal hyperostosis on bone mineral density measurements of the spine. Rheumatol. 2009;48(9):1133-6.
8. Diederichs G, Engelken F, Marshall LM, et al. Diffuse idiopathic skeletal hyperostosis (DISH): relation to vertebral fractures and bone density. Osteoporos Int. 2011;22(6):1789-97.
9. Kaperus JS, Samsour L, Buckens CF, et al. Bone mineral density changes over time in diffuse idiopathic skeletal hyperostosis of the thoracic spine. Bone. 2018;112:90-6.
10. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier’s disease with extraspinal manifestations. Radiology. 1975;115(3):513-24.
11. Horie S, Sawaji Y, Endo K, 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.
12. Furukawa M, Okuyama K, Ninomiya K, et al. Association of continuous vertebral bone bridges and bone mineral density with the risk of fractures in patients with diffuse idiopathic skeletal hyperostosis. Asian Spine J. 2020;16:1-7.
13. Diederichs G, Engelken F, Marshall LM, et al. Osteoporotic fractures in men (MrOS) research group. Osteoporos Int. 2011;22(6):1789-97.
14. Resnick D, Shaul SR, Robins JM. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier’s disease with extraspinal manifestations. Radiology. 1975;115(3):513-24.
15. Felson DT, Zhang Y, Hannan MT, et al. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. J Bone Miner Res. 1993;8(5):567-73.
16. Pillai S, Littlejohn G. Metabolic factors in diffuse idiopathic skeletal hyperostosis: A Review of clinical data. Open Rheumatol J. 2014;8:116-28.
17. Mader R, Novofestowski I, Aday M, et al. Metabolic syndrome and cardiovascular risk in patients with diffuse idiopathic skeletal hyperostosis. Semin Arthritis Rheum. 2009;38(5):361-35.
18. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. Nat Rev Rheumatol. 2013;9(12):741-50.
19. Furukawa M, Okuyama K, Ninomiya K, et al. Maximum number of bone cross-linked vertebrae: an index for BMD in diffuse idiopathic skeletal hyperostosis. J Bone Miner Metab. 2022;40:308-16.
20. Senolt L, Hulejova H, Krystufkova O, et al. Low circulating Dickkopf-1 and its link with severity of spinal involvement in diffuse idiopathic skeletal hyperostosis. Ann Rheum Dis. 2012;71(1):71-4.
21. Aebeli D, Schett G, Eser P, et al. Serum Dkk-1 levels of DISH patients are not different from healthy controls. Joint Bone Spine. 2011;78(4):422-3.
22. Shao J, Zhou SS, Qu Y, et al. Correlation between bone turnover and metabolic markers with age and gender: a cross-sectional study of hospital information system data. BMC Musculoskeletal Disord. 2020;21(1):603.
23. Wlosikowsa M, Jakubicz D, Stipiécki K, et al. Serum concentrations of formation (PINP) and resorption (CTX) bone turnover markers in rheumatoid arthritis. Rheumatol Int. 2009;29:1469-76.
24. Cavalier E, Lukas P, Carlisi A, et al. Aminoterminal propeptide of type I procollagen (PINP) in chronic kidney disease patients: the assay matters. Clin Chim Acta. 2013;425:117-8.
25. Rozental TD, Herder LM, Walley KC, et al. 25-hydroxyvitamin-D and bone turnover marker levels in patients with distal radial fracture. J Bone Joint Surg Am. 2015;97(20):1685-93.
26. Ivaska KK, Gerdhem P, Akesson K, et al. Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. J Bone Miner Res. 2007;22(8):1155-64.
27. Ikegami S, Kamimura M, Nakagawa H, et al. Comparison in bone turnover markers during early healing of femoral neck fracture and trochanteric fracture in elderly patients. Orthop Rev (Pavia). 2009;1(2):e21.
28. Fournier DE, Kiser PK, Beach RJ, et al. Dystrophic calcification and heterotropic ossification in fibrocartilaginous tissues of the spine in diffuse idiopathic skeletal hyperostosis (DISH). Bone Res. 2020;8:16.
29. Suda RK, Billings PC, Egan KP, et al. Circulating osteogenic precursor cells in heterotropic bone formation. Stem Cells. 2009;27(9):2199-209.
30. Hamano H, Takahata M, Ota M, et al. Teriparatide improves trabecular osteoporosis but simultaneously promotes ankylosis of the spine in the twy mouse model for diffuse idiopathic skeletal hyperostosis. Calcif Tissue Int. 2016;98(2):140-8.