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Obesity, insulin resistance, and type 2 diabetes as determinants of bone mineral density in pre- and postmenopausal women: A systematic review

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Systematic Review

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Abstract

Background.

Osteoporosis represents a major global health burden, particularly affecting women. While estrogen deficiency following menopause is the classical driver of bone loss, metabolic factors including obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) are increasingly recognized as modulators of bone mineral density (BMD). Whether these metabolic factors exert distinct effects in premenopausal versus postmenopausal women remains incompletely characterized.

Methods.

We conducted a systematic PubMed search (2016–2026) for papers representing original studies that: (a) analyzed women with at least one of obesity, insulin resistance, or T2DM; (b) assessed BMD, osteoporosis, or fracture risk as an outcome; and (c) simultaneously included both pre- and postmenopausal women as distinct subgroups or compared results across menopausal status.

Results.

From 107 papers that mentioned both menopausal groups, we identified 14 original studies meeting all inclusion criteria and providing sufficient quantitative data. These studies gathered approximately 1,5 million women, including database records, with premenopausal and postmenopausal women split almost equally. The key determinants of low BMD and the character of the association between BMD and osteoporosis markers differed substantially between the menopausal groups. In premenopausal women, visceral adipose tissue, body fat percentage, and elevated HOMA-IR, and central obesity (waist circumference) emerged as the dominant predictors of low BMD. In postmenopausal women, lean body mass loss (sarcopenia), subcutaneous adipose tissue distribution, metabolic syndrome components (particularly hyperglycemia and insulin resistance in the context of obesity), sclerostin levels, and adipokine dysregulation (leptin, adiponectin) were the principal determinants.

Conclusions.

The relationship between metabolic disorders and BMD is strongly modified by menopausal status. Visceral adiposity is the key bone-detrimental factor in premenopausal women, whereas sarcopenic obesity and adipokine imbalance drive bone loss in postmenopausal women. These findings have important implications for sex- and menopausal-status-specific strategies for osteoporosis prevention and treatment.

1. Introduction

Osteoporosis is among the most prevalent chronic skeletal disorders worldwide, characterized by reduced bone mass and microarchitectural deterioration of bone tissue, culminating in bone fragility and susceptibility to fracture [1]. The clinical and economic consequences of the disease are substantial: fragility fractures of the hip, vertebrae, and distal forearm are associated with chronic pain, loss of independence, long-term disability, and, in the case of hip fractures, an excess mortality that may exceed 20% in the first year following the event [2–6]. Women bear a disproportionate share of this burden, both because they attain a lower peak bone mass than men and because the menopausal transition precipitates an accelerated phase of bone loss. With ageing populations across high-, middle-, and low-income countries, the absolute number of osteoporotic fractures is projected to rise steeply over the coming decades, making the identification of modifiable determinants of bone mineral density (BMD) a public-health priority [7, 8].

The scale of this burden is difficult to overstate. Worldwide, fragility fractures number in the tens of millions each year, and a woman aged fifty has approximately a one-in-two lifetime probability of sustaining an osteoporotic fracture, which is a risk that exceeds her combined lifetime risk of breast, endometrial, and ovarian cancer [9]. Hip fractures are the most devastating manifestation: roughly half of affected individuals never recover their previous level of function, a substantial fraction require long-term institutional care, and excess mortality clusters in the first year after the event [7]. Vertebral fractures, though often clinically silent, lead to height loss, kyphosis, restrictive ventilatory impairment, and chronic back pain, which are powerful predictors of subsequent fractures [9, 10]. The direct and indirect costs of osteoporotic fractures consume a large and rising share of healthcare budgets in ageing societies [11]. In this context, any modifiable determinant of BMD holds substantial public health implications, particularly the metabolic factors investigated in this study, which are readily amenable to intervention.

One of the canonical drivers of postmenopausal bone loss is the decline in circulating estrogen. Estrogen is a master regulator of bone remodeling: it restrains osteoclast formation and activity, promotes osteoclast apoptosis, and prolongs the functional lifespan of bone-forming osteoblasts and osteocytes [3, 12]. When estrogen withdraws at menopause, the receptor activator of nuclear factor-κB ligand (RANKL) to osteoprotegerin (OPG) ratio shifts in favor of resorption; osteoclastogenesis is disinhibited, and the lifespan of osteoblasts is shortened. The net effect is a significant acceleration of bone turnover in which resorption outpaces formation, producing the rapid trabecular bone loss that characterizes the early postmenopausal years [9, 10]. This framework explains why menopausal status is the single most powerful clinical predictor of declining BMD in women and why antiresorptive therapy has been the cornerstone of osteoporosis management.

Beyond the sex steroids, there is growing recognition that obesity, insulin resistance, and T2DM are intimately linked to bone metabolism. Adipose tissue is no longer regarded as inert ballast but as an active endocrine organ that secretes leptin, adiponectin, and inflammatory cytokines, all of which influence the bone remodeling unit [13, 14]. For many years, obesity was considered protective for the skeleton because greater body weight imposes a larger mechanical load that stimulates bone formation, and because adipose-derived aromatization of androgens to estrogens partially preserves the hormonal milieu. Contemporary epidemiology has complicated this picture: obesity is now known to carry a paradoxical

increase in fracture risk at certain skeletal sites, notably the proximal humerus, ankle, and, in some analyses, the lower leg, even when areal BMD appears preserved or elevated [15, 16]. Diabetes adds a further layer of complexity: individuals with T2DM frequently exhibit normal or high BMD yet experience elevated fracture rates, reflecting impaired bone quality driven by advanced glycation end-products, increased marrow adiposity, and altered insulin signaling in osteoblasts [17].

Crucially, the biology that links adiposity and metabolic dysfunction to the skeleton is unlikely to be uniform across a woman's reproductive life. The premenopausal and postmenopausal states differ fundamentally in their hormonal context, in the distribution and metabolic activity of adipose tissue, and in the prevailing rate of bone turnover [18, 19]. In the estrogen-replete premenopausal state, estrogen derived from adipose and a comparatively low rate of bone resorption may buffer the skeleton against some metabolic insults, while specific depots such as visceral adipose tissue exert specific harmful effects. After menopause, the loss of ovarian estrogen unmasks and may amplify the detrimental influence of adiposity and insulin resistance, while shifting which fat compartments and adipokines are most strongly associated with BMD [20, 21]. These considerations suggest that the metabolic determinants of BMD may differ qualitatively, and not merely quantitatively, between pre- and postmenopausal women.

Menopausal status should be conceptualized as an effect modifier rather than a simple covariate, a distinction grounded in bone physiology. Bone remodeling operates through basic multicellular units that couple osteoclastic resorption to subsequent osteoblastic formation [22]. This coupling is regulated by systemic hormones (estrogen, parathyroid hormone, vitamin D, insulin, IGF-1) and local signaling molecules, including the RANKL/OPG system and the osteocyte-derived Wnt-pathway inhibitor sclerostin [23–27]. Adipose tissue intersects this regulatory network via aromatization of androgens to estrogens, secretion of leptin and adiponectin, and contribution to chronic low-grade inflammation characteristic of obesity. Since estrogen restrains sclerostin and modulates adipokine signaling, its loss at menopause does not simply add to the metabolic burden but qualitatively reconfigures how that burden is transmitted to bone.

Despite this biological plausibility, the literature remains fragmented. The overwhelming majority of studies on metabolic bone disease enroll postmenopausal women exclusively, both because osteoporosis is more prevalent in this group and because premenopausal low BMD is comparatively understudied and harder to define diagnostically. Studies that simultaneously characterize both pre- and postmenopausal women with obesity, insulin resistance, or T2DM are scarce. As a result, clinical guidance on screening and risk stratification often applies a uniform model across the menopausal divide, potentially overlooking determinants that are specific to one group or the other.

The present systematic review was designed to address this gap. Our aim was to identify original studies that analyzed both pre- and postmenopausal women with at least one metabolic exposure (obesity, insulin resistance, or T2DM) and that reported BMD, osteoporosis, or risk factors of fractures as an outcome, and then to characterize how the determinants of BMD differ between these two groups, i. e. premenopausal vs postmenopausal women. By synthesizing evidence across multiple countries, ethnicities, and study designs, we sought to clarify whether visceral adiposity, lean mass, adipokines, sclerostin, and insulin

resistance act differently before and after menopause, and to draw out the implications for diagnosis, screening, and treatment of osteoporosis in women with metabolic disorders.

2. Methods

2.1 Search strategy

A systematic search of the PubMed/MEDLINE database was performed in May 2026. Three complementary search queries were constructed to capture each of the three metabolic exposures of interest, each restricted to women and to the publication window 2016–2026, and each requiring a term related to menopause, so that the retrieved literature would be relevant to the comparison of pre- and postmenopausal women.

Query 1 (obesity): (obesity OR “body mass index” OR BMI) AND (osteoporosis OR “bone mineral density” OR BMD OR “bone loss” OR fracture OR “fracture risk”) AND (premenopausal OR postmenopausal OR menopausal) AND women AND (2016:2026[dp]) — yielding 1,440 results.

Query 2 (T2DM): (“type 2 diabetes” OR T2DM) AND (osteoporosis OR “bone mineral density” OR BMD OR fracture OR “fracture risk”) AND (premenopausal OR postmenopausal OR menopausal) AND women AND (2016:2026[dp]) — yielding 286 results.

Query 3 (insulin resistance): (“insulin resistance” OR “insulin sensitivity” OR HOMA-IR OR hyperinsulinemia) AND (osteoporosis OR “bone mineral density” OR BMD OR fracture OR “fracture risk”) AND (premenopausal OR postmenopausal OR menopausal) AND women AND (2016:2026[dp]) — yielding 158 results.

These three queries returned a combined 1,884 records. A further targeted query that explicitly required the simultaneous presence of both premenopausal and postmenopausal groups within the same record narrowed the field to 107 results, which formed the core pool for screening.

2.2 Inclusion/exclusion criteria

Studies were eligible for inclusion if they satisfied all of the following: (a) original research (excluding reviews and editorials); (b) publication between 2016 and 2026; (c) human female participants; (d) at least one metabolic exposure: obesity or overweight, insulin resistance, or T2DM; (e) BMD, osteoporosis, or fractures reported as an outcome; and (f) inclusion of both pre- and postmenopausal women within the same study as distinct subgroups, or use of menopausal status as a moderating variable in the analysis. Records were excluded if they were narrative reviews or meta-analyses, animal studies, studies that did not provide quantitative BMD data, or studies whose design did not permit extraction of results associated with the menopausal status.

Titles and abstracts of the 107 targeted papers were screened against the eligibility criteria. Records passing this stage advanced to full-text assessment, where 25 studies were assessed in detail for

eligibility. Following full-text evaluation, 14 studies met the inclusion criteria and provided sufficient quantitative data for the review (Fig. 1).

From each included study, the following information was extracted in a standardized fashion: study design; country of origin; sample size, separately for premenopausal and postmenopausal participants; the nature of the metabolic exposure (obesity, insulin resistance, or T2DM); the method of BMD measurement; the key determinants of BMD identified; and the statistical significance of each association. Reported effect estimates specific to menopausal status were recorded separately, so that direct pre- versus postmenopausal comparisons could be assembled.

3. Results

3.1 Study characteristics and demographics

Fourteen original studies met all inclusion criteria and provided extractable data related to menopause. The studies were geographically and ethnically diverse, originating from Italy, the United States, the United Kingdom, Brazil, South Korea, Iran, Egypt, and Romania, and spanning a wide range of designs from small cross-sectional case series to very large nested case-control and longitudinal cohort investigations (Table 1). Together, the included studies encompassed a combined population of approximately 1,5 million women, when the large Korean clinical-database study is counted, with pre- and postmenopausal participants split almost equally [20, 21, 28–39]. Participant ages spanned roughly the third through the seventh decades of life, capturing the full menopausal transition.

The study designs also were diverse. As a few examples, three large national studies from South Korea — the KNHANES cross-sectional survey by Kim and colleagues [36], the KNHIS nationwide population-based epidemiologic study by Kim and colleagues [37], and the nested case-control investigation of Rhee and colleagues [31] — contributed population-level generalizability and the statistical power to detect modest effects such as the small but significant excess osteoporosis risk associated with the metabolic syndrome after menopause. The two longitudinal cohorts reported by Shieh and colleagues [29, 32], drawn from the Study of Women's Health Across the Nation, uniquely captured change over the menopausal transition and, therefore, permitted inference about temporal sequence rather than mere association. Although limited in sample size, the smaller cross-sectional series from Italy, Brazil, and Egypt contributed a depth of body-composition phenotyping, encompassing direct measurement of visceral and subcutaneous adipose depots and circulating bone-turnover markers, which large database studies usually are unable to provide [21, 28, 34]. The UK Biobank imaging study occupied a middle ground, pairing dual-energy X-ray absorptiometry (DXA) with MRI in several thousand women and thereby enabling depot-specific adiposity analyses [20].

The dominant exposure was obesity, defined variably by body mass index (BMI) category, by severe obesity thresholds (BMI ≥ 40), or by direct measures of adiposity and fat distribution; several studies additionally or alternatively examined insulin resistance (HOMA-IR), prediabetes, the metabolic syndrome, or T2DM. With respect to bone assessment, all studies used BMD information measured by DXA, obtained

either by direct measurements or from the databases. The characteristics of the included studies are summarized in Table 1.

Table 1

Characteristics of the fourteen studies included in the review. BMI, body mass index (kg/m^2); MT, menopausal transition; FPG, fasting plasma glucose (mg/dL); VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; CT, computer tomography; WC, waist circumference; DXA, dual-energy X-ray absorptiometry.

Study	Year	Country	Design	n (Pre)	n (Post)	Metabolic Exposure	BMD Method
Marzullo et al. [21]	2021	Italy	Cross-sectional	28	28	Severe obesity (BMI > 35)	DXA
Shieh et al. [29]	2022	USA	Longitudinal	861	571 (MT); 693 (post)	Insulin resistance (HOMA-IR)	DXA
Shieh et al. [32]	2023	USA	Longitudinal	1,690	same cohort after menopause transition	Prediabetes (FPG = 100–125)	DXA
Bland et al. [20]	2022	UK	Cross-sectional	231	1,579	Adiposity (VAT, SAT, total fat)	DXA
Crivelli et al. [28]	2021	Brazil	Cross-sectional	37	21	Severe obesity (BMI > 40)	DXA
Haam et al. [33]	2017	S. Korea	Cross-sectional	158	97	Central obesity	DXA
Rhee et al. [31]	2022	S. Korea	Nested case-control	293,048	95,393	Metabolic syndrome	DXA or CT
Salamat et al. [35]	2016	Iran	Cross-sectional	1,832	3,468	Obesity (BMI categories)	DXA
Kim et al. [36]	2016	S. Korea	Cross-sectional	5,455	4,633	Obesity (BMI, fat mass)	DXA
Hassan et al. [34]	2020	Egypt	Cross-sectional	51	65	Obesity (BMI, fat distribution)	DXA
Hua et al. [30]	2021	USA	Cross-sectional	1120	1206	Central obesity (waist circumference, BMI)	DXA
Kim et al. [37]	2021	S. Korea	Cohort	1,156,174	1,368,005	Obesity (BMI, waist circumference, waist-to-height ratio)	–

Study	Year	Country	Design	n (Pre)	n (Post)	Metabolic Exposure	BMD Method
Chain et al. [38]	2017	Brazil	Cross-sectional	100	166	Fat mass	DXA
Bilha et al. [39]	2018	Romania	Cross-sectional	38	55	Body composition, adipokines	DXA

3.2 BMD determinants: Differences between pre- and postmenopausal women

Table 2 assembles the effect estimates associated with menopausal status extracted from the included studies. Two large studies directly examined BMI, the simplest exposure metric. Salamat and colleagues and Kim and colleagues both reported the classical positive association between higher BMI and higher BMD in pre- and postmenopausal women alike [35, 36]. These findings appear to endorse the view that obesity is protective. However, other results suggest that the observed association at the BMI level is a crude average, which masks opposing, compartment-specific effects. When adiposity is decomposed into its visceral, subcutaneous, and marrow components and lean mass is considered, the relationship transforms into the menopause-dependent pattern.

Table 2

Menopausal-status-specific determinants of BMD and fractures. BMI, body mass index; OR, odds ratio; FN, femoral neck; LM, lean mass; FM, fat mass; FP, fat percentage; WC, waist circumference; LS, lumbar spine; WB, whole body; CO, central obesity; HMW, high-molecular-weight; MT, menopausal transition; HR, hazard ratio; BMR, basal metabolic rate; WHtR, waist-to-height ratio.

Factor	Effect (Pre)	Effect (Post)	p-value (Pre)	p-value (Post)	Reference
Obesity (BMI)	BMD was higher in obese and overweight vs normal weight women		< 0.001 (FN)	< 0.001	Salamat et al. [35]
	OR = 0.18 (0.07) of FN (hip) osteoporosis in obese vs normal weight women	OR = 0.15 (0.06) of FN (hip) osteoporosis in obese vs normal weight women	< 0.05 (hip)		
Body composition parameters (BMI, LM, FM, FP, WC)	All parameters correlate with BMD. LM, FM, FP, and WC strongly affect LS, FN, and hip BMD		< 0.001		Kim et al. [36]
Visceral adipose tissue in women with severe obesity	Inversely associated with femoral neck strength	Not significant	0.04	> 0.05	Crivelli et al. [28]
Subcutaneous adipose tissue in women with severe obesity	Not significant	Inversely associated with femoral BMD	> 0.05	0.021	Crivelli et al. [28]
HOMA-IR (low–moderate values)	Greater HOMA-IR is associated with slower BMD decline	Similar (post); weaker (MT)	0.01 (LS); 0.004 (FN)	0.004 (LS); 0.04 (FN)	Shieh et al. [29]
HOMA-IR change rate	Positive association with BMD change rate in women with decreasing HOMA-IR; negative association in women with increasing HOMA-IR	Similar (post); weaker (MT)	< 0.05	< 0.05	Shieh et al. [29]
Sclerostin in obese women	Strong predictor of lumbar BMD; shows a trend to increase at menopause transition		< 0.01		Marzullo et al. [21]
Lean body mass in obese women	Strong predictor of total BMD	Similar effect; decreased compared to pre ($p < 0.05$)	< 0.01		Marzullo et al. [21]
Menopausal status in obese women	—	Lower BMD hip/FN/WB BMD	—	< 0.01 (hip); < 0.001 (FN)	Marzullo et al. [21]

Factor	Effect (Pre)	Effect (Post)	p-value (Pre)	p-value (Post)	Reference
				< 0.05 (WB)	
Adiposity measures	Negative association with WB and FN BMD	Positive association with WB and FN BMD	< 0.05	< 0.05	Bland et al. [20]
WC as a marker of obesity	Inverse association with lumbar BMD, more pronounced for women with BMI < 25	Inverse association with lumbar BMD (BMI < 25 only)	< 0.001	< 0.01	Hua et al. [30]
Metabolic syndrome	No association with osteoporosis in women with all obesity statuses	High occurrence of osteoporosis in obese women	< 0.001	< 0.001	Rhee et al. [31]
Prediabetes before MT	—	Higher fracture risk (HR = 2.20)	—	0.02	Shieh et al. [32]
Leptin, in relation to central obesity	Not significant	Negatively associated with non-vertebral BMD in women without CO	> 0.05	0.006 (hip) 0.007 (FN)	Haam et al. [33]
HMW adiponectin, in relation to central obesity	Positively associated with hip BMD in women without CO	Negatively associated with BMD in women without CO	0.010	0.012 (LS) 0.007 (FN)	Haam et al. [33]
Fat mass and its distribution, in relation to energy intake (via BMR)	Positive association of FN BMD with BMR and LS BMD with BMR, BMI, and WC	Positive association of FN BMD with visceral fat and LS BMD with BMR	< 0.01	< 0.05	Hassan et al. [34]
Obesity/abdominal obesity via body composite indices (BMI, WC, WHtR)	High fracture risk in women with obesity (HR = 1.24) and even higher in women with abdominal obesity (HR = 1.35)	Similar but weaker effect: HR = 1.04 for obesity and HR = 1.13 for abdominal obesity	No data	No data	Kim et al. [37]
Fat mass	Negatively associated with WB and FN BMD when adjusted for total body mass	Positively associated with BMD at all sites when adjusted for lean mass	< 0.01 (WB) < 0.05 (FN)	< 0.01	Chain et al. [38]
Body composition and adipokines	Lean mass was the only independent	Trunk-to-leg fat ratio was the dominant BMD	< 0.01 (WB)	< 0.05 (WB and	Bilha et al. [39]

Factor	Effect (Pre)	Effect (Post)	p-value (Pre)	p-value (Post)	Reference
	predictor of WB and FN BMD	predictor at various sites	< 0.001 (FN)	radius BMD) < 0.01 (LS)	

The central observation of this review is that the determinants of BMD differ markedly between premenopausal and postmenopausal women. In premenopausal women, central and visceral adiposity were repeatedly identified as bone-detrimental, whereas in postmenopausal women, the adverse adiposity compartment shifted toward subcutaneous fat and the dominant risks were lean-mass loss, adipokine dysregulation, and the metabolic syndrome [20, 21, 28, 29, 31, 33].

A good example is the Brazilian study of women with severe obesity, in which the two principal adipose compartments behaved in opposite directions across menopause: visceral adipose tissue was inversely related to bone strength in premenopausal women ($p = 0.04$) but not in postmenopausal women, whereas subcutaneous adipose tissue was inversely associated with femoral BMD specifically in the postmenopausal group ($p = 0.021$) [28]. This depot switch is among the clearest demonstrations that the same total fat mass can be skeletally benign or harmful depending on its anatomical distribution and the hormonal context.

The longitudinal cohort data on insulin resistance revealed a nuanced, non-linear relationship. At low-to-moderate levels, HOMA-IR was associated with a slower rate of BMD loss, providing a paradoxically protective signal observed in both groups, but statistically clearest for different sites ($p = 0.004$ for femoral neck in premenopausal women and lumbar spine in postmenopausal women) [29]. However, a rapidly rising HOMA-IR trajectory was detrimental in both groups, indicating that it is the dynamics of insulin resistance, and not merely a single cross-sectional value, that determine skeletal consequences.

In women with severe obesity, sclerostin emerged as the strongest predictor of lumbar BMD in the premenopausal group ($p < 0.01$), with no significant difference between pre- and postmenopausal levels, while lean body mass was the stronger predictor of total BMD in pre- than postmenopausal women ($p < 0.05$) [21]. Menopausal status itself remained a powerful independent determinant of lower hip, femoral neck, and total BMD ($p < 0.05$), reaffirming that metabolic determinants act on top of, rather than instead of, the estrogen-withdrawal effect.

The adipokine data deserve special attention. In the absence of central obesity, high-molecular-weight adiponectin was positively associated with hip BMD in premenopausal women ($p = 0.010$) but reversed to an inverse association with lumbar and femoral BMD after menopause ($p \leq 0.012$), while leptin became inversely associated with hip and femoral neck BMD only in postmenopausal women ($p \leq 0.007$) [33]. The large Korean case-control analysis showed that the metabolic syndrome in the context of obesity carried no excess osteoporosis risk before menopause but a statistically significant excess risk afterwards ($p =$

0.001) [31]. Prediabetes present before the menopausal transition more than doubled subsequent fracture risk (HR = 2.20, p = 0.02) [32].

Two further patterns deserve comment. First, the behavior of waist circumference, a simple indicator of central adiposity, was inverse with respect to lumbar BMD in both groups but essential only among women of normal weight (BMI < 25), implying that central fat accumulation is skeletally harmful even when overall body mass is not elevated, and that this harm is partly masked in obese individuals by the countervailing effect of mechanical loading [30]. Second, in the Egyptian cohort the basal metabolic rate was the single strongest predictor of femoral-neck BMD in premenopausal women, accounting for approximately 56% of the variance, while its predictive dominance weakened after menopause [34]. Because basal metabolic rate is closely tied to lean mass, this observation reinforces the view that metabolically active muscle, rather than fat, is the principal determinant of premenopausal bone strength. Taken together, the data assembled in Table 2 portray a coherent biological narrative: a premenopausal skeleton protected by lean mass and threatened by visceral fat, transitions after menopause to a skeleton in which subcutaneous fat, adipokine reversal, and the metabolic syndrome become detrimental.

3.3 Fracture outcomes: Differences between pre- and postmenopausal women

An important dimension of skeletal risk beyond BMD is the actual occurrence of fractures. Direct evidence comes from Crivelli and colleagues [28], who documented a high prevalence of morphometric vertebral fractures in severely obese women (32% of pre- vs 55% of postmenopausal women). This difference is particularly striking because BMD at all measured sites was comparable or only modestly lower in postmenopausal women despite the higher fracture burden. This demonstrates the quintessential dissociation between bone density and bone quality in obesity: postmenopausal women carry a disproportionately greater fracture risk not fully explained by their DXA measurements, consistent with microarchitectural and material changes driven by estrogen withdrawal, adipokine reversal, and elevated bone turnover markers in the postmenopausal state.

Prospective longitudinal evidence on the metabolic pathway to fracture is provided by Shieh and colleagues [32]. Women with prediabetes before the menopause transition (MT) faced an HR of 2.20 (95% CI 1.11–4.37, p = 0.02) for incident fracture during or after the MT compared with normoglycemic women. In absolute terms, women with prediabetes at all pre-MT visits experienced approximately 7 additional fractures per 1,000 person-years above the baseline rate of 6.3 fractures per 1,000 person-years. Most fractures in this cohort occurred at non-hip, non-vertebral sites, which is a fracture phenotype known to carry a 2-fold greater risk of subsequent vertebral or hip fracture. The prediabetes–fracture association was independent of BMD, implicating bone quality deficits (glycation-driven collagen crosslink abnormalities, Wnt pathway suppression) rather than bone mass as the mediating mechanism.

In the Italian cohort of women with severe obesity [21], osteoporosis defined by BMD values was detected in only one premenopausal woman (1/28, 3.6%) compared with none among the 28 postmenopausal women. However, the postmenopausal group showed significantly lower BMD at all appendicular sites (p

< 0.001), providing a DXA-based indicator for elevated fracture risk. From a broader adipokine perspective, a meta-analysis of 14 studies comparing postmenopausal osteoporotic women to those with normal BMD found that blood leptin was significantly lower (MD = − 1.94, 95% CI − 3.83 to − 0.06) and adiponectin significantly higher (MD = 3.48, 95% CI 2.36–4.60) in the osteoporosis group. Moreover, adiponectin was negatively correlated with BMD (r = − 0.33) and showed the highest predictive probability for postmenopausal osteoporosis (84%) [40]. A longitudinal analysis of older adults in another study found that higher adiponectin was associated with increased fracture risk in older men but not women, suggesting that the adipokine–fracture association is conditioned by sex [41]. Taken together, the evidence indicates that postmenopausal women with obesity, prediabetes, or T2DM experience substantially higher fracture rates than their premenopausal counterparts, which are approximately 1.7-fold higher for vertebral fractures in severe obesity [28] and more than 2-fold higher when prediabetes is present across the MT [32]. These excess fractures are driven primarily by bone quality impairment rather than bone quantity loss [17, 28, 32].

Kim and colleagues [37] added more on the menopause-conditioned association between obesity and vertebral fracture risk. Obesity was associated with incident vertebral fracture in both pre- (adjusted HR 1.24, 95% CI 1.19–1.30) and postmenopausal women (adjusted HR 1.04, 95% CI 1.03–1.05). Abdominal obesity was associated with even higher fracture risk: HR 1.35 (95% CI 1.27–1.43) in pre- and HR 1.13 (95% CI 1.11–1.14) in postmenopausal women. Counter-intuitively, the fracture risk associated with both general and abdominal obesity was substantially higher in premenopausal than postmenopausal women, a pattern the authors attributed to greater abdominal adiposity-related inflammatory and biomechanical effects in the estrogen-replete state.

3.4 Diagnostic markers for osteoporosis by menopausal status

The diagnostic utility of individual bone and metabolic markers, and their relationship to obesity, also varied by menopausal status. DXA-based BMD values remain the diagnostic foundation in both pre- and postmenopausal women, but their connection to various metabolic disorders differs for pre- and postmenopausal women, as discussed above (Table 2). The trabecular bone score as a complementing bone quality indicator adds value mostly in postmenopausal women with T2DM, in whom areal BMD can be misleadingly preserved [42, 43]. Among biochemical markers, HOMA-IR and the TyG-BMI/METS-IR indices behave as metabolic risk markers that are paradoxically associated with preserved BMD at lower levels [29, 44], serum sclerostin serves as a good predictor of lumbar BMD regardless of the menopause status [21]. Resorption (CTX) and formation (osteocalcin) markers and leptin all show the same general pattern: relatively favorable or neutral before menopause and unfavorable afterwards.

Taken together, these findings imply that screening cannot rely on a single marker; instead, the optimal panel should be stratified by menopausal status. In premenopausal women, a combination of lumbar DXA, waist circumference, a HOMA-IR estimate, and serum sclerostin captures the variance in bone status attributable to metabolic factors. In postmenopausal women, hip and femoral-neck DXA, the trabecular bone score, and selective measurement of leptin or resorption markers provide complementary

information, which areal BMD alone misses [20, 21, 29, 31, 44]. Taken together, these marker specific findings inform the proposed menopause stratified panel, which we extend in the discussion of clinical applications below.

3.5 Bone turnover markers: Differences between pre- and postmenopausal women

Bone turnover markers consistently reflected the lower remodeling rate of the estrogen-replete premenopausal skeleton and the accelerated turnover that follows menopause. Table 3 contrasts the principal resorption and formation markers across the two groups.

Table 3
Bone turnover markers compared between pre- and postmenopausal women with metabolic disorders. CTX, C-terminal crosslinking telopeptide; NTX, N-terminal crosslinking telopeptide; LS, lumbar spine.

Bone Turnover Marker	Premenopausal Women	Postmenopausal Women	Direction	Ref
CTX (C-terminal telopeptide)	Lower levels (obesity is protective?)	Significantly elevated	Post > Pre	Marzullo 2021 [21]
NTX (N-terminal telopeptide)	Lower levels	Significantly elevated	Post > Pre	Marzullo 2021 [21]
Sclerostin	Strong predictor of lumbar BMD		Post ≥ Pre (trend)	Marzullo 2021 [21]
Osteocalcin	Standard levels		Post = Pre	Crivelli 2021 [28]
C-terminal peptide	Lower in obese women vs post	Positive correlation with LS BMD	Post > Pre in obese women	Hassan 2020 [34]

Both resorption markers (CTX, NTX) were higher in postmenopausal vs premenopausal women, consistent with estrogen withdrawal. In obese women, these markers were relatively suppressed vs non-obese, yet postmenopausal obese still had higher levels than premenopausal obese. Sclerostin tended to be higher postmenopausally but not significantly ($p > 0.05$) [21]. Osteocalcin was elevated in postmenopausal women vs premenopausal, but suppressed in T2DM vs non-diabetic obese postmenopausal ($p < 0.01$) [21], and inversely associated with glucose metabolism [21, 28]. Osteoporotic women had higher osteocalcin and lower TBCa vs normal pre-/postmenopausal women ($p < 0.001$) [45–47], suggesting high osteocalcin indicates low skeletal mass. However, low resorption in obesity/diabetes may indicate low bone turnover, impairing removal of damaged matrix, and new bone formation [17]. This frozen remodeling leads to microdamage and advanced glycation end-products, degrading bone quality despite preserved BMD, explaining normal/elevated BMD with increased fracture risk in T2DM [17, 21, 31, 48–50]. Thus, quality-sensitive measures like trabecular bone score and turnover markers are needed.

3.6 Osteoporosis medications in women with obesity, insulin resistance, or T2DM

Although this review focuses on determinants of BMD rather than on treatment trials, a brief review of the pharmacological management in women with metabolic disorders is necessary because the choice of medications depends on metabolic state.

The pharmacological management of low BMD in women with metabolic disorders is almost exclusively informed by postmenopausal evidence, necessitating a clear distinction in therapeutic strategy according to menopausal status. Bisphosphonates constitute the standard first-line antiresorptive therapy, though their already limited oral bioavailability may be further compromised in obesity, favouring intravenous administration in selected cases [9, 51–53]. Denosumab offers a convenient subcutaneous alternative without renal dose restriction and has demonstrated fracture risk reduction in postmenopausal women with T2DM, yet its discontinuation requires careful monitoring for rebound bone loss [9, 54, 55]. Romosozumab, given its dual anabolic and antiresorptive mechanism, appears particularly pertinent in T2DM with elevated sclerostin levels observed in this population, having been shown to improve trabecular bone score beyond areal BMD [56]. The skeletal effects of SGLT2 inhibitors and GLP-1 receptor agonists remain under investigation, with mixed fracture data for the former and preliminary bone-protective signals for the latter [57–59]. Selective estrogen receptor modulators, such as raloxifene, may exert complex interactions affecting both skeletal and cardiometabolic outcomes [9]. Crucially, extrapolation of these findings to premenopausal women is unwarranted; in this group, pharmacotherapy is reserved for clear secondary osteoporosis or overt fragility fractures, while primary emphasis is placed on optimising modifiable determinants including body composition, glycaemic control, vitamin D status, calcium intake, and mechanical loading. By contrast, in postmenopausal women, the decision-making threshold is determined by absolute fracture risk, and the choice among antiresorptive, anabolic, and anti-sclerostin agents can be tailored to the underlying metabolic milieu, with romosozumab representing a logical preference where sclerostin elevation and impaired bone quality are dominant concerns [9, 56].

This menopause-conditioned divergence constitutes the core conceptual framework integrating metabolic exposures, diagnostic markers, bone turnover, and pharmacological strategy.

3.7 Hormone therapy status of postmenopausal participants in the reviewed studies

A key methodological point is whether postmenopausal participants in reviewed studies received hormone therapy (HT), which modifies BMD, bone turnover, and metabolic effects on skeleton. HT treatment varied across studies. Most excluded current/recent women on HT; some did not report or adjusted for it. In the Italian [21] and Brazilian [28] cohorts, HT users were excluded. The two SWAN cohorts [29, 32] adjusted for time-varying HT use (HT prevalence in this population declined from ~ 26.9% in 2002 to 4.7% in later years [60]). The Korean study [33] excluded HT, while the UK Biobank analysis [20] adjusted for it.

Thus, most postmenopausal women were not on HT at assessment. Therefore, observed lower femoral neck/hip BMD, elevated CTX/NTX, and adipokine reversal in pre- vs postmenopausal women reflect natural estrogen deficiency, unconfounded by exogenous hormones. If women on HT were included without adjustment, BMD differences would be attenuated, as HT preserves BMD and reduces spinal fracture risk

by ~ 1/3 [60]. Moreover, a meta-analysis (17 randomized controlled trials, 5,772 women on HT vs 2,128 on placebo) confirmed that HT significantly reduces HOMA-IR in healthy non-diabetic postmenopausal women, with estrogen alone producing greater reductions than combined estrogen–progestogen regimens [61]. Consequently, postmenopausal women on HT may show attenuated insulin-resistance contribution to bone loss vs HT-naïve cohorts. Clinically, in a postmenopausal woman with obesity/T2DM receiving HT, CTX/NTX would be lower (closer to premenopausal), and the threshold for additional bone-active therapy may require upward adjustment [61].

3.8 Ethnic heterogeneity among the included studies and beyond

The studies reviewed derive from eight countries and at least four ethnic groups. Well-documented ethnic differences in BMD, body composition, and menopausal biology must be considered when interpreting the presented findings. Absolute BMD is consistently lower in East Asian women than in Caucasians when assessed against Caucasian NHANES III reference data [62, 63]. Femoral neck BMD in Filipino, Chinese, and Japanese women is 0.29–0.72 T-score units lower than in non-Hispanic White women [64]. Applying ethnic-specific references reduces estimated osteoporosis prevalence in Chinese women (29.6% to 12.6%) [62], reflecting differences in skeletal geometry that lower fracture risk per T-score unit [63] and lead to higher densitometric osteoporosis prevalence but lower hip fracture incidence (1.03 vs. 3.39 per 1000 person-years) at equivalent T-scores [65].

Menopausal symptomatology and hormonal trajectories differ by ethnicity, with vasomotor symptoms less prevalent in Chinese and Japanese women (~ 20%) than in Caucasian, Black, and Hispanic women (> 30–46%) [66]. A more gradual estrogen decline and distinct FSH dynamics, with FSH elevation independently driving bone resorption [32], may contribute to inter-ethnic variation in postmenopausal bone loss rates despite similar mean age at natural menopause [66, 68].

The obesity–BMD relationship also shows ethnic specificity: body weight protects lumbar spine BMD in both Asian and White overweight women, whereas central adiposity reduces BMD only in normal-weight women of both ethnicities [30]. South Asian women have earlier osteoporotic fractures [69, 70], higher android-to-gynoid fat ratio and lower vitamin D levels [69], and in Korean cohorts even modest BMD decrements are clinically important and may be underestimated by Caucasian-calibrated tools [31, 62, 63]. Diagnostic discordance between T-score and FRAX, higher diabetes prevalence, broadly similar responses to bisphosphonates and teriparatide, and greater benefit from vitamin D analogues in Asian women further underscore the need for ethnic-specific reference data [62, 63, 65, 69–73].

4. Discussion and Conclusions

The principal finding of this review is that obesity, insulin resistance, and T2DM exert fundamentally different effects on bone health depending on menopausal status. Rather than acting as a uniform metabolic insult across the female lifespan, these conditions interact with the prevailing hormonal environment, the distribution of adipose tissue, and the rate of bone remodeling to produce menopause-

specific patterns of determinants [20, 21, 28, 29, 31, 33]. This conclusion reframes the metabolic regulation of bone as a context-dependent phenomenon and argues against a single explanatory model (Fig. 2).

In premenopausal women, the fat–bone relationship is predominantly negative when it is driven by visceral and central adiposity rather than by total body weight. Visceral adipose tissue, body fat percentage, and waist circumference each emerged as adverse correlates of BMD, and serum sclerostin acted as a key mediator and the strongest predictor of lumbar BMD in obese premenopausal women [21]. A particularly instructive observation is that moderate elevations of HOMA-IR were associated with a slower rate of BMD loss, a paradox most plausibly explained by anabolic hyperinsulinaemia acting through IGF-1 signaling together with the mechanical stimulation provided by greater body mass [29]. Importantly, the dominant predictor of total-body BMD in this group was lean body mass, not fat mass per se, underscoring that muscle, rather than adiposity, is the principal skeletal ally before menopause [21].

In postmenopausal women, the withdrawal of ovarian estrogen resets the fat–bone axis [9, 10]. Subcutaneous, rather than visceral fat became the adverse adiposity compartment for femoral BMD [28], and the metabolic syndrome in combination with obesity — neutral or even protective before menopause — emerged as a net driver of osteoporosis [31]. Adipokines underwent a qualitative reversal: leptin became inversely related to femoral-neck BMD, and the favourable association of high-molecular-weight adiponectin with hip BMD seen before menopause inverted to a detrimental association with lumbar and femoral BMD afterwards [33].

These findings allow a resolution of the long-standing paradox of obesity and bone. The traditional view that obesity protects the skeleton through mechanical loading is not wholly wrong: BMI-defined obesity did correlate with higher BMD in both groups [35, 36]. What this review clarifies is that the composition of body weight, not its absolute magnitude, determines whether it is protective or harmful. Visceral fat is detrimental in premenopausal women [28], and sarcopenic obesity — the combination of excess fat with deficient muscle — is the most dangerous phenotype after menopause; Sun and colleagues (2025) reported an odds ratio for osteoporosis of 3.37 in this phenotype [74].

The role of insulin resistance is similarly biphasic. At low-to-moderate levels, HOMA-IR likely reflects compensatory hyperinsulinaemia that stimulates osteoblast activity via IGF-1 signaling, accounting for the paradoxically slower BMD loss observed [29]. At high HOMA-IR levels and in established T2DM, this benefit disappears and bone quality deteriorates through the accumulation of advanced glycation end-products in collagen, expansion of bone marrow adiposity, and impaired insulin signaling within osteoblasts [17]. Clinically that means, that a single HOMA-IR value is insufficient; its level and trajectory must be interpreted together.

These insights carry concrete implications for diagnosis and screening. In premenopausal women with obesity or T2DM, standard DXA should be supplemented by assessment of visceral fat — by body composition analysis or simply by waist circumference — and, where available, by serum sclerostin, which is the most discriminating biochemical marker in this group [21]. In postmenopausal women with the

metabolic syndrome, the trabecular bone score provides bone-quality information beyond the T-score and is particularly valuable when areal BMD is misleadingly preserved, as is common in T2DM [31, 56].

The therapeutic implications follow directly. Anti-sclerostin therapywith romosozumab is emerging as particularly appropriate for postmenopausal women with T2DM, given elevated sclerostin levels and impaired bone quality in this population, and its demonstrated improvement in trabecular bone score [56]. GLP-1 receptor agonists, increasingly used for metabolic disease and obesity, may confer bone-protective effects warranting dedicated investigation. Management of sarcopenic obesity—through resistance exercise, adequate protein intake, and judicious weight reduction—may be as consequential for postmenopausal bone health as antiresorptive pharmacotherapy itself [74].

Concerning fracture risk assessment among the included studies, the large Korean cohort by Kim and colleagues [37] provides the only direct comparison of incident vertebral fracture hazard ratios across menopausal groups in the context of obesity, confirming that obesity-associated fracture risk is not lower premenopausally. Indeed, it appears paradoxically higher for vertebral fractures driven by abdominal obesity (HR 1.35 pre vs. HR 1.13 post). This aligns with John Kanis's framework that fracture risk represents a broader construct than BMD-defined osteoporosis alone, incorporating bone quality, fall risk, and biomechanical factors that may operate differently across the hormonal lifespan [4].

Several limitations restrict these conclusions. Some included studies had small sample sizes, and there was substantial heterogeneity in obesity definition. Few studies originated from low- and middle-income countries, limiting generalizability, and longitudinal data in premenopausal women were sparse, leaving the temporal direction of several associations uncertain. Important confounders (physical activity, dietary calcium and vitamin D, and concomitant medications) were not uniformly measured or adjusted across studies. The reliance on areal BMD by DXA in most studies may underestimate fracture risk in obese and diabetic women, in whom bone quality is impaired independently of bone quantity [17, 56].

As such, menopausal status is a critical modifier of the relationship between metabolic disorders and bone health. Premenopausal women with obesity are principally threatened by visceral adiposity and by an unfavorable HOMA-IR trajectory [21, 28, 29], whereas postmenopausal women are most at risk from sarcopenic obesity, adipokine imbalance, and the compounding effect of estrogen deficiency on metabolic bone disease [31–33, 74]. Screening, diagnostic, and therapeutic strategies should therefore be tailored to menopausal status rather than applying a uniform approach and future research should prioritize longitudinal designs that span the menopausal transition and that integrate measures of bone quality alongside conventional BMD.

Translating these findings into practice, a pragmatic framework can be proposed. In a premenopausal woman with obesity or T2DM, clinicians should not be reassured by a high BMI alone; assessment should include waist circumference or DXA-derived regional fat to gauge central and visceral adiposity, a fasting metabolic panel from which HOMA-IR can be derived, and serum sclerostin [21]. Lean mass should be quantified, because its preservation is the dominant determinant of total-body bone strength before menopause and a modifiable target through resistance training and adequate protein intake. In a

postmenopausal woman with the same metabolic profile, the emphasis shifts: hip and femoral-neck DXA become essential, the trabecular bone score should supplement the T-score to capture the bone-quality deficit of T2DM [31, 56], and screening for sarcopenic obesity should be routine [74]. Adipokine and turnover-marker panels may refine risk in selected cases [33, 40, 41].

The gaps exposed by this review define a clear research agenda. First, prospective cohorts that enroll women before menopause and follow them through the transition are needed to establish the temporal sequence linking visceral adiposity, insulin-resistance trajectory, and incident low BMD [29, 32]. Second, studies should move beyond areal BMD to incorporate measures of bone quality — trabecular bone score, peripheral quantitative computed tomography, and where feasible marrow-fat quantification by magnetic resonance spectroscopy [17, 56]. Third, interventional trials are required to test whether treating sarcopenic obesity, or deploying anabolic and anti-sclerostin agents preferentially in diabetic postmenopausal women, reduces fractures more effectively than a uniform antiresorptive strategy [56, 74]. Finally, the bone effects of the increasingly prescribed GLP-1 receptor agonists and dual incretin agents demand dedicated skeletal endpoints in ongoing and future cardiometabolic trials.

Abbreviations

T2DM
type 2 diabetes mellitus
BMD
bone mineral density
HOMA-IR
homeostasis model assessment of insulin resistance
RANKL
receptor activator of nuclear factor-κB ligand
OPG
osteoprotegerin
IGF-1
insulin-like growth factor 1
DXA
dual-energy X-ray absorptiometry
KNHANES
Korea National Health and Nutrition Examination Survey
KNHIS
Korean National Health Insurance Service
BMI
body mass index
MT
menopausal transition
FPG

fasting plasma glucose
VAT
visceral adipose tissue
SAT
subcutaneous adipose tissue
CT
computer tomography
WC
waist circumference
OR
odds ratio
FN
femoral neck
LM
lean mass
FM
fat mass
FP
fat percentage
LS
lumbar spine
WB
whole body
CO
central obesity
HMW
high-molecular-weight
HR
hazard ratio
BMR
basal metabolic rate
WHtR
waist-to-height ratio
SWAN
Study of Women’s Health Across the Nation,
CI
confidence interval
MD
mean difference
CTX
C-terminal crosslinking telopeptide

NTX
N-terminal crosslinking telopeptide
HT or MHT
hormone therapy
FSH
follicle stimulating hormone

Declarations

Vitaly V. Gursky, Julia V. Sopova, Anton Y. Isaenko, Olga A. Krasnova, Elena V. Shmidt, Olga M. Lesnyak, and Irina E. Neganova declare that they have no conflict of interest. The funders had no role in the design of this study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Author contributions

I.E.N. provided the idea for the article; V.V.G. and I.E.N. performed the literature search and data extraction; all authors performed the analysis of the selected papers and extracted data; V.V.G., J.V.S., and I.E.N. drafted and critically revised the work.

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Figures

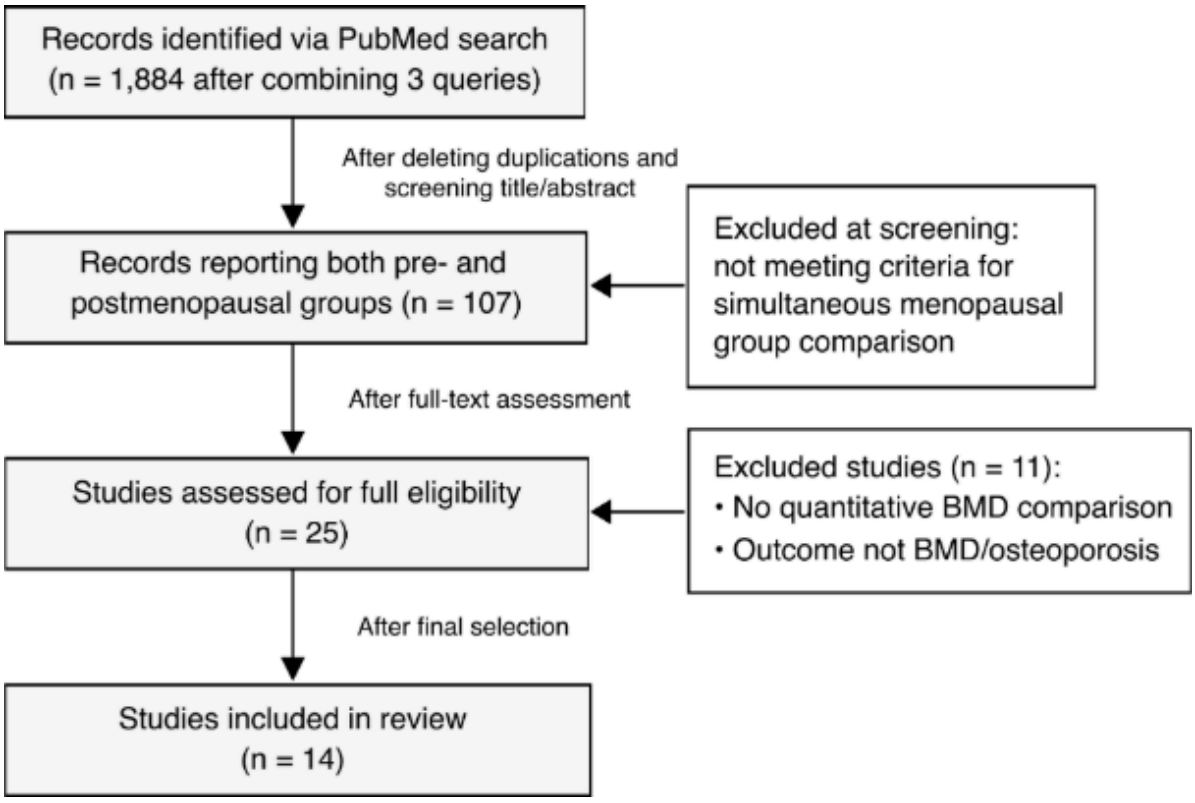


Figure 1

Flow diagram of study identification, screening, eligibility assessment, and inclusion in the review

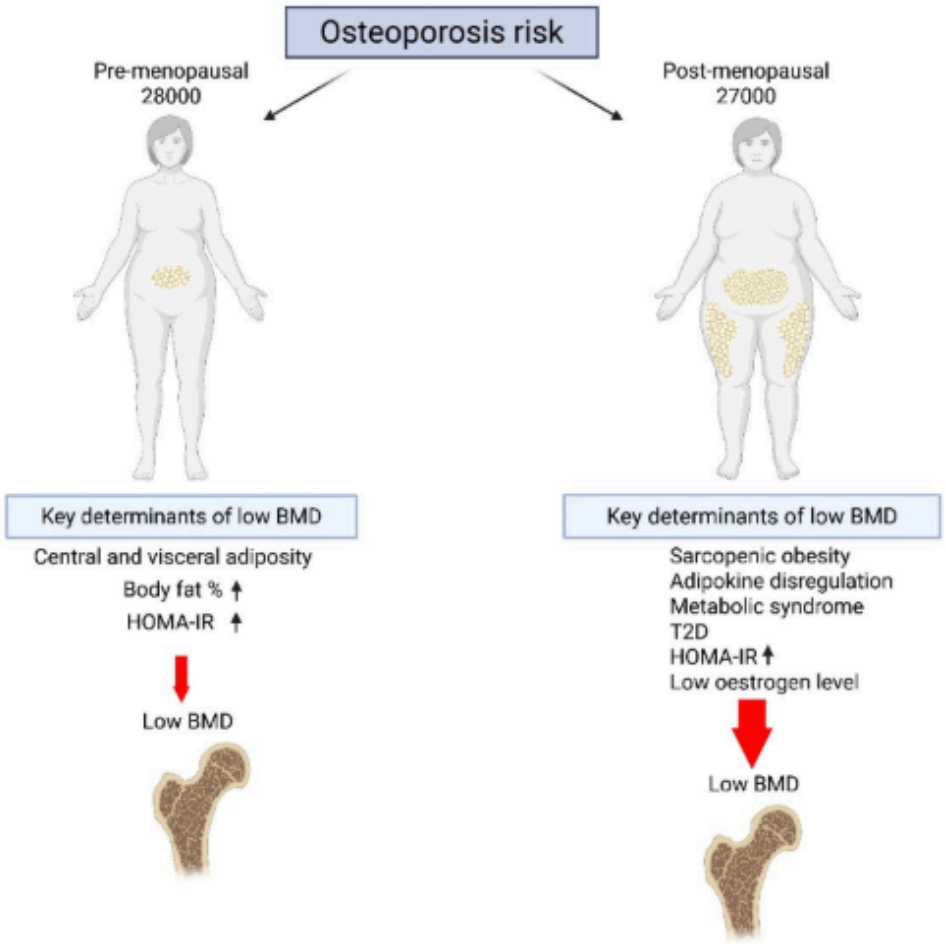


Figure 2

The predictive impact of obesity on BMD in pre-menopausal and post-menopausal women. Created with BioRender