Bone Mineral Density in Diabetes Mellitus Foot Patients for Prediction of Diabetic Neuropathic Osteoarthropathic Fracture

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Received: July 13, 2020
Revised: August 19, 2020
Accepted: August 20, 2020

INTRODUCTION

Diabetic neuropathic osteoarthropathy (DNOAP) is a destructive process of a denervated joint. The bony components and DNOAP can be frequently noticed with foot and ankle fractures. Although it was initially associated with tertiary syphilis, diabetes is the main cause of neuropathic arthropathy in the developed
countries. The pathophysiology of this joint destroying process is not well known, but is considered to be multifactorial, and neuropathy seems to be binding.[1-4] The presence of dense peripheral sensory neuropathy, abnormal circulation, and history of preceding trauma seems to be the primary risk factors for this possibly limb-threatening deformity.[5]

All patients with diabetes have an increased risk for fractures, and it has been suggested that the presence of peripheral osteopenia may play a role.[6] Furthermore, foot deformities, prior amputations, joint infections, or surgical trauma may result in excessive stress that can lead to diabetic neuropathic arthropathy.[7] The neurotraumatic theory shows that loss of protective sensation can lead to repeated microtrauma, which can make DNOAP. There is also the neurovascular theory, which suggests that when there is a high flow vascular state in affected patients, the increased blood flow washes out local calcium in bone and can create localized osteopenia.[8]

Osteoporosis has also been hypothesized to have a role in DNOAP development, but it is still controversial.[9,10] Current concepts suggest that osteopenic bones show more initial microfracture, and there is evidence that both neuropathy and diabetes are related with osteopenia.[11] Diabetic induced neuropathy causes bone dissolution and increases osteoclast activity by increasing the expression of receptor activator of nuclear transcription factor β ligand, which can lead to increased activation of nuclear transcription factor β.[12] This osteolysis pathway can further be enhanced by the presence of free radicals, hyperlipidemia, increased ambient glucose concentration and advanced glycation end-products present in diabetic patients.[13] These things contribute to the fracture risk in osteoporosis.

Since most diabetic neuropathic arthropathy is diagnosed when suffering from painless fracture or destructive deformity of the joint, we can deduce that bone mineral density (BMD) will be significantly lower in DNOAP patients with foot and ankle fracture than in diabetic patients without neuropathic arthropathy. When deformity progresses or fractures occur, diabetic neuropathic arthropathy patients require surgical treatment, but it is very important to predict the course of the disease in advance because of the high infection rate and reoperation rate.[14]

This study configures the hypothesis: The diabetic neuropathic arthropathy precedes diabetic foot. And diabetic neuropathic arthropathy patients show significantly lower BMD levels than diabetic foot patients.

The aim of study is twofold:
(1) to compare BMD among diabetic foot and diabetic neuropathic arthropathy patients;
(2) to investigate the impact of BMD on the progression of diabetic foot into diabetic neuropathic arthropathy

**METHODS**

1. **Study group selection**

This retrospective study was evaluated at our institution and approved by the Inje University Seoul Paik Hospital Institutional Review Board (PAIK2018-08-007). In this study, patients with BMD among patients diagnosed with DNOAP and diabetic foot were selected from our university hospitals from March 2012 to December 2018.

In this study, 2 subgroups from 25 DNOAP patients were examined in a cross-sectional study design (Fig. 1). The mean diabetic neuropathic arthropathy patient group age at the time of diagnosis was 70.8 years (range, 63-88 years), and
the minimum follow-up period was 14.2 months. Subgroup A (n = 21) was a new patient who was diagnosed with foot and ankle fracture-related with DNOAP. Total 15 patients who were non-plantigrade foot or recurrent history of ulceration or fracture were treated with surgical treatment, while the other 6 case is treated by conservative treatment such as non-weight bearing and cast protection. Patients who underwent surgical treatment were confirmed through clinical features, radiography, and pathology. Patients who received non-surgical treatment were diagnosed through characteristic fracture patterns and clinical features of the ankle or Lisfranc joints that occur without external impact.

Subgroup B (n = 4) was a patient diagnosed with DNOAP while already being treated with diabetic foot. Diagnosis was based on clinical features including unilateral redness, swelling, and a skin temperature > 2°C compared with the contralateral foot using an infrared thermometer. The group B patients have consecutive BMD score follow-up data from diabetic foot to DNOAP. The control group was composed of 30 diabetic foot patients with neuropathy without evidence of DNOAP. The average age of the group was 71 years (range, 65-87 year).

2. Measurement

Foot and ankle weight bearing radiographs were obtained from all patients. The talo-1st metatarsal angle and calcaneal pitch were measured in the weight-bearing foot lateral view, and the talo-1st metatarsal angle and navicular coverage angle were measured in the weight-bearing foot anteroposterior (AP) view. In the weight-bearing ankle AP view, an ankle fracture or progression of ankle arthritis were compared. Clinical workup was compared by using Short Form-36 (SF-36) in a cross-sectional manner.[15]

All subjects underwent full medical history examination (with emphasis on presence or absence of diabetic complications) and thorough clinical examination including a full assessment of the diabetic foot. Laboratory investigations were done for all subjects, which included fasting blood sugar, postprandial blood sugar, Hba1c%, calcium, phosphorus, and alkaline phosphatase.

A dual energy X-ray absorptiometry (DXA) scanner (E-Lunar Inc., Madison, WI, USA) was used for scanning. The whole body, lumbar spine, and unilateral hip were scanned. The T-score and Z-score were registered. The World Health Organization definitions of osteopenia and osteoporosis were used osteopenia (-2.5 < T < -1) and osteoporosis (T ≤ -2.5).[16] The Z-score was calculated according to a normal reference (incorporated in the scanner) for age, weight, sex, and ethnic matched material. In 4 cases, BMD values obtained from ellipses were adopted, and the results of the same DXA scanner were also confirmed to be taken.

3. Statistical analysis

We compared the demographic finding, clinical and radiologic findings, laboratory data, comorbidities as well as the BMD between the DNOAP group and control group. Parametric data were represented as mean ± standard deviation (SD), while nonparametric data were represented as the median and interquartile range. Differences between the 2 groups were detected using the student’s t-test for parametric data and Mann-Whitney U test for nonparametric data.

We allocated each patient’s T-score into three categorical groups; normal, osteopenia, osteoporosis. After yielding each group’s odds ratio, the P-value was measured. The cut-off point for the decrease of BMD that allowed the prediction of DNOAP was determined by receiver operating characteristic (ROC) curve analysis. This analysis was performed using the last BMD measured in diabetic foot management before DNOAP diagnosis in group B patients, and they are evaluated with a control group. Cut-off points were selected based on the maximal sensitivity and specificity sum. For all tests, P-values of less than 0.05 were considered significant. Statistical analyses were performed using the software package SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA).

4. Power analysis

The effect size for the difference in the BMD (femoral T score) between the group B and control group was 4.31, which is calculated using the means and SDs of BMD group A and control group (-1.87 and -0.34 in both groups, respectively). The effect size of 4.31 indicated that a minimum sample size of 2 in each group would be required to detect the difference with 80% power at a 5% significance level. Given an anticipated dropout rate of 20%, a total of 3.2 patients was required in each group. Therefore, the sample size in group B (n = 4) was minimally satisfied to demonstrate that such a difference existed.
Table 1. Characteristic of diabetic neuropathic arthropathy group and control group (diabetic foot with neuropathy patient group)

| Variables                          | DNOAP group (n=25) | Control group (n=30) |
|------------------------------------|--------------------|----------------------|
| Diabetes type                      |                    |                      |
| Type 1                             | 5                  | 8                    |
| Type 2                             | 20                 | 22                   |
| Diabetes duration (yr)             | 16.4               | 10.1                 |
| Diabetes treatment                 |                    |                      |
| Insulin                            | 8                  | 9                    |
| Oral hypoglycemic                  | 12                 | 18                   |
| Diet and exercise                  | 1                  | 3                    |
| No treatment                       | 4                  | 0                    |
| Charcot stage                      |                    |                      |
| Stage 1                            | 6                  | -                    |
| Stage 2                            | 15                 | -                    |
| Stage 3                            | 3                  | -                    |
| Unknown                            | 1                  | -                    |
| Charcot location^a                  |                    |                      |
| Lisfranc                           | 16                 | -                    |
| Hindfoot                           | 4                  | -                    |
| Forefoot                           | 7                  | -                    |
| Ankle                              | 8                  | -                    |
| Wagner classification              |                    |                      |
| Grade 1/2                          | -                  | 21                   |
| Grade 3                            | -                  | 7                    |
| Grade 4/5                          | -                  | 2                    |

The data is presented as number.
^aSome feet had more than one site of involvement.
DNOAP, diabetic neuropathic osteoarthropathy.

RESULTS

Total 25 patients of DNOAP group and 30 patients of control group were included in this study. And diabetes duration was 16.4 years in DNOAP and 10.1 years in control group. Oral hypoglycemic was the most common diabetic treatment in both groups. In the DNOAP group, the charcot stage 2 was most common, and Lisfranc joint was most common location. In the control group, Grade 1 or 2 was the most marked in Wagner classification (Table 1).

Table 2. Patients’ demographics

|                              | DNOAP group (n=25) | Control group (n=30) |
|------------------------------|--------------------|----------------------|
| Age (yr)                     | 70.8 (63 to 88)    | 71 (65 to 87)        |
| Sex                          |                    |                      |
| Male                         | 9                  | 11                   |
| Female                       | 16                 | 19                   |
| BMI                          | 26.9 ± 6.32        | 27.2 ± 5.94          |
| Comorbidity                  |                    |                      |
| Hypertension                 | 24                 | 30                   |
| Ischemic heart disease       | 10                 | 15                   |
| Retinopathy                  | 4                  | 4                    |
| Nephropathy                  | 7                  | 6                    |
| Peripheral arterial disease  | 12                 | 15                   |

The data is presented as mean ± standard deviation, median (range), or number.
DNOAP, diabetic neuropathic osteoarthropathy; BMI, body mass index.

Fig. 2. Radiographic findings of diabetic neuropathic osteoarthropathy. (A) Weight bearing foot anteroposterior view. (B) Weight bearing foot lateral view.
All patients with DNOAP were diagnosed after lower limb fracture or deformity (Fig. 2). Subgroup B patients were found while undergoing diabetic foot management. In the DNOAP group, diabetic and other complications follow, 24 patients showed hypertension disease, 10 ischemic heart disease (IHD) patients, 4 retinopathy patients, 7 nephropathy patients, and 12 peripheral arterial disease (PAD) patients. And for the control group, 30 patients with hypertension and other diabetic complications such as IHD patients, 4 retinopathy patients, 6 nephropathy patients and 15 patients with PAD. The DNOAP patient group and control group did not show significant differences in patient demographics such as age, sex, and body mass index (BMI; Table 2).

The DNOAP group showed poor radiological results. In the weight-bearing foot lateral view, both the lateral talo-1st metatarsal angle and calcaneal pitch were significantly lower in the DNOAP group (P<0.01), and in the weight-bearing foot AP view, the AP talo-1st metatarsal angle and navicular coverage angle were also meaningfully lower compared to the control group (P<0.05). SF-36 level appeared low to the diabetic neuropathic group in all sections except pain (P<0.05; Table 3). There was no statistically significant difference regarding descriptive data and laboratory data between both groups (Table 4).

DNOAP group showed a significantly lower median lumbar T score and Z score compared with control group. However, the femur T score showed significantly different in the logistic regression analysis (Table 5).

The ROC curve showed that femur T score was useful to determine cut-off values for DNOAP (P<0.05; Fig. 3). The area under the curve for femur T score was 0.755 (0.589-0.921), and the appropriate cut-off value was -1.65.

### Table 3. Comparison of radiographic and clinical result between diabetic neuropathic arthropathy group and control group

| Radiographic result                  | DNOAP group | Control group | P-value |
|--------------------------------------|-------------|---------------|---------|
| Foot lateral view                    |             |               |         |
| Lateral talo-1st metatarsal angle    | 17.5±6.4    | 3.3±4.9       | <0.01   |
| Calcaneal pitch                      | 16.3±3.6    | 22.8±4.7      | <0.01   |
| Weight bearing foot anteroposterior view | 11.5±5.8    | 15.9±4.1      | <0.05   |
| AP talo-1st metatarsal angle         | 22.3±6.7    | 10.4±4.2      | <0.01   |
| Navicular coverage angle             |             |               |         |

The data is presented as mean ± standard deviation. DNOAP, diabetic neuropathic osteoarthritis; AP, anteroposterior; SF-36, short form-36; PCS, physical component summary; MCS, mental component summary; ag, age- and gender-adjusted; NS, not significant.

### Table 4. Laboratory results of diabetic neuropathic arthropathy group and control group

|                     | DNOAP group | Control group | P-value |
|---------------------|-------------|---------------|---------|
| SBP                 | 135.8±15.5  | 134.7±14.9    | 0.57    |
| DBP                 | 82.2±9.8    | 82.6±8.8      | 0.54    |
| FBS                 | 156.4±43.5  | 151.3±48.8    | 0.18    |
| 2hrpp               | 208.2±62.1  | 204.7±63.3    | 0.63    |
| HbA1c               | 8.82±1.1    | 8.79±1.32     | 0.81    |
| Ca                  | 9.5±0.6     | 9.2±0.6       | 0.38    |
| Po4                 | 4.12±0.8    | 4.13±0.9      | 0.82    |
| ALP                 | 220.8±85.7  | 227.8±79.6    | 0.88    |

The data is presented as mean ± standard deviation. Stands for P<0.01 highly significant.

### Table 5. Comparisons of bone mineral density between diabetic neuropathic osteoarthropathy group and diabetic foot with neuropathy

|                     | DNOAP group | Control group | P-value<sup>a</sup> | P-value (OR [95% CI])<sup>b</sup> |
|---------------------|-------------|---------------|----------------------|----------------------------------|
| T score             |             |               |                      |                                  |
| Spine 2-5           | -1.77 (IQR = 1.98) | -1.14 (IQR = 2.11) | 0.023                | 0.428 (1.12 [0.99 to 1.27])     |
| Femur               | -1.96 (IQR = 1.72) | -0.34 (IQR = 2.55) | <0.001               | <0.05 (1.96 [1.59 to 2.44])     |
| Z score             |             |               |                      |                                  |
| Spine 2-5           | -1.11 (IQR = 2.27) | -0.71 (IQR = 2.12) | 0.024                | 0.372 (1.05 [0.94 to 1.18])     |
| Femur               | -1.48 (IQR = 2.08) | -0.69 (IQR = 2.46) | 0.022                | 0.185 (1.04 [0.84 to 1.30])     |

Stands for P<0.05 significant.

<sup>a</sup>Comparison of both group using Mann-Whitney test.  <sup>b</sup>Logistic regression analysis

DNOAP, diabetic neuropathic osteoarthropathy; IQR, interquartile range; OR, odds ratio; CI, confidence interval.
DISCUSSION

Osteoporosis has been considered as a major risk factor in the development of DNOAP.[14] There is evidence that a higher risk of fractures can happen to the patients suffering from diabetes mellitus.[17] Mixed with the frequent fractures in DNOAP foot, this has led to the idea that low BMD may affect neuropathic arthropathy development. [2,17] Reduced peripheral, but not axial BMD, has been indicated in patients with neuropathic arthropathy.[9,13,17] A causal relationship between neuropathic arthropathy and regional osteopenia has been considered. And recently, diabetes is the main cause of neuropathic arthropathy. The purpose of this paper is to figure out whether BMD is significantly lower in DNOAP patients with fractures at foot and ankle levels, and a chance of it as risk predictor.

Analysis of BMD and neuropathic osteoarthropathy patients was done in previous studies.[10,18,19] There are 2 methods for measuring BMD of DNOAP: central BMD and calcaneal BMD measurement. Although calcaneal BMD has the benefit that it is been measured at a location adjacent to the progression of DNOAP disease, it reflects limited osseous demineralization of the peripheral part, various errors may occur due to patient specificity. Therefore, central BMD measurement is more meaningful than the calcaneal BMD, and also since changes according to DNOAP tend to show general osteoporosis in patients, this study performed central BMD measurement. Furthermore, the previous investigations of BMD and DNOAP in patients with diabetes have compared patients with a control group that consisted of healthy volunteers but have not compared patients with DNOAP with a control group of patients with diabetes mellitus (DM) without neuropathy. Until now, progression of DM foot patients with neuropathy to DNOAP was unclear. There are multiple factors, but it is common for the patient to be diagnosed because of fractures in the lower limb. This paper is meaningful because comparison of DNOAP patients and DM foot patients with neuropathy were done, and also this is the first study to present BMD values for prediction of DNOAP.

In this study, at least one foot and ankle fracture was accompanied in all DNOAP patients, and clear medial foot arch disappearance was confirmed. It should be noted that patients with this pattern are more likely to develop additional fractures or progress to osteomyelitis, which can lead to amputation. Therefore, as the study result suggests, Low

![Fig. 3. Receiver operator characteristic curve of femur T-score to predict diabetic neuropathic osteoarthropathy for diabetic foot patient with neuropathy.](image-url)
femoral T score in patients with DNOAP group with foot and ankle fracture requires careful monitoring in diabetic foot patients with neuropathy.

On the other hand, there are many reports that the reduction of BMD is significant in diabetic patients.[6] In the control group, the mean BMD was lower than the age average in both T-score and Z-score. However, even lower BMD was observed in the DNOAP group. It is thought to be pronounced deficiency in systemic BMD rather than site-specific among the neuropathic arthropathy fracture groups reported by Herbst et al. [14]. It is predicted that while progression of the diabetic foot to DNOAP. Systemic changes occur which lead to neuropathic osteoarthropathy.

There have been several studies analyzing risk factors in DNOAP. Age is a debated but associated risk factor with DNOAP. Petrova et al. [20] reported the Charcot neuropathy typically presents in patients with diabetes during age between fifties and sixties. Other studies report the most patients with DNOAP in their sixth and seventh decades. [21,22] Fauzi et al. [23] and Nobrega et al. [24] reported that age below 60 and 55 years were significant risk factors for DNOAP individually. Most studies showed the ratio of DNOAP in men and women was approximately the same and difference by sex is not definite.[25] However, Nehring et al. [26] reported that male gender was more likely to suffer from DNOAP. Whether weight is associated with increased risk of DNOAP was yet to be argued. Some studies reported positive correlations.[26-28] However, no association was found in other studies between DNOAP and a BMI of more than 25 kg/m².[23,29]

Most studies confirmed that the diabetes duration was a risk factor for DNOAP occurrence.[23,25,29] However, the demographic features of patients with type 1 and type 2 diabetes developing the DNOAP showed type differences. [16] Patients with type 1 had a longer duration of diabetes than those with type 2, but developed Charcot at a younger age. Petrova et al. [20] included 83 patients, 44 with type 1 diabetes presented DNOAP mostly between 40 to 49 year, while 41 type 2 patients in 50 to 59 years; however, the type 1 patients developed DNOAP with a significantly longer duration than those with type 2 diabetes (24 ± 8.4 vs. 13 ± 8.1 years). Pakarinen et al. [27] reported the average duration of type 1 was 28 years, and that of type 2 was 14 years for 36 patients.

The relationship between BMD and DNOAP is not well known. It is unknown whether regional osteopenia is a result of the inflammatory process that accompanies the bone injury or is a risk factor for neuropathic joint disorders developments. Jones and Wolf [30] reported primary resorption of bone without subluxation, dislocation, and/or fracture in the active Charcot process.

Nonetheless, osteopenia, reduced bone stiffness, and decreased BMD in acute and chronic DNOAP patients have been confirmed radiographically.[14,20] Sinacore et al. [31] reported that inflammation in DNOAP might contribute to or exacerbate a rapid loss of BMD. The relation between BMD loss and immobilization or off-loading is still in question. Some studies reported the BMD might further decrease during casting and no weight bearing.[20] However, Pakarinen et al. [27] reported that for patients with acute DNOAP after 6 months of treatment, immobilization and off-loading does not lead to marked disuse osteoporosis. BMD of DNOAP is also different according to the pattern of initial destruction. Herbst et al. [14] divided 61 Charcot feet or ankles into three subtypes, fracture pattern, dislocation pattern, and combined fracture-dislocation pattern, and reported that the fracture pattern was associated with a peripheral deficiency of BMD, while the dislocation pattern was not. El Oraby et al. [32] analyzed the effects of BMD and PAD to the diabetes patients and DNOAP patients, focusing on type II DM patients. In this study, female gender, femur T score, and PAD were analyzed as significant risk factors. It showed that the femur T score was a significant risk factor for DNOAP, which is the same as this study. However, this paper was conducted to both type I and type II DM patients, and DM foot patients with neuropathy was chosen to be the control group instead of DM patients. Also, an optimal range through BMD analysis before DNOAP occurred is provided. Therefore, the importance of BMD monitoring in diabetic foot patients with neuropathy in the disease process can be explained in more detail.

In this study, femur T score -1.65 was calculated as optimal threshold in diabetic foot patients with neuropathy. This suggests that DM foot patients with neuropathy need more strict BMD management. Usually, under score of -1.0 is diagnosed as osteopenia and osteoporosis drugs is required, but in the DM foot patient with neuropathy,[33] and we should consider active osteoporosis drugs from T score below -1.65 to prevent progression of DM foot to DNOAP. Our study has several drawbacks. First, the sample size
of Group B sample size is small. This is because people who measured BMD within a year before DNOAP occurs were few. On the other hand, the overall DNOAP group is 25 cases, and it is hard to say that the number of DNOAPs is small because the occurrence of DNOAP is quite rare. Second, PAD was confirmed as a complication, but risk factor analysis was not performed. The reason is that the control group was a DM foot patient with neuropathy, many of whom had already had PAD, and the neuropathy was already considered to be accompanied by microvascular complications. Finally, the severity of foot and ankle fracture was not considered. As mentioned earlier, since DNOAP occurs rarely it is hard to divide into sub-group. The association between foot and ankle fracture severity and BMD in DNOAP patients will also be analyzed when the case is more recruited.

Nevertheless, in this study, DNOAP patients with foot and ankle fractures confirmed a low femoral T score. Treatment goal of acute-phase DNOAP patients with foot and ankle fracture is immobilization and stability of protection destructive component. However, diabetic foot patients with neuropathy need constant BMD monitoring before these dystrophic lesions occur.

CONCLUSIONS

Low BMD shows greater incidence in foot and ankle fracture patients associated with neuropathic arthropathy. And femur T score can be a risk predictor of diabetic neuropathic arthropathy for diabetic foot patients.

DECLARATIONS

Acknowledgments
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2018R1C15042849).

Ethics approval and consent to participate
This study was approved by the Inje University Seoul Paik Hospital Research Ethics Committee (PAIK2018-08-007).

Conflict of interest
No potential conflict of interest relevant to this article was reported.

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