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REVIEW

Open Access

# Clinical factors associated with bone mineral density among individuals with osteoarthritis of the hip and/or knee: a systematic review

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## Abstract

**Background and objective** The association of clinical factors of osteoarthritis (OA) with bone mineral density (BMD) is not well understood. We aimed to synthesize evidence regarding the associated clinical factors for low BMD in people with knee and/or hip osteoarthritis.

**Methods** A systematic literature search limited to human studies was conducted from inception to September 12, 2022. CINAHL, Cochrane, Medline, PsycINFO, PubMed, Web of Science, and African Journal online databases were searched for all clinical factors associated with low BMD (either as osteopenia or osteoporosis). Gray literature or abstracts or protocols, studies with a mixed population of OA without a subgroup analysis for hip and or KOA and non-English were excluded. Following the title and abstract, full-text, screenings, and data extraction, data from eligible studies were synthesized based on the main objective of the study. The Joanna Brigg's Institute (JBI) Critical Assessment tool was used for quality appraisal. Narrative synthesis and best evidence synthesis were used in the study.

**Result** Five studies (2 case–control, 3 cross-sectional) were included after screening 3355 titles and abstracts. Clinical factors reported in the five studies included: body mass index (BMI); pain, function, and stiffness; symptom duration; presence of varus/valgus deformity; quality of life; and knee function. Whilst there was limited evidence to support the association between BMD measured at any site of the body and BMI, as well as conflicting evidence for the association of BMD with age and gender, there was insufficient evidence to support the association of BMD with other identified clinical factors of hip and or/ knee OA ($p < 0.05$). In addition, there is conflicting evidence for the association between BMD measured at the lumbar spine and BMI.

**Conclusion** There is insufficient evidence on the association between BMD and its associated clinical factors. With the attendant likelihood of bias in existing studies, there is a need for well-designed studies on bone health in OA.

## Introduction

Osteoarthritis (OA) and osteoporosis (OP) are two common age-related musculoskeletal disorders with a prevalence of 7% and 18.3%, respectively [15, 35]. Although earlier believed to be mutually exclusive [5, 16], some studies have indicated that both OA and OP are not mutually exclusive, and are common musculoskeletal disorders that could coexist in the same individual [1, 4, 12, 14]. The relationship between these two diseases remains

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unclear and is a subject of ongoing research. Studies focusing on the relationship between OA and bone mineral density (BMD) (indicating osteoporosis) posit that both diseases can have a direct relationship where higher BMD is observed in individuals with OA [3, 7, 18, 22, 30]. On the other hand, Foss et al. [13] as far back as 40 years ago, suggested an apparent inverse relationship between the two diseases. Similarly, other reports suggest an inverse relationship between the presence of OA and OP [10, 41].

Studies on radiographic OA of the hip and BMD showed an increase in BMD measurements taken at remote proximal and distal sites of the radius and at the calcaneus in women with severe hip OA compared to individuals without OA [17, 29]. Lingard et al. [27] submitted that a significant proportion of patients with OA have OP but that the diagnosis may be missed unless BMD measurements are performed at sites distant from the joints affected by OA. This is because OA characteristic features such as osteophyte formation and subchondral sclerosis that are presented at the joint can alter/increase the BMD measurements done by central dual-energy x-ray absorptiometry (DEXA) of the spine and hip [29]. Thus, whether there is a direct or inverse correlation between OA and OP, and whether low BMD may be a comorbidity of OA are separate questions. El Miedany et al. [12] submitted that an increase in BMD did not appear to be related to patient characteristics of body weight, age, physical activity, or medication use. Some of the clinical correlates of OA that have been documented in the literature include BMI, symptom duration, pain, function and stiffness, quality of life, etc. [33, 34]. Considering the possible interrelationship between OA and OP, clinical measures directed at ameliorating OA symptoms may improve BMD, and this might be an important therapeutic pathway. This systematic review seeks to synthesize the current evidence and offer direction on the knee OA-OP nexus to provide clinical care guidelines.

## Methods

The Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) [31] and the protocol defined by the Joanna Briggs Institute (JBI) Methodology for Systematic Reviews were followed in this review. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022334000).

### Study selection criteria

#### *Population, exposure, study types, settings, and outcomes*

The population of interest of this review was male and female adults (≥40 years) diagnosed with hip and/or knee OA using the American College of Rheumatology Criteria (ACR), KL system of classification, doctor diagnosis, and Ahlback grading scale. Studies with general rheumatic and osteoarthritis conditions were considered only if subgroup results for hip and knee OA were presented. Studies that assessed BMD (either reported as BMD, osteopenia, or osteoporosis) at sites including the spine, femur, total hip, and /or a combination of these sites in individuals with hip and/or knee OA were included. We included all types of observational studies, i.e., cohort, case–control, and cross-sectional studies from all settings. All clinical outcomes reported in eligible studies were identified and included.

### Eligibility criteria

#### *Inclusion and exclusion criteria*

Peer-reviewed studies that included a knee and/or hip OA population or sub-sample of knee and/or hip OA diagnosed using radiographic evidence and/or clinical diagnosis (as defined by the American College of Rheumatology criteria) [2] or according to Kellgren Lawrence (KL) grading [23] and that assessed the BMD as a measure of Osteoporosis.

According to the World Health Organization [39], OP was defined as a BMD T-score at the hip and/ or the spine of < 2.5 standard deviations (SD) for postmenopausal women, and T-scores of between − 1 and − 2.5 SD for men and women over the age of 50 years [21, 28]. Gray literature, abstracts, protocols, or non-human studies with a mixed population of OA without a subgroup analysis for hip and or knee OA and non-English were excluded.

### Search strategy

Online electronic databases of CINAHL, Cochrane, Medline, PsycINFO, Pubmed, Web of Science, and African Journal (from inception to September 12, 2022). The initial keywords used in the review were "bone mineral density" OR "bone density" OR "Osteoporosis" OR "Osteopenia" OR "fracture"; "risk factors" OR "outcomes" OR "correlates" OR "Prevalence"; and "Knee osteoarthritis" OR "hip osteoarthritis". The complete search strategy implemented is presented in Supplementary material (see Appendix). Also, the reference list of included studies and two related systematic reviews were screened to extract related articles. Eligible study design included prospective longitudinal cohort, cross-sectional, and case studies.

### Screening and selection of studies

Duplicate citations were eliminated by one of the authors (BAA). In the first phase, three independent assessors (IO, HF, and OO) screened the titles and abstracts of the articles returned by the search. BAA arbitrated the searches of the two assessors where there were contentions on the inclusion/exclusion of articles. In the second

phase, full-text manuscripts of possibly eligible studies were retrieved and reviewed by each of the independent assessors using a standardized Microsoft Excel screening spreadsheet to identify relevant studies. Data were extracted on study setting, study population, sample size, study design, measures of BMD and OA used, statistical analysis, and main findings. To ensure quality control of data extraction, both virtual and physical meetings were held among the assessors (IO, HF, and OO) and the third reviewer (BAA) to discuss cases.

### Quality assessment of selected studies

Assessment of reporting quality and the risk of bias for each paper was done using the Joanna Brigg's Institute (JBI) Critical Assessment tool which is a widely used and recommended assessment tool by Cochrane for evaluating qualities of observational and cross-sectional and case–control studies. The tool for observational and cross-sectional studies comprises 8 items (all applicable to cross-sectional studies) while that for case–control studies comprise 10 items. The quality assessment for each included study was carried out by two independent assessors (OI and HO) using the scoring system of yes (Y), No (N), Unclear (U), or not applicable (NA). An arbitrator (BAA) acted as a tie-breaker whenever a consensus could not be reached.

### Data synthesis

Meta-analysis was not performed due to the high heterogeneity levels with regard to study designs and methodology. However, findings were presented using a narrative synthesis to report the association between clinical factors of hip and/or knee OA and BMD. Further, we performed the best evidence synthesis of clinical factors that were investigated in two or more studies and ranked evidence grading based on previous studies [38, 40] to grade the level of evidence supporting the association (see Appendix). We classified studies according to study design, with the preferred being cohort study followed by case–control design, and lastly cross-sectional design. Studies were ranked according to their methodological quality score. Identified clinical factors were classified in the direction and strength of association by using correlation or standardized coefficient as weak ($<0.3$), moderate ($>0.3<0.7$), and strong ($\geq 0.7$) [19] or with odds ratio [9] where these were reported. We adjudged results as consistent if BMD was significantly associated with the identified clinical factor of OA in the same direction of the association.

## Results

### Literature search and study selection

Three thousand, three hundred and fifty-five (3355) articles were identified through database searches, and 3 articles were identified through a review of the reference lists of relevant papers and a hand search. Of these articles, we removed 1751 duplicates. The titles and abstracts of the 1604 remaining articles were screened, and of these, 25 full papers were accessed for further review of eligibility. Twenty-one articles were excluded and the remaining 5 articles ((3 cross-sectional studies [11, 27, 37] and 2 case–control studies [8, 32])) The PRISMA flow diagram on the search strategy results of this review is shown in Fig. 1.

### Study characteristics and association between BMD and OA clinical factors

Extracted data included data for 1295 participants. All five studies were completed in different countries, viz; Germany [11], Korea [8], UK [27], China [37], and Poland [32]. Two of the studies [11, 27]) had more female than male participants, while 3 recruited only female participants [8, 32, 37]. Furthermore, one of the studies specifically recruited only post-menopausal women [32].

Three of the studies [8, 11, 37] diagnosed BMD using Kellgren-Lawrence (KL) scores. One study [27] only required a doctor's diagnosis while the final study [32] made use of the American College of Rheumatology (ACR) clinical classification criteria for Knee OA.

Clinical factors assessed by the studies were: BMI [11, 27, 32, 37],pain, function, and stiffness [8, 27],symptom duration [37],presence of varus/valgus deformity [37],quality of life [8],and knee function [8]. Tables 1 and 2 show the summary of all the studies included in the review.

Results across four studies showed BMI to be an important clinical factor associated with BMD among people with osteoarthritis [11, 27, 32, 37]. Pain, function, and stiffness [8], female gender [27], varus deformity [37], QoL-physical component [8], and knee function [8] were all also significantly associated with BMD.

However, mental component summary QoL [8], symptom duration [37], valgus deformity [37], and incidence of bilateral KOA [37], did not demonstrate significant associations with BMD among the population.

### Quality assessment

Three (3 cross-sectional studies [11, 27, 37], and two case–control studies [8, 32] were rated as having good quality and included in the review. The summary of the quality assessment is presented in Tables 3 and 4.

### Best evidence synthesis

Following the best evidence synthesis, there was limited evidence to support the association between BMD measured at any site of the body and BMI. In addition, there was a conflicting evidence for the association of BMD

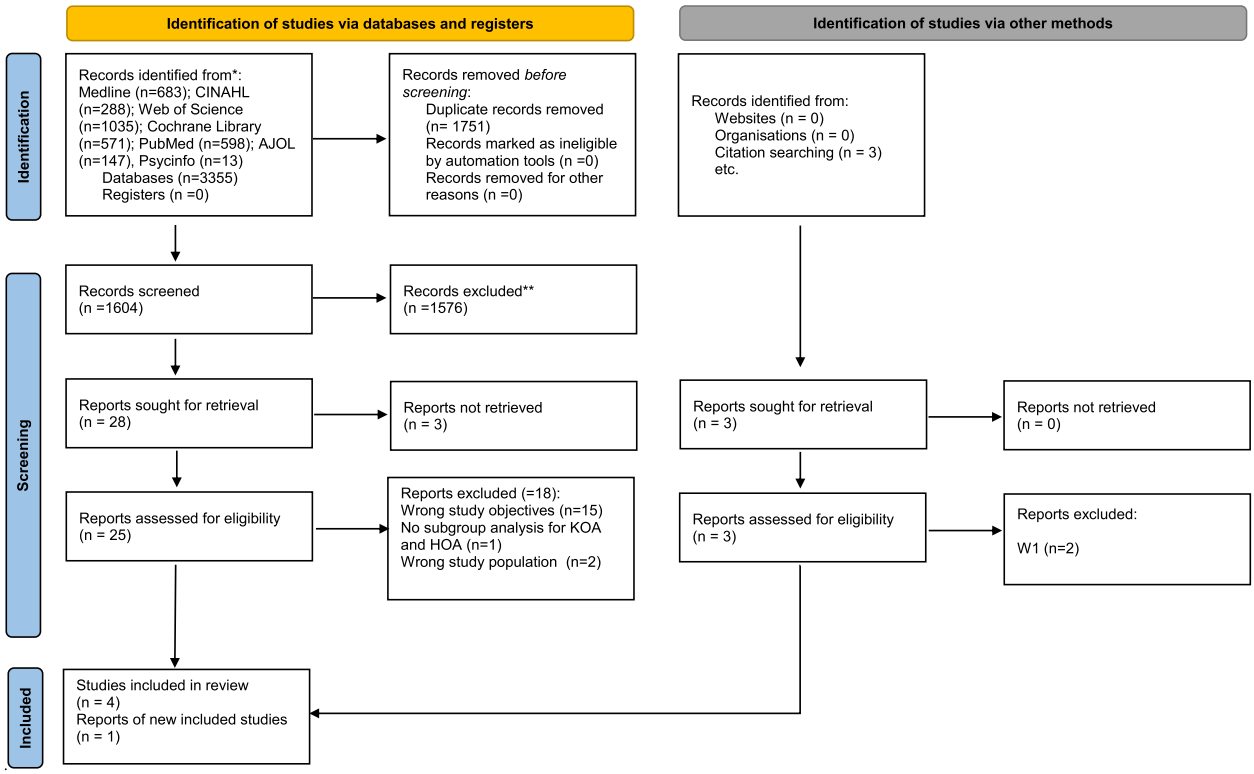


**Fig. 1** PRISMA flow diagram (source— [31])

with age and gender. When BMD was measured at the lumbar spine, the evidence for the association between BMD and BMI became conflicting. For other identified clinical factors, there was insufficient evidence to support an association with BMD. Strengths of association and levels of best evidence are summarized in Tables 5 and 6, respectively.

## Discussion

This systematic review aimed to summarize current epidemiological evidence on the association between BMD and clinical factors of hip and/or knee OA. Due to high heterogeneity levels in study designs and limited number of studies, the review employed a narrative and best evidence synthesis, which enabled grading of factors into different levels of evidence. There were five studies that evaluated the association of BMI with BMD, with majority having longitudinal design. The best evidence synthesis found limited evidence for the positive association between low BMI and poor BMD measured at any site of the body. Conflicting evidence was found for the association between BMD and each of age and gender. When BMD was measured at the lumbar spine, the evidence for the association between BMD and BMI became conflicting. All other factors identified had insufficient evidence. From the table above, all the studies reviewed were from Europe and Asia. No study was found from Africa or America. Furthermore, most of the reviewed studies recruited knee OA alone and only one recruited patients with hip and knee OA [27].

The association between bone mineral density and OA has long been a subject of debate in the literature [18, 36]. Although the exact pathophysiology remains unclear, this association between OA and OP has been known from early cross-sectional studies [6, 20, 26, 33]. Bone is considered an integral structure in the pathogenesis of OA and the role of local and systemic bone mineral density (BMD) is gaining increasing interest [33]. A relatively recent review demonstrated the similarities in etiology, risk factors, and shared mechanisms between BMD and OA, which suggests a possible association with clinical factors of OA like BMI [14]. It is important to note that high BMI may be protective of BMD especially in among males and black populations populations [25]. However, excessive BMI may be harmful to BMD as Li [25] reported an inverted U-shaped association between BMD and BMI. More studies are needed to understand these associations among the blacks and especially in the African

**Table 1** Summary of the included studies

| Authors' ID/ Country | Aim of study | Study design | Study participant's characteristics (OA type, mean age/range, and gender) | Sample size | Diagnosis of OA | Prevalence of OP | Measure of BMD/location of BMD measure |
|---|---|---|---|---|---|---|---|
| Delsmann et al. [11] Germany | secondarily to determine the independent influence of age, gender, BMI and KL score on BMD in older adults with knee OA | Retrospective Cross-sectional | Knee OA, [Female, mean age = 78.0 (4.1)], [Male, mean age = 77.7 (4.3)] Females = 72, Males = 37 | 109 | KL scores | 18.10% | Dual-energy x-ray absorptiometry/ left and right proximal femur and lumbar spine (L1 = L4) **Note:** ***Based on the T-score, osteoporosis, and osteopenia were diagnosed according to World Health Organization (WHO) guidelines (i.e., normal T-score > − 1.0, osteopenia T-score > − 2.5 ≤ − 1.0, osteoporosis T-score ≤ − 2.5)*** |
| Lingard et al. [27] UK | to determine the prevalence of osteoporosis among patients with osteoarthritis awaiting total knee arthroplasty | Cross-sectional | hip OA and Knee OA, mean age; 72.2 (SD 4.0), 113 F | 199 | Doctor diagnosis | 23.00% | Areal BMD (g/cm$^2$) of the proximal femora, lumbar spine (from L1 to L4), and forearm was measured by dual-energy X-ray absorptiometry (DEXA) using a Hologic QDR-4500A scanner |
| Tao et al. [37] China | To explore the preoperative risk factors for OP | retrospective cross-sectional | Knee OA, [Female, mean age = 69.7 ± 8.5] | *n* = 204 (non OP = 82; OP = 122) | KL scores | 59.80% | Areal BMD at the sites: lumbar spine, proximal femur, (PF), and femoral neck. The World Health Organization (WHO) classifications for osteopenia and OP were used for each bone site: normal (T-score greater than − 1.0), osteopenia (*T*-score between − 1.0 and 2.5), and osteoporosis (*T*-score below − 2.5) |

| Authors' ID/ country | Identified clinical factors and assessment tools | Main statistical methods | Mean (SD)/median [IQR] of BMD and clinical factors identified | Association between BMD and identified clinical factors (result of association, strength of association) | Limitations/strengths | Clinical implications | Future recommendations |
|---|---|---|---|---|---|---|---|
| Delsmann et al. [11] Germany | KL scores, BMI (kg/m$^2$) | Linear regression with enter method | [BMD minimum, *F* = 0.8 (0.2); *M* = 1.0 (0.2)]; [*T* score min, *F* = − 1.3 (1.2); *M* = − 1.1 (1.4)]; [*F*, mean age = 78.0 (4.1); *M*, mean age = 77.7 (4.3)]; [BMI, *F* = 29.8 (SD = 5.6); *M* = 28.3 (3.7)]; [KL score, *F* = 3.5 (0.6); *M* = 3.7 (0.6)]; osteoporosis, *F* = 13/72 (18.1%); *M* = 6/37 (16.2%); osteopenia, *F* = 37/72 (51.4%); *M* = 13/37 (35.1%); normal BMD, *F* = 22/72 (30.6%); *M* = 18/37 (48.7%)] | [T-score minimum, age = − 0.124, *p* = 0.161; **KL score = − 0.247, *p* = 0.006**; gender = − 0.100, *p* = 0.273; **BMI = 0.263, *p* = 0.004**]; $R^2$ adjusted = 0.190 [*T*-score hip affected, age = − 0.143, *p* = 0.130; KL score = − 0.079, *p* = 0.411; gender = − 0.020, *p* = 0.838; **BMI = 0.233, *p* = 0.016**]; $R^2$ adjusted = 0.140 [*T*-score lumbar spine, age = 0.030, *p* = 0.763; KL score = − 0.161, *p* = 0.106; gender = − 0.159, *p* = 0.115; BMI = 0.112, *p* = 0.262]; $R^2$ adjusted = 0.067 | **Limitation:** retrospective design and inclusion of those with previous spinal fracturchene | BMI and knee OA grading are important factors associated with BMD | BMI and Knee OA grading association with BMD should be further investigated among individuals with Knee OA using longitudinal prospective designs |

**Table 1** (continued)

| Authors' ID/ Country | Aim of study | Study design | Study participant's characteristics (OA type, mean age/range, and gender) | Sample size | Diagnosis of OA | Prevalence of OP | Measure of BMD/location of BMD measure |
|---|---|---|---|---|---|---|---|
| Lingard et al. [27] UK | Pain, function, stiffness (WOMAC), BMI(weight/square of the height) | Logistic regression | Lumbar spine = 1.32 [0.34–2.43], proximal femur = 0.50 [− 0.27 to 1.34] contra-lateral proximal femur = 0.55 [0.02–1.54] forearm = 0.79[(− 0.15 to 1.52]. WOMAC (0–100, 100 best)<br>■ Pain: females with OP-35 (13, 75), females without OP-40 (15, 80), males with OP-48 (35, 55), males without OP -40 (20, 80)<br>■ Function: females with OP-35 (9, 71), females without OP-37 (12, 63), males with OP-40 (35, 63), males without OP-39 (10, 72)<br>■ Stiffness: females with OP-38 (13, 75), females without OP-38 (13, 75), males with OP-63 (38, 100), males without OP-50 (13, 75)<br>Timed Up and Go (TUG) (s) 17 (11, 38), 16 (10, 32), 14 (10, 17) 14 (9, 32) | **Female gender (OR = 7.8, 95% confidence interval 3.1, 20.0)** and **low BMI (< 25 kg/m$^2$, odds ratio 3.6, 95% confidence interval 1.5, 8.6)** were the only predictors of OP | 1. Cross-sectional study<br>2. Only older adults were recruited | Female gender and low BMI risk factor for low BMD. KOA-specific outcomes are not important risk factors for low BMD<br>2. Low BMD (osteoporosis) showed no association with items on the WOMAC and TUG test | Further research focus on the following questions<br>1. Does early detection and treatment of OP in patients with knee or hip OA have an effect on the progression of OA?<br>2. Does early detection and treatment of OP in patients with knee or hip OA have an effect on the outcome of joint replacement<br>3. Is the presence of OP at the forearm associated with a different outcome of joint replacement? |
| Tao et al. [37] China | BMI (kg/m$^2$), symptom duration, incidence of bilateral KOA, presence of valgus/varus deformity (hip-knee-ankle (HKA)angle using a full-length lower limb radiograph; HKA < 170° for varus deformity, HKA > 183° for valgus deformity) | Binary logistic regression | **BMD = unclear n = 122 (OP) Age = 70.55 [65.48, 75.85] years, BMI = 25.5 (4.07) kg/m$^2$, symptom duration = 8 [3, 10] years, valgus deformity 15.6%, varus deformity 71.3%, incidence of bilateral KOA = 90.2%** | **Age ≥ 60 (OR = 7.76, 95% CI = 2.49, 24.18; *P* < 0.001); BMI < 25 (OR = 1.85, 95% CI = 1.01, 3.40; *P* = 0.048)**; **presence of a knee varus deformity (OR = 2.10, 95% CI = 1.13, 3.92; *P* = 0.020).** Other factors (symptom duration, valgus deformity, incidence of bilateral KOA) were not reported due to non-statistical significance | Functional parameters of the knee, such as the WOMAC were not accessible for some participants. 3. data on bone turnover markers, vitamin D, and calcium intake were not all available | Age ≥ 60 years, a BMI < 25, and the presence of varus knee deformity are independent risk factors that can be used to predict preoperative OP in this population | 1. Future studies are needed to determine the exact role of various blood parameters, including bone turnover markers and vitamin D, in the pathophysiology of OP in patients awaiting TKA. 2. postmenopausal women aged ≥ 60 years awaiting TKA who have a BMI < 25 and varus knee deformity are recommended for OP screening preoperatively |

**Table 2** Summary of the included studies

| Authors' ID/ country | Aim of study | Study design | Study participant's characteristics (OA type, mean age/range, and gender) | Sample size | Diagnosis of OA | Prevalence of OP | Measure of BMD/ location of BMD measure |
|---|---|---|---|---|---|---|---|
| Chang et al. [8] Korea (D) | BMD conditions were compared between people with KOA and people without KOA. A secondary aim was to determine whether preoperative clinical factors are associated with BMD in people with KOA | Prospective case–control study | Case: Knee OA [female patients, age = 71.1 (4.5) years, range = 65–84 years]; control: [females, age = 71 (5.3) years, range = 65–86 years; community older adult without advanced knee OA] | Case: 212; control: 212 | Kellgren-Lawrence grade ≥ 2 | 31% (108/347) | Dual-energy x-ray absorptiometry/ left and right proximal femur and lumbar spine (L1–L4). Note: Based on the *T*-score, osteoporosis and osteopenia were diagnosed according to the BMD-*T* score was interpreted according to the the International Society for Clinical Densitometry (ISCD). BMD [[normal *T* score = (*T* score > − 1.0 SD)], [osteopenia = (− 2.5 < *T* score ≤ − 1.0)], [osteoporosis = (*T* score ≤ − 2.5 SD)]] |
| Povoronznyuk et al. [32] Poland (E) | This study explores the relationship between BMD and BMI of the patient with symptomatic KOA | Case–control study | Post-menopausal females: knee OA group [age = 65.4 (8.41) years] non-KOA group [65.8 (7.80) years] | *n* = 359 [KOA group = 117, non-KOA group = 242] | The American College of Rheumatology (ACR) clinical classification criteria for KOA | 16% | DEXA-based BMD measurement of L1–L4 and femoral neck. The World Health Organization (WHO) classifications for osteopenia and OP were used for each bone site: normal (*T*-score greater than − 1.0), osteopenia (*T*-score between − 1.0 and − 2.5), and osteoporosis (*T*-score ≤ − 2.5) |

**Table 2** (Continued)

| Authors' ID/ country | Aim of study | Study design | Study participant's characteristics (OA type, mean age/range, and gender) | Sample size | Diagnosis of OA | Prevalence of OP | Measure of BMD/ location of BMD measure |
|---|---|---|---|---|---|---|---|
| **Authors' ID/ country** | **Identified clinical factors and assessment tools** | **Main statistical methods** | **Mean (SD)/median [IQR] of BMD and clinical factors identified** | **Association between BMD and identified clinical factors (result of association strength of association)** | **Limitations/strengths** | **Clinical implications** | **Future recommendations** |
| Chang et al. [8] Korea | Pain, function, stiffness (WOMAC score), physical and mental component summary QoL (SF-36 score), knee and function (American Knee Society (AKS) score) | Multiple regression model | BMD (proximal neck of femur = − 1.81 (0.83), femur total = − 1.58 (1), lumbar spine = − 1.81 (1.17); [[**WOMAC score**: Pain Pain = 11.2 (4.1); function = 40.4 (12.5); stiffness = 4.8 (2.0)], **SF-36** score: physical component summary (PCS) = 28.6 (6.9); mental component summary (MCS) = 41.0 (10.9)], [A**KS score:** knee = 43.6 (10.3); Function = 55.3 (16.1)]] | Proximal femur WOMAC score **[Pain, B = − 0.038 95% CI = − 0.062, − 0.014; Function, B = − 0.015 95% CI = − 0.023, − 0.007; stiffness, B = − 0.052 95% CI = − 0.101, − 0.004; *P* < 0.05]. SF-36 score [PCS, B = 0.022 95% CI = − 0.008, 0.036, *P* < 0.05; MCS, B = 0.007 95% CI = − 0.002, 0.016,** *P* > 0.05]. AKS score **[Knee, B = 0.012 95% CI = 0.002, 0.021; Function, B = 0.018 95% CI = 0.012, 0.024, *P* < 0.05].** Lumbar spine **WOMAC score [Pain, B = − 0.070 95% CI = − 0.109, -0.032; Function, B = − 0.018 95% CI = − 0.030, -0.005, *P* < 0.05; stiffness, B = − 0.065 95% CI = − 0.143, 0.013; *P* > 0.05]. SF-36 score [PCS, B = 0.014 95% CI = − 0.009, 0.036; MCS, B = − 0.003 95% CI = − 0.017, 0.011, *P* > 0.05]. AKS score [Knee, B = − 0.002 95% CI = − 0.016, 0.013, *P* > 0.05; Function, B = 0.016 95% CI = 0.007, 0.026, *P* < 0.05]** | The study is limited due to its large sample size which can lead to overestimation of clinically meaningful differences between groups. Study was conducted among older adult females with advanced KOA; inference to other population, males and age group may be limited. | All clinical factors except MCS were associated with poor BMD level | More identification and treatment of osteoporosis should be targeted at female older adults with advanced KOA. |
| Povoronznyuk et al. [32] Poland | BMI | Linear regression/ correlation | Knee OA group BMI: 28.8 (5.68) kg/m$^2$ BMD lumbar spine = 0.90 (0.16); BMD right femoral neck = 0.67 (0.12); BMD left femoral neck = 0.66 (0.12) | BMI and BMD of lumbar spine ($R^2 = 0.20$, $P < 0.001$) | Only one gender (females) was included. Only univariate analysis was done which limits the understanding of the complexity of the relationship between BMD and BMI. | Obesity is higher in population with Knee OA and postmenopausal women with Knee OA had a significantly higher BMD of lumbar spine. | More sophisticated analysis is needed. Sample size should be increased. Longitudinal studies may offer more understanding on the causal relationships between BMD and BMI |

*BMI* body mass index, *KL* Kellgren-Lawrence, *BMD* bone mineral density, *OA* osteoarthritis, *P* level of significance at $p < 0.05$, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *TKA* Total Knee Arthroplasty

**Table 3** JBI critical appraisal checklist for analytical cross-sectional studies

| S. No | Study ID | | | | | | | | | Overall appraisal |
|---|---|---|---|---|---|---|---|---|---|---|
| | Questions | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| 1 | Delsmann et al. [11] | N | Y | Y | Y | N | N | Y | Y | Yes |
| 2 | Lingard et al. [27] | Y | Y | Y | U | N | N | Y | Y | Yes |
| 3 | Tao et al. [37] | Y | Y | Y | Y | N | N | Y | Y | Yes |

Questions

1. Were the criteria for inclusion in the sample clearly defined? 2. Were the study subjects and the setting described in detail? 3. Was the exposure measured in a valid and reliable way? 4. Were objective, standard criteria used for measurement of the condition? 5. Were confounding factors identified? 6. Were strategies to deal with confounding factors stated? 7. Were the outcomes measured in a valid and reliable way? 8. Was appropriate statistical analysis used?

Answers: Yes, no, unclear, or not applicable

**Table 4** JBI critical appraisal checklist for case–control studies

| S. No | Study ID | | | | | | | | | | Overall appraisal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Questions | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 1 | Chang et al. [8] | Y | Y | Y | Y | N | Y | Y | Y | U | Y | Yes |
| 2 | Povoroznyuk et al. [32] | Y | Y | U | Y | Y | N | N | Y | U | U | Yes |

1. Were the groups comparable other than presence of disease in cases or absence of disease in controls? 2. Were cases and controls matched appropriately? 3. Were the same criteria used for identification of cases and controls? 4. Was exposure measured in a standard, valid, and reliable way? 5. Was exposure measured in the same way for cases and controls? 6. Were confounding factors identified? 7. Were strategies to deal with confounding factors stated? 8. Were outcomes assessed in a standard, valid and reliable way for cases and controls? 9. Was the exposure period of interest long enough to be meaningful? 10. Was appropriate statistical analysis used?

Answers: Yes, no, unclear, or not applicable

**Table 5** Strength of association between Bone Mineral Density and identified clinical factors

| Site of BMD Author's ID | Clinical factor | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pain | Function | Stiffness | QoL[a] | QoL[b] | AKS_Knee | AKS_ Function | BMI | KL score | Gender | Age | Presence of varus deformity | Symptom duration | Valgus deformity | Bilateral KOA Incidence |
| **BMD at any site** | | | | | | | | | | | | | | | |
| Lingard et al. [27] | | | | | | | | β++ | | β+++ | | | | | |
| Dels-mann et al. [11] | | | | | | | | + | − | 0 | 0 | | | | |
| Tao et al. [37] | | | | | | | | β++ | | | β+++ | β++ | Ω | Ω | Ω |
| **BMD hip** | | | | | | | | | | | | | | | |
| Dels-mann et al. [11] | | | | | | | | + | 0 | 0 | 0 | | | | |
| **BMD proximal femur** | | | | | | | | | | | | | | | |
| Chang et al. [8] | − | | − | − | + | + | + | + | | | | | | | |
| **BMD lumbar spine** | | | | | | | | | | | | | | | |
| Dels-mann et al. [11] | | | | | | | | 0 | 0 | 0 | 0 | | | | |
| Chang et al. [8] | − | | − | 0 | 0 | 0 | 0 | + | | | | | | | |
| Povo-ronznyuk et al. [32] | | | | | | | | + | | | | | | | |

Odds ratio were interpreted as weak association (≤ 1.5 or ≥ 0.59) = ≤ 0.2; Moderate association (1.6 to 5 or 0.59 to 0.29) = 0.3–0.7; strong association (> 5 or ≤ 0.15) = ≥ 0.8

[a] physical component summary of QoL

[b] mental component summary of QoL; + = weak positive association (< 0.3); + + = moderate positive association (> 0.3 < 0.7); + + + = strong positive association (≥ 0.7); 0 = Non significant; − = weak negative association (< 0.3); − − = moderate negative association (> 0.3 < 0.7); − − − = strong negative association (≥ 0.7); Ψ = unadjusted analysis; $\beta$ = odds ratio; Ω = No coefficient of association or non association reported. All associations are adjusted analysis unless otherwise indicated

**Table 6** Overview and best evidence synthesis regarding the association between clinical factors of hip and /or knee osteoarthritis and poor bone mineral density

| ***BMD at any site*** | | | |
|---|---|---|---|
| | **Association found** | **No association found** | **Best evidence** |
| **Clinical factors** | | | |
| Low body mass index | Three good quality cross-sectional studies [11, 27, 37] | | Limited evidence |
| Increased KL score | One good quality cross-sectional study [11] | | Insufficient evidence |
| Gender | Being female<br>One good quality cross-sectional study [27] | One good quality cross-sectional study [11] | Conflicting evidence |
| Age | ≥ 60 years<br>One good quality cross-sectional study [37] | One good quality cross-sectional study [11] | Conflicting evidence |
| Presence of varus deformity | One good quality cross-sectional study [37] | | Insufficient evidence |
| Symptoms duration | | One good quality cross-sectional study [37] | Insufficient evidence |
| Valgus deformity | | One good quality cross-sectional study [37] | Insufficient evidence |
| Bilateral KOA incidence | | One good quality cross-sectional study [37] | Insufficient evidence |
| **BMD hip** | | | |
| Low body mass index | One good quality cross-sectional study [11] | | Insufficient evidence |
| Increased KL score | | One good quality cross-sectional study [11] | Insufficient evidence |
| Gender | | One good quality cross-sectional study [11] | Insufficient evidence |
| Age | | One good quality cross-sectional study [11] | Insufficient evidence |
| ***BMD proximal femur*** | | | |
| Increased pain | One good quality case–control study [8] | | Insufficient evidence |
| Poor function | One good quality case–control study [8] | | Insufficient evidence |
| Increased stiffness | One good quality case–control study [8] | | Insufficient evidence |
| Poor physical component summary QoL | One good quality case–control study [8] | | Insufficient evidence |
| Good mental component summary QoL | One good quality case–control study [8] | | Insufficient evidence |
| Poor American Knee Society score_pain | One good quality case–control study [8] | | Insufficient evidence |
| Poor American Knee Society score_function | One good quality case–control study [8] | | Insufficient evidence |
| ***BMD lumbar spine*** | | | |
| Increased pain | One good quality case–control study [8] | | Insufficient evidence |
| Poor function | One good quality case–control study [8] | | Insufficient evidence |
| Reduced stiffness | | One good quality case–control study [8] | Insufficient evidence |
| Physical component summary QoL | | One good quality case–control study [8] | Insufficient evidence |
| Mental component summary QoL | | One good quality case–control study [8] | Insufficient evidence |
| American Knee Society score_pain | | One good quality case–control study [8] | Insufficient evidence |
| Poor American Knee Society score_function | One good quality case–control study [8] | | Insufficient evidence |
| Low body mass Index | One good quality case–control study [32] | One good quality cross-sectional study [11] | Conflicting evidence |
| Increased KL score | | One good quality cross-sectional study [11] | Insufficient evidence |
| Gender | | One good quality cross-sectional study [11] | Insufficient evidence |
| Age | | One good quality cross-sectional study [11] | Insufficient evidence |

*QoL* quality of life, *KL* Kellgren Lawrence, *BMD* bone mineral density

population. Longitudinal BMD loss has been reported to be associated with progressive cartilage loss in knees with OA Patients thus suggesting that severity of knee OA may be directly related to the BMD of the individual [24]. With the advent of therapies that modify bone turnover, a better understanding of the relationship between BMD and structural/ clinical changes in knee OA may have important implications for important clinical outcomes of the disease like,onset and/or progression [24].

There was considerable variation in the assessment sites for BMD in the studies. The studies by some of the authors [8, 11] had BMD measurements made at the proximal femur and lumbar spines in their studies. In one study [37], BMD was assessed at the proximal femur, femoral neck and lumbar spines. In the fifth study [32], BMD assessment was done at the proximal femur and lumbar spine. Lingard et al. [27] who made measurements at the forearm in addition to the spine and proximal femur,

reported significant proportion of patients with severe OA had low BMD and that the diagnosis may be missed unless BMD measurements are performed at sites distant from the joints affected by OA.

### Implications for clinical practice

Clinicians should potentially target increased BMI, especially by strengthening skeletal muscles which may improve BMD of patients with osteoporosis and osteopenia in the long run. In addition, an increase in BMI may promote mechanical stress on the body density, subsequently improving BMD.

### Implications for further research

Well-conducted longitudinal studies with adequate sample sizes and diverse OA populations are needed as this would provide more comprehensive understanding of the association between clinical factors and BMD in osteoarthritis. In addition, it is important to investigate clinical factors associated with BMD in other climes such as Africa and America as environmental factors may influence the perpetuation and presentation of OA. Further, future studies may consider other potentially relevant factors that may be associated with BMD, including: medication use, physical activity levels, sedentary behavior patterns, and dietary habits.

### Strengths and limitations

This study is the first to investigate the association between BMD and clinical factors of hip and or knee OA. In addition, we used best evidence synthesis to adjudge the current level of evidence for the association. This study is however with limitations. These study findings were based on only five studies a higher proportion of which were cross-sectional designs, limiting the ability to draw robust conclusions. As noted by one of the studies the variability of assessment sites might influence BMD detection [27]. The use of convenience sampling techniques would also negatively impact the internal validity of these studies. In addition, our search might have missed some studies published in non-English journals, thus, other clinical factors might not have been identified.

## Conclusion

This systematic review synthesizes current evidence on BMD and its associated clinical factors. High likelihood of bias and limited evidence at best suggests a need for well-designed studies on the relationship between OA and BMD.

## Appendix

Search strategy

# S1 TI bone mineral density OR TI BMD OR TI bone density OR TI BD OR TI osteoporosis OR TI osteopenia
#S2 AB bone mineral density OR AB BMD OR AB bone density OR AB BD OR AB osteoporosis OR AB
Osteopenia
#S3 TI clinical factors OR TI outcomes OR TI correlates OR TI determinants OR TI prevalence OR TI
predictors OR TI predictor
#S4 AB clinical factors OR AB outcomes OR AB correlates OR AB determinants OR AB prevalence OR AB predictors OR AB predictor
#S5 TI osteoarthritis OR TI knee osteoarthritis OR TI KOA OR TI hip osteoarthritis OR TI HOA
#S6 AB osteoarthritis OR AB knee osteoarthritis OR AB KOA OR AB hip osteoarthritis OR AB HOA
#S7 S1 OR S2
#S8 S3 OR S4
#S9 S5 OR S6
#S10 S7 AND S8 AND S9

Search strategy for Medline

#S1 TI bone mineral density OR TI BMD OR TI bone density OR TI BD OR TI osteoporosis OR TI osteopenia
#S2 AB bone mineral density OR AB BMD OR AB bone density OR AB BD OR AB osteoporosis OR AB
Osteopenia
#S3 TI clinical factors OR TI outcomes OR TI correlates OR TI determinants OR TI prevalence OR TI
predictors OR TI predictor
#S4 AB clinical factors OR AB outcomes OR AB correlates OR AB determinants OR AB prevalence OR AB predictors OR AB predictor
#S5 TI osteoarthritis OR TI knee osteoarthritis OR TI KOA OR TI hip osteoarthritis OR TI HOA
#S6 AB osteoarthritis OR AB knee osteoarthritis OR AB KOA OR AB hip osteoarthritis OR AB HOA
#S7 S1 OR S2
#S8 S3 OR S4
#S9 S5 OR S6
#S10 S7 AND S8 AND S9

### Search strategy for PsyCINFO

#S1 TI bone mineral density OR TI BMD OR TI BD OR TI Bone density OR TI osteoporosis OR TI osteopenia
#S2 AB bone mineral density OR AB BMD OR AB BD OR AB Bone density OR AB osteoporosis OR AB osteopenia
#S3 TI clinical factors OR TI outcomes OR TI correlates OR TI determinants OR TI predictors OR TI predictor
#S4 AB clinical factors OR AB outcomes OR AB correlates OR AB determinants OR AB predictors OR TI predictor
#S5 TI osteoarthritis OR TI knee osteoarthritis OR TI KOA OR TI hip osteoarthritis OR TI HOA
#S6 S1 OR S2
#S7 S3 OR S4
#S8 AB osteoarthritis OR AB knee osteoarthritis OR AB KOA OR AB hip osteoarthritis OR AB HOA
#S9 S5 OR S8
#S10 S6 AND S7 AND S9

### Search strategy for web of science

1. bone mineral density (Title) OR BMD (Title) OR bone density (Title) OR BD (Title) OR Osteoporosis (Title) OR osteopenia (Title)
2. bone mineral density (Abstract) OR BMD (Abstract) OR bone density (Abstract) OR BD (Abstract) OR Osteoporosis (Abstract) OR osteopenia (Abstract)
3. #1 OR #2
4. clinical factors (Title) OR risk factors (Title) OR outcomes (Title) OR determinants (Title) OR predictor (Title) OR prevalence (Title)
5. clinical factors (Title) OR risk factors (Abstract) OR outcomes (Abstract) OR determinants (Abstract) OR predictor (Abstract) OR prevalence (Abstract)
6. 6: #5 OR #4
7. osteoarthritis (Title) OR knee osteoarthritis (Title) OR KOA (Title) OR hip osteoarthritis (Title) OR HOA (Title)
8. osteoarthritis (Abstract) OR knee osteoarthritis (Abstract) OR KOA (Abstract) OR hip osteoarthritis (Abstract) OR HOA (Abstract)
9. #8 OR #7
10. #9 AND #6 AND #3

### Modified best-evidence synthesis

| | |
|---|---|
| Strong evidence | Generally, consistent findings in multiple high-quality cohort studies. |
| Moderate evidence | When one high-quality cohort study and two or more high-quality case–control studies or at least three high-quality case–control studies generally show consistent findings. |
| Limited evidence | Generally consistent findings in a single cohort study and/or in maximum two case–control studies, or in multiple cross-sectional studies. |
| Conflicting evidence | Less than 75% of the studies reported consistent findings. |
| Insufficient evidence | Less than two studies available. |
| No evidence | When no study could be found. |

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**Authors' contributions**
BA: Conceptualization, study design, write-up. CE: Conceptualization data collection and write-up. OA: Data collection, analysis, and write-up. AA: Data collection, analysis, and write-up. OA: Data collection and write-up. HO: Data collection and write-up. J: Data collection and write-up. T: Data collection and write-up. AO: Conceptualization and study design

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**Availability of data and materials**
Data from this study were pooled from Online electronic databases of CINAHL, Cochrane, Medline, PsycINFO, PubMed, Web of Science, and African Journal (from inception to September 12, 2022).

## Declarations

**Ethics approval and consent to participate**
This study was reviewed and approved by The University of Ibadan/University College Hospital Ibadan ethics review committee in Oyo state, Nigeria.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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