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Comparative Analysis of T-Score Discordance between a Registry-Based Korean Population and Atypical Femoral Fracture Patients of a Single Institution

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Background: The purpose of this study was to analyze the epidemiology of T-score discordance between the spine and femur in the South Korean population and compare the prevalence of T-score discordance between the Korean osteoporosis population and atypical femoral fracture (AFF) patients.

Methods: A total of 12,422 subjects from the Korea National Health and Nutrition Examination Survey were reviewed retrospectively. T-score discordance was defined as a difference of ≥ 1 standard deviation between the lumbar spine (LS) and femoral neck (FN) bone mineral density (BMD). The prevalence of T-score discordance (low LS [LS BMD < FN BMD], low FN [LS BMD > FN BMD], and total [low LS + low FN]) was investigated in the osteoporosis and non-osteoporosis groups and stratified by sex and age. T-score discordance of 63 patients with AFFs diagnosed at a single institution was compared with that of the Korean osteoporosis population using propensity score matching.

Results: T-score discordance was prevalent in the Korean osteoporosis population (44.8%), and low LS discordance (37.5%) was more frequently seen than low FN discordance (7.2%) ($p < 0.001$). The prevalence of total and low LS discordance was significantly higher in AFF patients than in the Korean osteoporosis population (total discordance: 69.8% and 42.5%, respectively; low LS discordance: 63.5% and 31.7%, respectively; $p < 0.001$).

Conclusions: T-score discordance was highly prevalent in the Korean osteoporosis population, and low LS discordance was more common than low FN discordance. Nevertheless, the prevalence of low LS discordance was significantly higher in AFF patients than in the Korean osteoporosis population.

Keywords: *T-score discordance, Atypical femoral fracture, Osteoporosis, Korean osteoporosis population*

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Although atypical femoral fractures (AFFs) are a rare disease that accounts for 0.26% to 2.95% of all femoral fractures,[1-4] they have been receiving constant interest since they occur in long-term bisphosphonate (BP) users who have not suffered any major trauma.[5,6] In addition to BP use, osteopenia or osteoporosis, rheumatoid arthritis, increased anterior/lateral femoral curvatures, and thicker lateral femoral cortex have been reported as risk factors for AFF.[4,7,8] However, the etiology of AFF still remains unknown.

Recently, Lee et al.[9] reported that the prevalence of T-score discordance was significantly higher in AFF cases than in intertrochanteric fracture cases and thus could be a risk factor for AFF. In particular, the majority of discordances showed a lower T-score of the lumbar spine (LS) than the femur. Weil et al.[10] also reported that bone mineral density (BMD) of the LS in AFF cases was significantly lower than that of the femoral neck (FN). Furthermore, in a similar study, Chou et al.[11] reported that femur BMD in AFF cases was significantly higher than that in osteoporotic femoral fracture cases.

On the other hand, T-score discordance has also been reported in the general population.[12-15] Hong et al.[14] reported that 12.9% of men aged ≥ 50 years and 10% of postmenopausal women in South Korea had differences in BMD. Additionally, Moayyeri et al.[15] reported BMD discordance in 41.7% out of 4,229 patients, and the majority of these patients (77.9%, with either major or minor discordance) had a lower BMD in the LS than in the total femur (TF). Thus, T-score discordance could be a general phenomenon observed during BMD assessment.

However, it is not yet clear whether there is a significant difference in T-score discordance between AFF patients and the general osteoporosis populations. Moreover, there have been only a limited number of comparative studies that have investigated differences in T-score discordance between these two groups. Additionally, registry data has been mostly analyzed using factors related to T-score discordance, and many did not divide the discordance into distinct groups such as LS BMD < femur BMD and LS BMD > femur BMD.

Therefore, the purpose of this study was to (1) analyze the epidemiology of T-score discordance between the spine and femur in the Korean population and (2) compare the prevalence of T-score discordance between the osteoporosis population and AFF patients from a single institution using propensity score matching. We hypothesized that the prevalence of low low LS/high FN T-score discordance would be significantly higher in AFF patients than in the general Korean osteoporosis population.

METHODS

The study related with AFF patients of our hospital was approved by the Institutional Review Board of SMG-SNU Boramae Medical Center (IRB No. 20-2021-51). Informed consent was waived by the Board because of its retrospective nature. All studies were carried out in accordance with the relevant guidelines and regulations.

Data Collection

This study was conducted using registry data acquired from the Korea National Health and Nutrition Examination Survey (KNHANES IV and V) performed between 2008 and 2011. The KNHANES is a nationwide cross-sectional survey conducted annually by the Korea Disease Control and Prevention Agency since 1998. Samples are stratified and extracted to represent the entire country. Data of a total of 12,422 participants aged ≥ 40 years (5,354 men and 7,068 women; age, 58 ± 11.5 years), consisting of 9,207 without osteoporosis and 3,215 with osteoporosis were available, and their characteristics such as age, height, weight, body mass index (BMI), and T-scores for the LS and FN were collected retrospectively. All participants provided informed consent before registering for the survey. The study related with registry data (KNHANES) was approved for exemption by the IRB of SMG-SNU Boramae Medical Center and conducted in accordance with the relevant guidelines and regulations.

In addition, medical records of 169 patients diagnosed with AFF from a single institution between 2010 and 2021 were reviewed retrospectively. The inclusion criteria were as follows: (1) treated with BP therapy for at least 3 years before AFF, (2) underwent dual X-ray absorptiometry (DXA) within 1 month before and after AFF, and (3) met

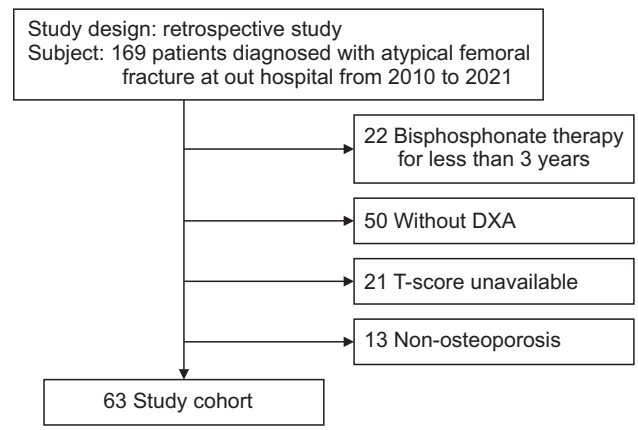

Fig. 1. Patient enrollment flowchart.

the criteria for diagnosing osteoporosis (Fig. 1). Overall, a total of 63 patients (1 men and 62 women; age, 73.7 ± 7.4 years) were enrolled in the AFF group, and their demographic data, fracture site, the average duration of BP therapy, and T-scores for the LS and FN were collected. The average duration of BP therapy was 70 ± 24 months, while subtrochanteric and diaphyseal fractures accounted for 30% and 70% of all AFFs, respectively.

BMD Measurement

The BMD values of the participants registered in the KNHANES database and of the AFF patients in our hospital were measured at the LS (L1–L4), FN, and TF by DXA using the Hologic QDR4500A (Hologic Inc., Waltham MA, USA) and Lunar DPXMD densitometer (GE Healthcare, Madison WI, USA). The precision errors for BMD measurements of both instruments were 1.9% and 1.5% in the LS and 1.8%–2.5% and 1.3%–2.2% in the femoral regions. To calibrate the BMD values of the AFF patients (from Lunar) to the KNHANES data (from Hologic), a cross-calibration equation as per a previous study[16] was applied.

T-score was standardized using the reference value provided by the World Health Organization (WHO).[13] The T-score of FN was generated by comparing the FN BMD values of the subjects with reference FN BMD values of Caucasian women aged 20–29 years derived from the National Health and Nutrition Survey III.[17,18] The T-score of LS was generated by comparing the LS BMD values of the subjects with reference LS BMD values of Caucasian women aged 20–29 years derived from Hologic.[18,19]

Osteoporosis was diagnosed based on the definition provided by the WHO: the lowest T-score among the FN, TF, and LS should be –2.5 or less, provided the T-scores of the FN and TF were measured in the unfractured femur.

Data Analysis

T-score discordance was defined as a difference of ≥ 1 standard deviation between the LS and FN BMD[13,20] and was divided into three categories: low LS discordance (LS BMD < FN BMD), low FN discordance (LS BMD > FN BMD), and total discordance (low LS discordance + low FN discordance).

To evaluate the epidemiology of T-score discordance between the spine and femur in the Korean population, the prevalence of low LS, low FN, and total discordances was investigated in the osteoporosis and non-osteoporosis groups and stratified by sex and age. In addition, to understand the difference in T-score discordance among age groups, the T-score values of the LS and FN were also analyzed separately and stratified by sex and age.

Finally, to evaluate whether there was a significant difference in T-score discordance between the general Korean osteoporosis population and AFF patients, the prevalence of discordance was compared between the two groups. The mean T-score values of LS and FN were also analyzed between the two groups.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Chi-square test was used to determine whether there was a significant difference in T-score discordance, while a Student *t*-test and Mann-Whitney test were used to evaluate the difference in mean T-score between the groups. Propensity score matching was used to evaluate the difference in the prevalence of T-score discordance between the general Korean osteoporosis population and AFF patients. Furthermore, 63 AFF patients were matched to the 252 subjects with osteoporosis after a 1 : 4 propensity score matching for age, sex, height, weight, and BMI.

RESULTS

T-score discordance was highly prevalent in the Korean population, especially in those with osteoporosis (osteoporosis: 44.8%; non-osteoporosis: 27.1%, $p < 0.001$), and low LS discordance was more frequently observed than low FN discordance (low LS: 37.5%; low FN: 7.2%, $p < 0.001$) in those with osteoporosis (Table 1). Men showed significantly higher prevalence of total T-score discordance than did women (men: 57.8%; women: 41.4%, $p < 0.05$). Furthermore, when the osteoporosis population was stratified according to age group, the total as well as low LS discordance gradually decreased with age (Fig. 2). This finding was associated with a greater decrease in the FN T-score with age than in the LS T-score (Fig. 3).

In the propensity score matching analysis, the prevalence of total and low LS discordance in the AFF patients was significantly higher than that in the Korean osteoporosis population (total discordance: 69.8% vs. 42.5%, low LS discordance: 63.5% vs. 31.7%; $p < 0.001$) (Table 2). While low LS discordance in the AFF patients accounted for 91% of total discordance cases, it accounted for 74% of the cases in the osteoporosis population. In addition, the mean T-score of FN in the AFF patients was significantly higher than that in the osteoporosis population (–1.9 and –2.3, respectively, $p < 0.001$). However, there was no significant difference in LS T-scores between the two groups.

Table 1. Comparison of T-score Discordance (Spine vs. Femur Neck) According to Sex and Age between Non-osteoporosis Group and Osteoporosis Group

Variable	Non-osteoporosis group in KNHANES					Osteoporosis group in KNHANES					*p*-value		
		Discordance					Discordance						
	N	LS < FN	LS > FN	Total	Mean T-score (LS / FN)	N	LS < FN	LS > FN	Total	Mean T-score (LS / FN)	LS < FN	LS > FN	Total
Sex													
Male	4,700	696 (14.8)	737 (15.7)	1,433 (30.5)	–0.6 / –0.6	654	329 (50.3)	49 (7.5)	378 (57.8)	–2.9 / –2.1	-	-	-
Female	4,507	253 (5.6)	806 (17.9)	1,059 (23.5)	–0.9 / –1.1	2,561	877 (34.2)	184 (7.2)	1,061 (41.4)	–3.2 / –2.6	-	-	-
Age													
40s	3,440	377 (11.0)	549 (16.0)	926 (27.0)	–0.5 / –0.6	151	83 (55.0)	3 (2.0)	86 (57.0)	–2.8 / –1.9	-	-	-
50s	2,727	338 (12.4)	369 (13.5)	707 (25.9)	–0.8 / –0.8	600	287 (47.8)	15 (2.5)	302 (50.3)	–2.9 / –2.0	-	-	-
60s	1,961	184 (9.4)	313 (16.0)	497 (25.4)	–1.0 / –1.1	1,068	437 (40.9)	56 (5.2)	493 (46.1)	–3.0 / –2.4	-	-	-
70s	954	43 (4.5)	271 (28.4)	314 (32.9)	–0.9 / –1.4	1,086	330 (30.3)	111 (10.2)	441 (40.5)	–3.1 / –2.7	-	-	-
80s	125	7 (5.6)	41 (32.8)	48 (38.4)	–0.8 / –1.5	310	69 (22.3)	48 (15.5)	117 (37.8)	–3.3 / –3.2	-	-	-
Total	9,207	949 (10.3)	1,543 (16.8)	2,492 (27.1)	–0.7 / –0.8	3,215	1,206 (37.5)	233 (7.2)	1,439 (44.8)	–3.1 / –2.5	< 0.001*	< 0.001†	< 0.001*

Values are presented as number (%).
KNHANES: Korea National Health and Nutrition Examination Survey, LS: lumbar spine, FN: femur neck, LS < FN: low LS discordance, LS > FN: low FN discordance, Total: total discordance including low LS discordance and low FN discordance.
*Discordance of osteoporosis group was higher than that of non-osteoporosis group. †Discordance of non-osteoporosis group was higher than that of osteoporosis group.

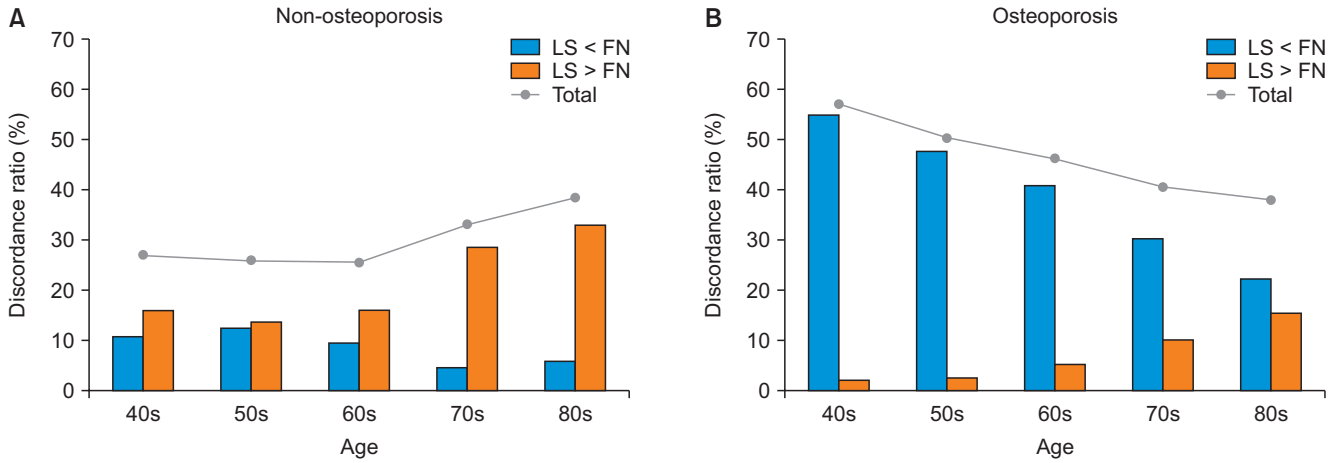

Fig. 2. (A) Change in T-score discordance according to age in patients without osteoporosis. (B) Change in T-score discordance according to age in patients with osteoporosis. LS: lumbar spine, FN: femur neck, LS < FN: low LS discordance, LS > FN: low FN discordance, Total: LS < FN + FN > LS.

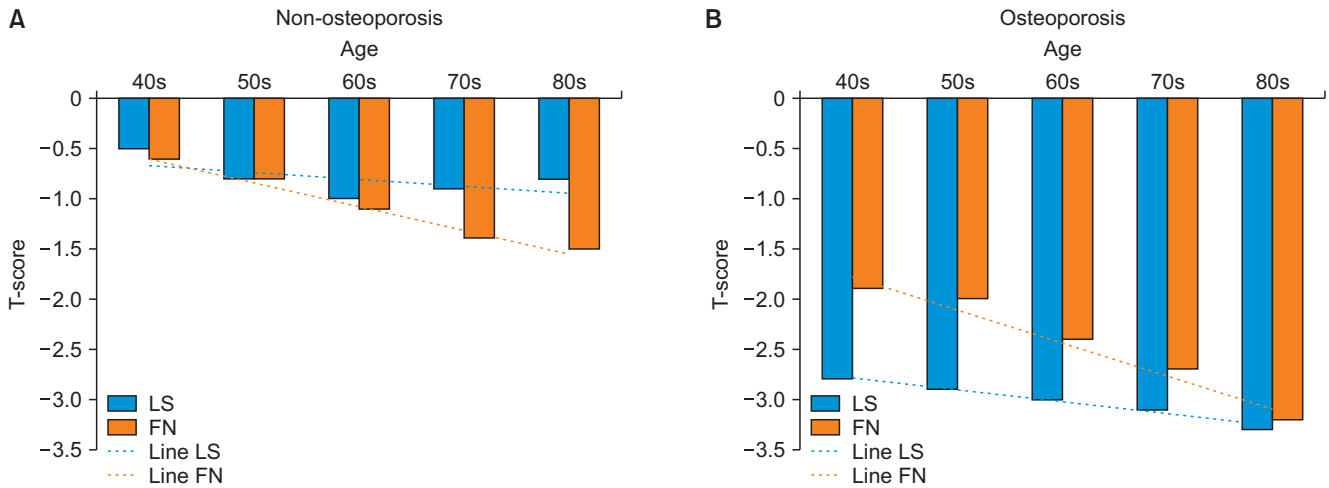

Fig. 3. (A) Change in mean T-score according to age in patients without osteoporosis. (B) Change in mean T-score according to age in patients with osteoporosis. LS: lumbar spine, FN: femur neck, LS < FN: low LS discordance, LS > FN: low FN discordance, Total: LS < FN + FN > LS.

DISCUSSION

The principal finding of this study is that even though T-score discordance was highly prevalent in the Korean population with osteoporosis, the prevalence of total and low LS T-score discordances in the AFF patients were significantly higher than that in the Korean population with osteoporosis. Our findings support the hypothesis that the prevalence of low LS T-score discordance would be significantly higher in AFF patients than in the Korean population with osteoporosis.

This study showed the high prevalence of T-score discordance and low LS discordance dominance in the Korean population with osteoporosis. According to previous studies, although T-score discordance was critically dependent upon the comparison site of the BMD (LS, FN, TF) and the definition of discordance, trends such as the high prevalence of T-score discordance and low LS discordance dominance were also observed in most countries (Table 3).[12-15,20-25] Mounach et al.[12] reported that T-score discordance was observed in 46% of 3,479 patients and that the majority of those patients (86.8%) had low LS discordance (40%). Seok et al.[20] also reported that T-score discordance was noted in 29.3% of 443 female patients and that the majority of those (73%) had low LS discordance (21.4%). This may be because cancellous bone, of which the vertebrae is mainly composed, has an accelerated metabolism and therefore might exhibit an earlier and more rapid loss than cortical bone, which is mainly present in the femur.[26] Thus, T-score discordance and low LS discordance dominance are general phenomena observed during BMD assessment, and our results reflect the phenomena.

Table 2. Propensity Score Matching between Patients with Atypical Femoral Fractures and Korean Osteoporosis Population

LS vs. FN	Atypical femoral fracture (n = 63)					Osteoporosis group in KNHANES (n = 252)					*p*-value		
	N	Discordance			Mean T-score (LS / FN)	N	Discordance			Mean T-score (LS / FN)	LS < FN	LS > FN	Total
		LS < FN	LS > FN	Total			LS < FN	LS > FN	Total				
	63	40 (63.5)	4 (6.3)	44 (69.8)	−3.1 / −1.9	252	80 (31.7)	27 (10.7)	107 (42.5)	−3.0 / −2.3	< 0.001*	0.298	< 0.001*

Values are presented as number (%).
KNHANES: Korea National Health and Nutrition Examination Survey, LS: spine, FN: femur neck, LS < FN: low LS discordance, LS > FN: low FN discordance, Total: total discordance including low LS discordance and low FN discordance.
*Discordance of the atypical femoral fracture group was higher than that of the osteoporosis group.

An interesting finding of this study is that the total and low LS T-score discordance in the Korean osteoporosis population gradually decreased with age (Fig. 2). Similar LS T-scores among age groups and a gradual decrease in FN T-score with age support this finding (Fig. 3). It can be attributed to different physiologic BMD change patterns between the spine and hip. The spine BMD reaches its peak and starts to decline 5 years or more earlier than does the hip BMD, which decreases relatively slowly.[27] Similarly, Singh et al.[25] reported that the mean age of patients with discordance (51.37 ± 8.87 years) was paradoxically lower than that of those without any discordance (53.11 ± 9.27 years). To the best of our knowledge, our study is the first to report a gradual change in T-score discordance with respect to age. Furthermore, T-score discordance was also different between sexes in this study, where men showed a higher prevalence of T-score discordance than did women. According to our study, not only the mean T-score of the spine but also the mean T-score of the FN tended to be smaller in women than in men. That is, the decrease in the mean T-score of the FN was smaller in men than in women (T-score of LS/FN in men and women: −2.9/−2.1 and −3.2/−2.6, respectively) (Table 1). The reason for this has not yet been clearly elucidated, and further study is needed.

Another important finding is that the prevalence of T-score discordance in the AFF patients was significantly higher than that in the Korean osteoporosis population. Lee et al.[9] reported that the prevalence of T-score discordance in 48 AFF patients who were long-term BP users (71%) was significantly higher than that in 114 intertrochanteric femoral fracture patients who were not BP user (23%). Nevertheless, it was not clear whether T-score discordance was a finding related to AFF occurrence or a common phenomenon observed in the general population. Considering that the prevalence of low LS discordance in the AFF patients (63.5%) was significantly higher than that in 3,215 Koreans with osteoporosis (37.5%), which persisted even after propensity score matching (252 participants with osteoporosis [31.7%] retained) in this study, low LS discordance does seem to be related to AFF occurrence. However, the pathomechanism remains unclear. A possible explanation could be the difference in response to BP therapy between the spine and the proximal femur.[28] It is well known that there is a risk of AFF in patients with long-term BP use. It was reported that bone turnover was severely suppressed in patients who used BP for a long time.[29] Long-term use of BP, an antiresorptive agent, induces an increased mineral content in bone tissue. The higher its tissue mineral content, the stiffer bone

Table 3. Summary of T-score Discordance in Population-Based Studies

Study	Definition of T-score discordance	Study cohort (no)	Age (yr)	Result (%)
Woodson[21] (2000, America)	LS vs. TF categorical*	Female: 5,051	-	Total discordance†: 44, low LS discordance‡: 19, low LS / total: 43.2
Moayyeri et al.[15] (2005, Iran)	LS vs. TF categorical*	Male: 340, female: 3,848	Male: 49.7 ± 16.3, female: 53.8 ± 11.2	Total discordance†: 41.7, low LS discordance‡: 32.5, low LS / total: 77.9
Mounach et al.[12] (2009, Morocco)	LS vs. TF categorical*	Male: 608, female: 2,871	Male: 51.1 ± 15.1, female: 55.7 ± 11.9	Total discordance†: 46, low LS discordance‡: 40, low LS / total: 86.8
Singh et al.[22] (2012, India)	LS vs. TF categorical*	Menopausal female: 348	53.6 ± 8.9 (27–84)	Total discordance†: 51.2, low LS discordance‡: 47.1, low LS / total: 92.1
Younes et al.[23] (2014, Tunisie)	LS vs. TF categorical*	Male: 174, female: 1,606	59.5 ± 14.3	Total discordance†: 50.5, low LS discordance‡: 41.2, low LS / total: 81.6
Seok et al.[20] (2014, Korea)	LS vs. FN scale§ (1 SD difference)	Female: 443	58.5 ± 7.0	Total discordance†: 29.3, low LS discordance‡: 21.4, low LS / total: 73
Alarkawi et al.[24] (2016, Australia)	LS vs. FN scale§ (0.6 SD difference)	Male: 1,373, female: 2,270	> 60	Total discordance†: 67.1, low LS discordance‡: 19.3, low LS / total: 28.7
Hong et al.[14] (2019, Korea)	LS vs. FN scale§ (1.5 SD difference)	Male: 3,233, menopausal female: 2,915	> 50	Total discordance†: 12.9, low LS discordance‡: 4.7, low LS / total: 36.4
Chan et al.[13] (2020, Malaysia)	LS vs. FN categorical scale§ (1 SD difference)	Male: 382, female: 404	57.2 ± 9.1	Total discordance†: 32.6, low LS discordance‡: 26, low LS / total: 79.8
Singh et al.[25] (2020, India)	LS vs. (TF or FN) categorical*	Female : 3,725	> 40	Total discordance†: 57.4, low LS discordance‡: 37.1, low LS / total, 64.6

Values are presented as mean ± SD.
LS: lumbar spine, TF: total femur, FN: femur neck, SD: standard deviation.
*Categorical: minor discordance was considered present when the difference between two sites was no more than one World Health Organization diagnostic class. Major discordance was considered present when one site was osteoporotic and the other was normal. †Total discordance: low LS discordance + low FN discordance. ‡Low LS discordance: LS T-score < FN T-score. §Scale: spine–femur discordance was defined as SD of difference between the FN and LS bone mineral density.

becomes, and the more peak stress it will tolerate. However, bones must also have enough elasticity to support the weight and withstand the pressure. In other words, when the bone is highly mineralized and homogeneous, the bone density can be measured high, but the durability of the bone becomes brittle, less rigid, and vulnerable to cracks and micro-damages.[30] It can be assumed that low LS discordance and AFF occurred more significantly in patients in whom this response to BP was more sensitive in the femur than in the spine. However, further studies are necessary to clarify. Although the clear relationship between T-score discordance and AFF has not yet been clearly elucidated, our finding may be clinically useful as it can serve as a basis to explain that care should be taken in relation to AFF when continuously administering BP to osteoporosis patients with low spine/high femur BMD.

This study has some limitations. First, for the participants with osteoporosis from the KNHANES database, who were compared with AFF patients, information about risk factors, such as BP use and radiologic findings (femoral bowing and lateral cortical thickness that can affect AFF occurrence), was not available; therefore, all risk factors could not be properly controlled. However, considering the large sample size of the KNHANES, the confounding effect of uncontrolled risk factors was probably minimal. Second, the DXA equipment used to measure BMD differed in the AFF patients and the KNHANES participants. Although the difference in BMD was adjusted using an appropriate cross-calibration equation, minor errors are inevitable. There is a possibility that accurate results can be obtained if similar equipment is used.

In conclusion, T-score discordance was highly prevalent in the Korean osteoporosis population, and low LS discordance was more frequently observed than low FN discordance. Nevertheless, the prevalence of low LS discordance was significantly higher in the AFF patients than in the Korean osteoporosis population. Further studies are necessary to clarify whether low spine/high femur BMD can increase the risk of AFF in patients with long-term BP use.

CONFLICT OF INTEREST

No other potential conflicts of interest relevant to this article were reported.

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