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Knee Varus as "Pre - Osteoarthritic Lesion" in Initiation and Progression of Knee Osteoarthritis in Perimenopausal Women

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Abstract: ***This study investigates the relationship between systemic bone mass, particularly osteoporosis, and knee varus deformity in perimenopausal women with knee pain. Through a comprehensive evaluation of clinical and radiological parameters, we found that osteoporosis significantly increases the risk of developing varus deformity, a condition linked to the progression of knee osteoarthritis. Our analysis revealed lower bone mineral density BMD in patients with varus deformity, particularly in the lumbar spine, femoral neck, and hip. The findings suggest that maintaining systemic bone mass may delay the progression of knee osteoarthritis, highlighting the need for early diagnosis and targeted interventions.***

Keywords: knee osteoarthritis, osteoporosis, varus deformity, bone mineral density, perimenopausal women

1. Introduction

Osteoarthritis (OA) is a leading cause of disability among elderly women, predominantly impacting weight - bearing joints such as knee and hip.[1, 2] The medial compartment of the knee is more frequently affected than the lateral side. Various factors, including mechanical, biological, and traumatic influences, or a combination, contribute to the causation and progression of OA. Mechanical factors[, 1, 4] such as the dynamic and static alignment of the limb, are strong predictors of knee osteoarthritis progression.[4, 5] The static alignment, defined as the hip - knee - ankle axis angle in the coronal plane, can be evaluated through long leg weight - bearing radiographs.6 In a varus arthritic knee, varus angulation is typically attributed to medial ligamentous tightness, laxity of lateral ligaments, and medial condylar wear, indicated by joint line convergence angle and joint orientation angles in a long leg radiograph. These factors and their relationship with limb alignment have been extensively studied.[7] However, the development of femoral and tibial shaft bowing and deformities of the distal femur and proximal tibia have rarely been considered in detail in these studies. Several Asian studies have found that the obliquity of the proximal tibial joint surface in knees with advanced OA can present with severe varus inclination. Knee osteoarthritis is often regarded as a disease of the joint articular cartilage, involving subchondral bone changes and localized inflammation[.8, 9] Recent studies have increasingly focused on the role of subchondral bone changes in the pathological process of knee osteoarthritis.[10, 11] Earlier research primarily examined sclerosis of the subchondral plate and the formation of osteophytes in patients with advanced knee osteoarthritis, suggesting an association with high bone density. However, recent findings indicate that, in the early stages of knee osteoarthritis, subchondral bone resorption increases and bone strength decreases, leading to cartilage degeneration[.12, 13] There is ongoing debate about whether systemic low bone mass exacerbates knee osteoarthritis progression in patients with both osteoporosis and knee osteoarthritis.[14] Varus deformity of the knee joint is a significant factor in the rapid degeneration of the knee joint and a key mode in the pathological process of knee osteoarthritis. Therefore, preventing varus deformity is crucial to slowing joint degeneration and treating severe knee osteoarthritis.[15, 16] Despite significant attention to the effect of periarticular bone mineral density (BMD) on limb alignment, the impact of systemic BMD, which represents overall bone mass, on limb alignment has not been adequately studied.[17, 22] Innovative approaches for the early diagnosis and treatment of pre - osteoarthritic conditions could enhance outcomes and lower both disability and costs associated with knee osteoarthritis. Consequently, to investigate the potential for knee varus initiation and progression as a pre - osteoarthritic lesion, we conducted a comprehensive evaluation of one clinical parameter and three radiological parameters in perimenopausal women presenting with knee pain.

Objective:
To determine the timeline of knee varus development in knee osteoarthritis among perimenopausal women with osteoporosis.

2. Methods

From February 2023 to September 2023, perimenopausal women with knee pain visiting our Orthopaedics outpatient department were included in this study. We performed full - length weight - bearing X - rays of both lower extremities and BMD measurements of the lumbar spine (L1 - L4) for all participants.1[8, 20] Clinical data such as age, pain duration, menstrual history, trauma history, and recent medication use were also collected.

To reduce bias, we established the following exclusion criteria:

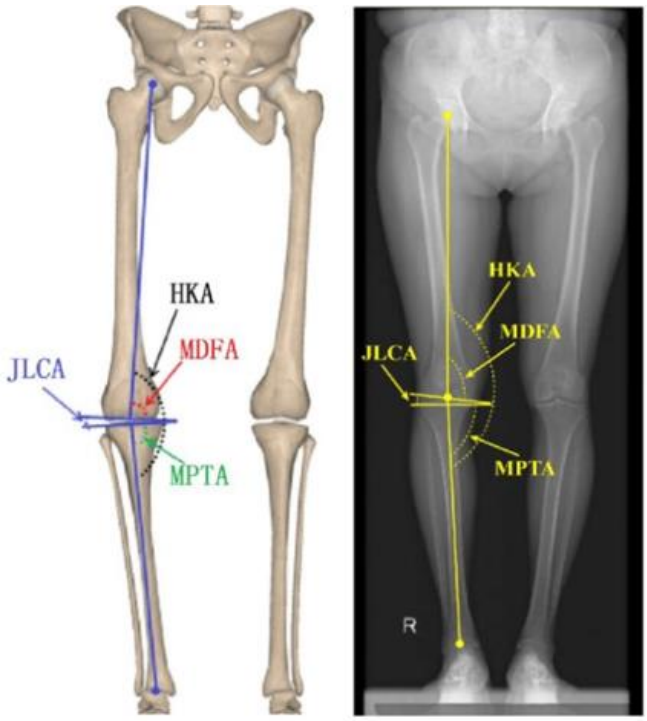
1) Patients with knee valgus deformity due to its clinical rarity and small case numbers [19].
2) Use of bone metabolism - affecting medications (e. g.,

bisphosphonates, hormones) in the last six months.

3) Nonstandard anteroposterior standing full - length X - rays to prevent alignment measurement errors caused by limb rotation.
4) Patients with extra - articular deformities (e. g., severe scoliosis, pelvic tilt, hip dysplasia, femoral or tibial shaft angular deformities) impacting knee force distribution.
5) Patients unable to walk due to severe pain, to avoid the effects of disuse osteoporosis.

Limb Alignment Angle Measurement:

Full - length weight - bearing X - rays of both lower limbs were taken to measure the hip - knee - ankle (HKA) angle. The mechanical axis of the femur was defined from the femoral head's center to the femoral condyle's center, while the tibia's mechanical axis was defined from the tibial plateau's center to the ankle joint's center.2^0 The degree of knee varus was determined by the HKA, with a smaller HKA indicating more severe varus deformity. Based on the standard physiological HKA range for Indian women, we classified 175.3° ≤ HKA ≤ 180.3° as normal limb alignment and HKA < 175.3° as varus deformity.[21, 22]



Schematic diagram of mechanical angle of lower extremity (HKA), distal medial femoral angle (MDFA), proximal medial tibial angle (MPTA) and angle of joint line (JLCA)

Measurement of bone density:

After admission, BMD was measured at the left femoral neck, left hip and lumbar spine (L1 - L4) by dual energy X - ray absorptiometry. The BMD of these three regions can sufficiently reflect the bone mass of the whole body and is the gold standard for the diagnosis of osteoporosis [22]. According to WHO diagnostic criteria, T≤ - 2.5 is diagnosed as osteo - porosis, - 2.5 < T< - 1 is diagnosed as osteopenia, and ≥ - 1 is normal bone density [23]. If the T - value of any of the three sites (spine, hip or femoral neck) met the diagnostic criteria for osteoporosis, the patient was diagnosed with osteoporosis.

Statistical analysis:

We used the software Stat Plus: mac for Macintosh to elaborate statistical data. We analysed the correlation between HKA median value and all other recorded median parameters. Every observation was made by the regression linear model using the ordinary least squares. An R2 was calculated based on the linear regression between the predicted values and the observed data. An R proximal to 1 was considered a good predictor of the dependent variable, while an R proximal to 0 represents the absence of correlation and - 1 represents a negative correlation. We put all data on the x–y graphics for each parameter to calculate the straight - line equation between all HKA values and all other parameters. This line estimates the nature of data correlation between HKA and all other parameters (directly vs inversely proportional). The "intraclass correlation coefficient" (ICC) was used to measure the variability in between the digitally planned cuts' thickness and the effective cuts performed intraoperatively. The ICC was also performed among different observers. An ICC between 0.75 and 1.00 was considered as excellent (almost no variability in between the two measurements).

3. Results

We analysed 226 perimenopausal women with knee pain from our orthopaedic outpatient department. Among them, 148 had varus deformity (HKA < 175.3°), including 71 with osteoporosis, 61 with osteopenia, and 16 with normal bone mass. There were no significant differences in age, BMI, or pain duration between those with varus deformity and those with normal limb alignment. The varus deformity group exhibited significantly lower BMD in the lumbar spine (L1 - L4), left femoral neck, and left hip compared to the normal limb alignment group, with a higher prevalence of osteoporosis (47.9% vs.25.9%, P < 0.05) (Table 1).

Table 1

	TOTAL	VARUS GROUP	NORMAL ALIGNMENT GROUP	p - value
NUMBERS	226	148	78	
AGE	65.5 +/ - 7.4 (yrs.)	66.1+/ - 7.6 (yrs.)	64.0+/ - 6.7 (yrs.)	0.068
BMI	26.2+/ - 3.8	26.1+/ - 3.9	26.3+/ - 3.3	0.808
PAIN	60 (0.5 - 360)	60 (0.5 - 360)	36 (1.0 - 240.0)	0.355
BMD (T - score)				
L1 - L4 SPINE	0.87+/ - 0.16	0.84+/ - 0.15	0.94+/ - 0.17	<0.001
FEMORAL NECK	0.69+/ - 0.14	0.67+/ - 0.13	0.74+/ - 0.13	0.002
TOTAL HIP	0.80+/ - 0.14	0.78+/ - 0.14	0.85+/ - 0.13	0.001
PREVALENCE				0.006
OSTEOPOROSIS (N, %)	92 (42)	69 (47.9)	21 (25.9)	
OSTEOPENIA (N%)	102 (47)	60 (41.7)	47 (58.6)	

NORMAL BMD (N%)	32 (11)	15 (10.4)	10 (15.5)	
AFFECTED SIDE				
LEFT (N, %)	127 (56%)	78 (54)	47 (60)	
RIGHT (N%)	99 (44%)	66 (46)	3140)	

Binary logistic regression showed osteoporosis as a significant factor in knee varus deformity occurrence. Multiple logistic regression, accounting for age, BMI, pain duration, and affected side, identified osteoporosis as an independent risk factor (p = 0.034), but not osteopenia (p = 0.929). Patients with osteoporosis had a 2.868 - fold higher risk of varus deformity compared to those with normal bone mass. Lower BMD in the lumbar spine (L1 - L4), left femoral neck, and left hip were also significantly linked to a reduced risk of varus deformity (p = 0.001, 0.011, 0.006, respectively) (Table 2).

Table 2: The influence of systemic bone mass on the varus deformity

	Crude			Adjusted		
	b	OR [95%CI]	p - value	b	OR [95%CI]	p - value
Bone mass state						
Osteoporosis	1.015	2.760 [1.018 - 7.483]	0.046	- 0.862	2.868 [1.035 - 7.645]	0.034
Osteopenia	0.057	1.059 [0.419 - 2.676]	0.904	- 0.046	0.955 [0.349 - 2.616]	0.929
Normal						
BMD						
L1 - L4 spine	- 3.693	0.025 [0.003 - 0.184]	<0.001	- 3.833	0.022 [0.002 - 0.192]	0.001
Femoral neck	- 3.507	0.030 [0.003 - 0.304]	0.003	- 3.610	0.027 [0.002 - 0.444]	0.011
Hip	- 3.917	0.020 [0.002 - 0.217]	0.001	- 3.985	0.019 [0.001 - 0.322]	0.006

Pearson correlation analysis revealed positive correlations between HKA and BMD of the lumbar spine (L1 - L4), left femoral neck, and left hip, and negative correlations with JLCA. MPTA correlated positively with BMD of the left femoral neck and left hip, but not the lumbar spine. MDFA showed no correlation with BMD values. Multiple linear regression, after adjusting for age, BMI, and pain duration, showed a significant positive impact of BMD on HKA (Table 3), indicating that higher BMD reduces varus deformity severity.

In the normal limb alignment group, HKA correlated negatively only with JLCA, with no significant correlation with MDFA or MPTA. In the varus deformity group, HKA correlated negatively with JLCA and positively with MDFA and MPTA.

4. Discussion

Although early studies recognized the role of osteoporosis in knee osteoarthritis, the relationship between the two remains debated. Differences in patient stages and indicators of disease progression across studies contribute to this controversy. KL grading focuses on osteophyte formation and joint space narrowing, while limb alignment more directly reflects the incidence of varus deformity, crucial for rapid knee osteoarthritis progression.

Previous research has mainly explored the link between subchondral BMD and limb alignment. Yoshinori et al. discovered that medial condyles had significantly higher BMD than lateral condyles in both femur and tibia in patients with medial compartment knee osteoarthritis. The medial - to - lateral BMD ratio negatively correlated with HKA and the tibial plateau's inclination angle. Lo et al. also reported a positive correlation between the severity of knee varus deformity and subchondral BMD of the medial tibia platform in knee osteoarthritis patients. These studies, however, only reflect periarticular BMD changes due to uneven mechanical stress and do not explain the impact of BMD on limb alignment. Local BMD cannot represent general bone mass, making it challenging to reveal the relationship between overall bone mass and limb alignment.

In our study, we measured BMD at the lumbar spine, hip joint, and femoral neck to represent general bone mass and evaluated different limb alignment angles to assess the relationship between knee varus deformity and systemic BMD. We found significantly lower BMD values in varus deformity patients compared to the normal limb alignment group, with a higher prevalence of osteoporosis in the varus deformity group. After adjusting for confounders like age, BMI, and pain duration, regression analysis showed that BMD at the lumbar spine (L1 - L4), left femoral neck, and left hip significantly positively influenced HKA. This suggests that a generalized low bone mass status may impact the severity of varus deformity in knee osteoarthritis patients. Our findings align with Im et al., who reported a negative correlation between proximal femur BMD and KL grading and a positive correlation with medial tibiofemoral joint space and HKA.

Recent studies show that subchondral bone and cartilage are closely related and mutually adaptable. In early - stage knee osteoarthritis, increased subchondral bone absorption reduces mechanical strength, and improper stress can cause subchondral microfractures, leading to bone marrow oedema and cartilage degeneration. Chen's study on tibial plateau specimens from knee osteoarthritis patients found that subchondral bone cysts degeneration resulted from increased local bone remodelling, accelerating overlying cartilage destruction. Zhu et al. suggested that knee osteoarthritis pain might be related to abnormal subchondral osteoclast activity, secreting Netrin - 1 and inducing neuronal axonal growth. We speculate that osteoporotic patients with knee osteoarthritis experience further reduced subchondral mechanical properties, accelerating osteoarthritis progression and varus deformity.

Our study also showed that BMD at the lumbar spine, femoral neck, and hip joint is significantly correlated with HKA, MPTA, and JLCA. Lower BMD correlates with more severe medial tibial plateau inclination and narrower medial articular space. In the normal limb alignment group, HKA was only negatively correlated with JLCA, whereas in the varus deformity group, HKA was negatively correlated with JLCA and positively correlated with MDFA and MPTA angles. These findings suggest that knee varus deformity is related not only to medial articular space narrowing but also to changes in the surrounding bone structure. Wang's group reached similar conclusions, identifying osteoporosis as a key risk factor for medial tibial plateau inclination, likely due to exacerbated subchondral microfractures in knee osteoarthritis patients.

Subchondral bone provides critical structural support for articular cartilage and functions in shock absorption, with its mechanical structure changes closely linked to cartilage degeneration. Given the increased fragility of subchondral bone in osteoporosis patients, enhanced remodeling of subchondral bone is likely in the early stages of knee osteoarthritis. Physiologically, the medial platform experiences higher stress than the lateral platform. Therefore, we hypothesize that in knee osteoarthritis patients with osteoporosis, weakened subchondral bone strength and improper stress stimulation may cause the medial platform to subside, exacerbating varus deformity due to cartilage wear.

Our study found a positive correlation between MTPA and BMD values at three different sites, supporting our hypothesis. As knee varus progresses, medial compartment stress increases, further damaging cartilage and creating a vicious cycle. One study reported that osteoporosis exacerbates bone structure attrition in advanced knee osteoarthritis, worsening joint deformity. These findings suggest that maintaining systemic bone mass may effectively delay knee osteoarthritis progression, especially in patients with osteoporosis.

There are several limitations to our study. The cross - sectional design only allows us to establish an association between osteoporosis and varus deformity, not causation. Prospective longitudinal studies are needed to determine causality. Additionally, we focused on perimenopausal Indian women due to the commonality of oestrogen deficiency - related osteoporosis and knee osteoarthritis in this group. To generalize our findings to men and other races, further research with larger, diverse samples is required. We also did not observe subchondral bone BMD changes, as our hospital does not routinely measure BMD around the knee joint. Future studies should explore the correlation between periarticular and systemic BMD in knee osteoarthritis patients.

Despite these limitations, our study reveals the relationship between systemic bone mass and limb alignment angles, suggesting osteoporosis may be an independent risk factor for varus deformity. Our findings provide a basis for further research on the temporality between osteoporosis, knee varus, and knee osteoarthritis.

5. Conclusions

To summarize, knee varus deformity is associated not only with joint space narrowing but also with changes in adjacent bone structures, with osteoporosis being a critical risk factor in perimenopausal women experiencing knee pain. Attention should be given to the progression of varus deformity in these women, but further longitudinal research is needed to substantiate this conclusion.

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