Femoral Neck Width Predict Low Bone Mass in Patients with Multiple Hereditary Exostoses

Kazu Matsumoto (✉ mkazuu@gifu-u.ac.jp)

Gifu University

Hiroyasu Ogawa

Gifu University

Satoshi Nozawa

Gifu University

Haruhiko Akiyama

Gifu University

Research Article

Keywords: bone mineral density, femoral neck width, multiple hereditary exostoses, osteoporosis

Posted Date: February 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-209032/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Recent report revealed multiple hereditary exostoses (MHE) patients showed the osteoporosis. This study aimed to determine if proximal femur deformities can indicate low bone mass in MHE patients and to investigate the correlation between Z-score or T-score and hip geometry parameters.

Patients and Methods: Twenty MHE patients from unrelated families were included in this study. Bone mineral density (BMD) of both femoral neck ($n = 40$) was examined using dual-energy x-ray absorptiometry. We examined femoral neck axis length (FNAL), femoral head diameter (FHD), femoral neck width (FNW), femoral shaft width (FSW), and femoral neck angle (FNA) and calculated the femoral head-neck ratio (FHNR=FHD/FNW). We examined the correlation between these parameters and Z-score or T-score using linear regression analysis followed by Spearman rank correlation coefficient.

Results: Of the patients, 91.7% (22 of 24) male and 100% (16 of 16) female had a Z-score <0 in the femoral neck area. Results also showed that the femoral neck area of 62.5% (15 of 24) male and 56.3% (9 of 16) female patients are within the range for osteopenia. The femoral neck are of seven patients (17.5%) were found to be within the range for osteoporosis. These results suggest that MHE patients tend to have low bone mass. We found a significant correlation between FNW and Z-score ($r = -0.3924$, $P = 0.0123$), but there was no significant difference between Z-score and FNAL, FHD, FSW, NSA, and FHNR. We also found that there were significant differences between T-score and FNW and T-score and FHNR ($r = -0.4787$, $P = 0.0018$ and $r = 0.3636$, $P = 0.0211$, respectively). There was no significant difference between T-score and the other parameters.

Conclusions: We found that the femoral neck width significantly correlates with Z-score or T-score. These results suggest that the femoral neck width may be a reliable predicting factor of bone mineral density.

Background

Multiple hereditary exostoses (MHE) is a relatively rare autosomal dominant skeletal disorder characterized by the formation of multiple exostoses and skeletal deformities, including limb length discrepancy, forearm bowing deformities, lower-limb valgus deformities, and scoliosis [1–4]. The exostosin-1 (*EXT1*) and exostosin-2 (*EXT2*) genes, which encode heparan sulfate glycosyltransferases, are major causative genes in MHE [5, 6]. MHE is a rare genetic disorder with an estimated prevalence of 1/50,000 among Western countries, and men tend to be affected more frequently than women [7, 8]. Exostosis is a cartilage-capped benign bone tumour that typically originates from the metaphysis of long bones or from the surface of flat bones. The symptoms are very frequently related to the tumour size, and some patients may undergo multiple surgeries during their life in an attempt to relieve the symptoms of this disorder [9]. The risk of malignant transformation toward chondrosarcoma, which is the most serious complication, occurs in 0.38–7.0% of patients [9–12].

Osteoporosis is a disease which causes bone fragility characterized by low bone mineral density and altered bone microstructure. Previously, Lemos et al. reported an association between MHE and

osteoporosis in Australian kindred with an *EXT1* splice site mutation [13]. Recently, several mice models were established, and understanding of MHE has advanced. Nozawa et al. reported that heparan sulfate (HS) regulates bone mass by interacting with osteoprotegerin and found that heparan sulfate modified transgenic mouse have low bone mass [14]. Recently, Matsumoto et al. reported that two-thirds of MHE patients exhibit osteopenia and have low bone mass in their femoral neck area [15]. However, there were no abnormalities in their bone metabolic factors which indicates that the low bone mass in their femoral neck may be due to the deformities related to exostoses.

Therefore, in this retrospective cohort study, we hypothesized that proximal femur deformities can be indicated by the low bone mass in MHE patients and investigated the correlation between osteopenia and femoral neck deformities.

Methods

Participants

All the MHE patients included in this study were from unrelated families. They were diagnosed with MHE and were followed up at the Department of Orthopedic Surgery of our University Hospital from April 2010 to March 2019. Information, such as age, ethnicity, menstrual status, medication history, and disease history, was obtained via questionnaire. The exclusion criteria were postmenopausal at the time of Bone Mineral Density (BMD) measurement, hip surgery history, and under 20 or over 50 years old. Twenty-six patients were eligible. None of the female subjects were postmenopausal at the time of BMD measurement. Patients who lacked data, including BMD measurement or hip X-ray, were also excluded. Finally, 20 MHE patients (40 hip joints) were enrolled in this study. The Ethics Committee of our University approved all procedures (Approval No. 22-221), and all participants provided written informed consent before any research procedure.

BMD Measurement

Both femoral neck ($n = 40$) was examined using dual-energy x-ray absorptiometry (DEXA) (Lunar DPX-NT, GE Healthcare, Japan). BMD and T-score were obtained from the measurements using the manufacturer's software (enCORE, GE Healthcare, Japan). BMD data were compared with reference values for normal Japanese populations of corresponding age and sex published by the Japanese Society for Bone and Mineral Research [14]. The enCORE reference database was used to determine the T-score for the femoral neck. Osteopenia was defined as a T-score between -1 and -2.5 while osteoporosis was defined as a score of -2.5 or lower, according to the criteria of the World Health Organization (WHO) [16]. The Z-score or the number of standard deviations above or below the mean for an age-matched population, was also analysed.

Hip Geometry Measurement

The hip geometry measurements are shown in **Figure 1**. Hip radiographs were taken for the clinical investigation of tumours around the hip to detect hip deformities caused by tumours, malignant transformation, and hip osteoarthritis. Anteroposterior radiographs were used to evaluate the shape of the proximal femur. We examined femoral neck axis length (FNAL) or the distance from the centre of the femoral head to the intersection of the neck and shaft axes, femoral head diameter (FHD), femoral neck width (FNW), femoral shaft width (FSW), and femoral neck angle (FNA) or the angle between derived axes of the neck and shaft. We also calculated the femoral head-neck ratio (FHDR=FHD/FNW) and examined the correlation between these parameters and BMD, Z-score, or T-score.

Statistical Analysis

All parameters were reported as mean $\pm$ standard deviation. Differences between the groups were compared using the Chi-square test for qualitative data. Correlations between BMD, Z-score, or T-score and hip geometry measurements and ratio were analysed using linear regression analysis followed by Spearman rank correlation coefficient. These analyses were performed using GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, CA, USA). A P value < 0.05 was considered significant.

Results

Patient Background

We examined the BMD parameters of 20 MHE patients, 12 male and 8 female, using DEXA. The mean age was 39.7 years for male (range: 29–48 years; $n = 12$) and 36.6 years (range: 29–45 years; $n = 8$) for female. The mean femoral neck BMD value was 0.725 g/cm² for male (range: 0.542–1.029 g/cm²; $n = 24$) and 0.720 g/cm² for female (range: 0.508–0.919 g/cm²; $n = 16$). There was no significant difference in the femoral neck BMD values between male and female ($P = 0.315$) (**Table 1**). There were also no significant differences in the Z-scores and T-scores between male and female (**Table 1**).

We analysed femoral neck area Z-score and T-score and found that 91.7% (22 of 24) of male and 100% (16 of 16) of female patients had a Z-score < 0 in the femoral neck area (**Figure 2A**). According to the WHO criteria, 62.5% (15 of 24) of the male patients and 56.3% (9 of 16) of the female patients are within the range of osteopenia (**Figure 2B**). Three male and four female patients (17.5%) were within the range to have osteoporosis in the femoral neck area. We examined the differences in Z-score and T-score of the male and female patients but found no significant differences (**Figure 2**).

Correlation between Z-score or T-score and Hip Geometry Parameters

We examined the correlation between Z-score and the hip geometry parameters. The mean value of FNAL was 99.4 ± 10.1 mm and there was no significant difference between FNAL and Z-score ($r = -0.0334$, $P = 0.8374$, **Figure 3A**). The mean value of FHD and FNW were 51.3 ± 4.6 mm and 48.4 ± 11.7 mm, respectively. There was no significant difference between Z-score and FHD ($r = 0.0977$, $P = 0.5488$, **Figure 3B**), but there was a significant difference between Z-score and FNW ($r = -0.3924$, $P = 0.0123$, **Figure 3C**). The mean value of FSW and NSA were 33.5 ± 3.3 mm and 136.4 ± 7.5 degrees, respectively. There was no significant difference between Z-score and FSW and between Z-score and NSA ($r = 0.0936$, $P = 0.5658$ and $r = -0.1047$, $P = 0.5203$, respectively) (**Figure 3D-E**). The mean value of FHNR was 1.11 ± 0.3 and there was no significant difference between Z-score and FHNR ($r = 0.1640$, $P = 0.3120$, **Figure 3F**).

We further analysed the correlation between T-score and the hip geometry parameters. There was no significant difference between T-score and FNAL and between T-score and FHD ($r = -0.0088$, $P = 0.9569$ and $r = -0.1234$, $P = 0.4482$, respectively) (**Figure 4A-B**). There was a significant difference between T-score and FNW and between T-score and FHNR ($r = -0.4787$, $P = 0.0018$ and $r = 0.3636$, $P = 0.0211$) (**Figure 4C, 4F**). There was no significant difference between T-score and FSW and between T-score and NSA ($r = 0.0273$, $P = 0.8668$ and $r = -0.2074$, $P = 0.1992$) (**Figure 4D-E**).

Discussion

In this study, we examined the BMD and the correlation between Z-score or T-score and geometry parameters of the proximal femur. We found that three-fourths of MHE patients show a range of osteopenia or osteoporosis and that femoral neck width significantly correlates with Z-score and T-score. These results suggest that femoral neck width may be a reliable predicting factor of bone mineral density.

MHE is an autosomal dominant disorder mainly caused by germline and heterozygous mutations in *EXT1* and *EXT2*. MHE exhibits formation of multiple exostoses and skeletal deformities, including limb length discrepancy, forearm bowing deformities, lower-limb valgus deformities, and scoliosis [1–4]. Several mice models for this disease were established recently and understanding of this disease has been gradually advancing [3, 17, 18]. Nozawa S et al. reported that heparan sulfate (HS) regulate bone mass by interacting with osteoprotegerin and reduced bone mineral density in mice model [17]. However, there is few information about bone mineral density in MHE patients. Recently, Matsumoto et al. reported that MHE patients have low bone mass in the lumbar spine and femoral neck area [15]. In this study, the bone mineral density of most MHE patients in their femoral neck area (31 out of 40 hips) were within osteopenia or osteoporosis range.

Osteoporosis is a common disease characterized by reduced bone mass. The primary pathogenic mechanism of osteoporosis is an imbalance between bone formation and bone resorption, which are mediated by osteoclasts and osteoblasts, respectively. Recently, Matsumoto et al. reported that serum osteocalcin and urine NTx, the markers of bone formation and bone resorption, respectively, are within normal range in almost all MHE patients [15]. These results suggest low bone mass in this disease might not be due to the alterations in bone metabolism. Therefore, we hypothesized that the low bone mass in

MHE patients may be due to developmental abnormalities, such as proximal femur deformities, caused by the development of exostoses.

Hip exostoses are present in a high percentage of MHE patients, mainly in the proximal femur, which they have been reported in 30% to 90% of patients [19-21]. Furthermore, Duque Orozco et al. reported that hip exostoses were found in 90% of patients, and their most common location was the femoral neck [22]. In this study, we focused on the hip geometry parameters and examined the correlation between these parameters and Z-score or T-score. Interestingly, there was no significant correlation between Z-score or T-score and femoral neck axis length, femoral head width, femoral shaft width, and neck shaft angle. Only femoral neck width was found to have a significant correlation with Z-score and T-score. As we have mentioned above, femoral neck is the frequent site for exostoses. Taken together, these facts suggest that the low bone mass of MHE patients is not due to abnormal bone metabolism, but to the development of exostoses.

Although exostoses around the hip are often asymptomatic, they can produce various deformities including hip dysplasia, subluxation, impingement, and premature osteoarthritis [20, 23-25]. In this study, we focused on these characteristic deformities and examined the correlation between various hip geometry parameters and BMD. We found that the femoral neck width may be one reliable predictor of low bone mass. These results suggest that the wider the femoral neck is, the lower the bone mass. These data support the hypothesis that the low bone mass in MHE patients may be due to the deformities caused by exostoses. However, MHE patients show various deformities including hip dysplasia and subluxation. These deformities may alter normal weight bearing and may affect bone mineral density. The mechanisms that lead to low bone mass in MHE patients are still unclear and more evidence are needed to elucidate them.

There are several limitations in this study. First, there is a limited number of MHE patients from only one institution. Second, we did not evaluate the deformities in the lower legs which may affect the degree of low bone mass in these patients. However, this is the first report where the relationship between BMD and hip geometry parameters in MHE patients was examined in detail. When a wide femoral neck is observed, we should suspect low bone mass in the patients. These results could provide useful information in understanding the mechanisms of MHE.

Conclusions

We found that the femoral neck width significantly correlates with Z-score or T-score. These results suggest that the femoral neck width may be a reliable predicting factor of bone mineral density in MHE patients.

List Of Abbreviations

MHE: Multiple hereditary exostoses, *EXT1*: exostosin-1, *EXT2*: exostosin-2, HS: heparan sulfate, BMD: Bone Mineral Density, DEXA: dual-energy x-ray absorptiometry, WHO: World Health Organization, FNAL: femoral neck axis length, FHD: femoral head diameter, FNW: femoral neck width, FSW: femoral shaft width, FNA: femoral neck angle, FHNR: femoral head-neck ratio

Declarations

All methods were carried out in accordance with relevant guidelines and regulations.

Ethics approval and consent to participate

The Ethics Committee of our University approved all procedures (Approval No. 22-221), and all participants provided written informed consent before any research procedure.

Consent for publication

All participants accepted the publication.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors have no conflict of interests.

Funding

No fundings.

Authors' contributions

KM, and HA prepare the manuscript, and KM, HO, and SN collected and analysed the data.

Acknowledgements

N/A

References

1. Akita S, Murase T, Yonenobu K, Shimada K, Masada K, Yoshikawa H. Long- term results of surgery for forearm deformities in patients with multiple cartilaginous exostoses. J Bone Joint Surg Am.

- 2007;89(9):1993–9.
2. Matsumoto Y, Matsumoto K, Harimaya K, Okada S, Doi T, Iwamoto Y. Scoliosis in patients with multiple hereditary exostoses. *Eur Spine J.* 2015;24:1568–73.
 3. Matsumoto K, Irie F, Mackem S, Yamaguchi Y. A mouse model of chondrocyte-specific somatic mutation reveals a role for Ext1 loss of heterozygosity in multiple hereditary exostoses. *Proc Natl Acad Sci U S A.* 2010;107(24):10932–7.
 4. Ishimaru D, Gotoh M, Takayama S, Kosaki R, Matsumoto Y, Narimatsu H, Sato T, Kimata K, Akiyama H, Shimizu K, Matsumoto K. Large-scale mutational analysis in the EXT1 and EXT2 genes for Japanese patients with multiple osteochondromas. *BMC Genet.* 2016;9:17:52.
 5. Ahn J, Ludecke HJ, Lindow S, Horton WA, Lee B, Wagner MJ, Horsthemke B, Wells DE. Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (EXT1). *Nat Genet.* 1995;11(2):137–43.
 6. Stickens D, Clines G, Burbee D, Ramos P, Thomas S, Hogue D, Hecht JT, Lovett M, Evans GA. The EXT2 multiple exostoses gene defines a family of putative tumour suppressor genes. *Nat Genet.* 1996;14(1):25–32.
 7. Schmale GA, Conrad 3rd EU, Raskind WH. The natural history of hereditary multiple exostoses. *J Bone Joint Surg Am.* 1994;76(7):986–92.
 8. Bovee JV. Multiple osteochondromas. *Orphanet J Rare Dis.* 2008;3:3.
 9. Czajka CM, DiCaprio MR. What is the Proportion of Patients With Multiple Hereditary Exostoses Who Undergo Malignant Degeneration? *Clin Orthop Relat Res.* 2015;473:2355–61.
 10. Goud AL, de Lange J, Scholtes VA, Bulstra SK, Ham SJ. Pain, physical and social functioning, and quality of life in individuals with multiple hereditary exostoses in The Netherlands: a national cohort study. *J Bone Joint Surg Am.* 2012;94(11):1013–20.
 11. Legeai-Mallet L, Munnich A, Maroteaux P, Le Merrer M. Incomplete penetrance and expressivity skewing in hereditary multiple exostoses. *Clin Genet.* 1997;52(1):12–6.
 12. Pedrini E, Jennes I, Tremosini M, Milanesi A, Mordenti M, Parra A, Sgariglia F, Zuntini M, Campanacci L, Fabbri N, Pignotti E, Wuyts W, Sangiorgi L. Genotype-phenotype correlation study in 529 patients with multiple hereditary exostoses: identification of “protective” and “risk” factors. *J Bone Joint Surg Am.* 2011;93(24):2294–302.
 13. Lemos MC, Kotanko P, Christie PT, Harding B, Javor T, Smith C, Eastell R, Thakker RV. A novel EXT1 splice site mutation in a kindred with hereditary multiple exostosis and osteoporosis. *J Clin Endocrinol Metab.* 2005;90(9):5386–5392.
 14. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H. Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research. Diagnostic criteria for primary osteoporosis: year 2000 revision. *J Bone Miner Metab.* 2001;19(6):331–337.
 15. Matsumoto K, Ogawa H, Nozawa S, Akiyama H. An Analysis of Osteoporosis in Patients with Hereditary Multiple Exostoses. *Osteoporosis Int.* 2020;31(12):2355-2361.

16. [No authors listed]. Prevention and management of osteoporosis. World Health Organ Tech Rep Ser. 2003;921:1–164.
17. Nozawa S, Inubushi T, Irie F, Takigami I, Matsumoto K, Shimizu K, Akiyama H, Yamaguchi Y. Osteoblastic heparan sulfate regulates osteoprotegerin function and bone mass. JCI Insight. 2018;8;3(3):e89624.
18. Inubushi T, Nozawa S, Matsumoto K, Irie F, Yamaguchi Y. Aberrant perichondrial BMP signaling mediates multiple osteochondromagenesis in mice. JCI Insight. 2017;2(15):e90049.
19. Felix NA, Mazur JM, Loveless EA. Acetabular dysplasia associated with hereditary multiple exostoses. A case report. J Bone Joint Surg Br. 2000;82:555–557.
20. Solomon L. Chondrosarcoma in hereditary multiple exostosis. S Afr Med J. 1974;48:671–676.
21. Schmale GA, Conrad EU III, Raskind WH. The natural history of hereditary multiple exostoses. J Bone Joint Surg Am. 1994;76:986–992.
22. Duque Orozco MDP, Abousamra O, Rogers KJ, Thacker MM. Radiographic Analysis of the Pediatric Hip Patients With Hereditary Multiple Exostoses (HME). J Pediatr Orthop. 2018;38(6):305–311.
23. Makhdum AM, Jiang F, Hamdy RC, Benaroch TE, Lavigne M, Saran N. Hip joint osteochondroma: systematic review of the literature and report of three further cases. Adv Orthop. 2014;180254.
24. Porter DE, Benson MK, Hosney GA. The hip in hereditary multiple exostoses. J Bone Joint Surg Br. 2001;83:988–995.
25. El-Fiky TA, Chow W, Li YH, To M. Hereditary multiple exostoses of the hip. J Orthop Surg (Hong Kong). 2009;17:161–165.

Table

Table 1. Patients Demographic Data			
	Male	Female	p value
Number	12	8	N/A
Age (yr)	39.7 ± 5.8	36.6 ± 5.2	0.403
BMD (g/cm ²)	0.749 ± 0.166	0.731 ± 0.167	0.315
Z-score	-1.313 ± 1.197	-1.475 ± 1.238	0.516
T-score	-1.392 ± 1.197	-1.575 ± 1.238	0.325

Figures

Figure 1

The hip geometry parameters are shown. AB: Femoral Neck Axis Length (FNAL), CD: Femoral Head Diameter (FHD), EF: Femoral Neck Width (FNW), GH: Femoral Shaft Width (FSW), I: Femoral Neck Angle (FNA)

Figure 2

Comparison of (A) Z-score and (B) T-score of the femoral neck area in MHE patients. There were no significant differences between male and female. A T-score between -1 to -2.5 indicates osteopenia while a T-score <-2.5 indicates osteoporosis.

Figure 3

Correlation between Z-score and the hip geometry parameters. FNW was significantly correlated with Z-score.

Figure 4

Correlation between T-score and the hip geometry parameters. FNW and FHNR were significantly correlated with T-score.