REVIEW ARTICLE

The correlation between osteoporotic vertebrae fracture risk and bone mineral density measured by quantitative computed tomography and dual energy X-ray absorptiometry: a systematic review and meta-analysis

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Abstract

Summary This paper presents a comparison of quantitative computed tomography (QCT) and dual-energy X-ray absorptiometry (DXA) in osteoporosis with vertebral fracture and osteoporosis without fracture. It has been proved that the volumetric bone mineral density (vBMD) measured by QCT exhibits a stronger correlation with fracture risk than areal bone mineral density (aBMD) measured by DXA.

Purpose This study aims to systematically evaluate the ability of QCT and DXA to distinguish between osteoporosis with vertebral fracture and osteoporosis without fracture according to vBMD and aBMD.

Methods We conducted a primary literature search of the online databases up to 3 July, 2022, in both English and Chinese publications, combining synonyms for "QCT", "DXA" and "osteoporosis". The Newcastle–Ottawa scale (NOS) was employed to evaluate the quality of the selected articles. vBMD obtained through QCT and aBMD obtained through DXA were extracted, and were analyzed by Review Manager 5.4 and RStudio.

Results Six studies with 610 individuals aged 45 to 90, of which 179 had vertebral fractures, were included in the final analysis. The weighted mean difference (WMD) between osteoporosis with vertebral fracture and osteoporosis without fracture for vBMD was -27.08 (95% CI -31.24 to -22.92), while for aBMD was -0.05 (95% CI -0.08 to -0.03).

Conclusions Both vBMD detected by QCT and aBMD detected by DXA could discriminate fracture status in the spine, and vBMD performed a stronger correlation with fracture risk.

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Lin Chen and Xin-yi Wu have contributed equally to this work and share the first authorship.

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Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and deterioration of the microstructure of bone tissue, which can lead to an increase in bone fragility and fracture risk, with serious physical, psychosocial, and economic consequences [1, 2]. Osteoporosis can occur in all age groups, with a higher prevalence observed in postmenopausal women and older men [3]. Postmenopausal osteoporosis (Type I) and age-related osteoporosis (Type II) are the most common forms of bone loss in clinical practice [4]. In the early stages of osteoporosis, trabecular bone experiences the primary loss, while cortical bone loss becomes more prominent with advancing

age. This transition of bone loss site corresponds to the epidemiology of osteoporotic fracture. The loss of trabecular bone is more common in vertebral compression fractures in individuals under 65 years of age, whereas the loss of cortical bone is associated with hip fractures in those aged 65 and above [5]. During the initial phase of bone loss, bone resorption in the trabecular compartment leads to the thinning or loss of trabeculae, deterioration of the trabecular connections, and widening of trabecular spaces [6]. Decreased bone strength and decaying bone structure contribute to vertebral compression or other fragility fractures [7].

The prevention and treatment of osteoporosis have emerged as significant global public health challenges [8]. As the pathogenesis of osteoporosis is not completely clear and bone loss occurs insidiously, patients who initially show no symptoms mistakenly assume that they do not have osteoporosis, so the early diagnosis of osteoporosis is important [9, 10]. With the advance in technology, dual energy X-ray absorptiometry (DXA) has been applied to the measurement of areal bone mineral density (aBMD), and studies have revealed a progressive increase in fracture risk as BMD diminishes [11, 12]. According to the diagnostic criteria established by the World Health Organization, osteoporosis is defined by BMD measured by DXA [13]. However, the limitations of DXA in diagnosing osteoporosis and assessing fracture risk have been recognized as the understanding of osteoporosis updating. Firstly, spinal segments with severe end-plate sclerosis, osteophytes, and previous compression fractures must be excluded when using T-scores [14]. In addition, DXA cannot provide detailed information about bone microstructure, potentially resulting in the underdiagnosis of osteoporosis [15]. Notably, several studies have indicated that only about half of fracture patients meet the criteria for osteoporosis based on low aBMD [16].

With the increasing number of studies on the application of Quantitative computed tomography (QCT) in osteoporosis diagnosis, QCT has been identified as a supplement or even an alternative to DXA [17]. Quantitative computed tomography (QCT) is a three-dimensional technique for measuring BMD in the axial spine and peripheral bone (forearm, tibia), which not only provides measurements in volumetric bone mineral density (vBMD) units of mg/cm^3, but also allows for the selective assessment of trabecular or cortical bone mineral density (BMD) according to the region of interest [18]. Previous studies have demonstrated that QCT is more sensitive than DXA in the detection of bone mineral loss [19].

The purpose of this study was to systematically review the correlation between osteoporotic vertebral fractures and BMD, and to evaluate the capacity of QCT and DXA to distinguish between osteoporosis with vertebral fracture and osteoporosis without fracture based on vBMD and aBMD.

Methods

Literature search

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was registered at the International Prospective Register of Systematic Reviews (Number: CRD42022349185) [20]. The literature search was carried out in PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang Database, and China Science and Technology Journal Database up to 3 July, 2022, in both English and Chinese languages. The Medical Subject Headings (Mesh) and keywords used for retrieval are presented in the Online Resource by taking the form of PubMed as an example (Online Resource 1).

Inclusion and exclusion criteria

The included articles were selected by the following criteria: (a) the subjects were postmenopausal women or the elderly with osteoporosis; (b) the articles conducted both QCT and DXA tests and provided BMD; (c) the article provided clinical information related to occurrence of vertebral fracture.

The exclusion criteria were as follows: (a) duplicate publications; (b) reviews, letters, conference abstracts, posters, case reports, and meta-analyses; (c) articles with insufficient data or information about fracture sites.

Quality assessment

Two reviewers (Lin Chen and Xin-yi Wu) independently extracted the following data from qualified studies: first author's last name, year of publication, sample size, age of subjects, scanning site, and bone parameters assessed by QCT and DXA.

The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of articles using a star system based on nine questions. The criteria of NOS included the selection of study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case–control or cohort studies respectively [21]. Each study could obtain 0–9 stars, and a higher number of stars indicated a higher quality study.

Statistical analysis

The analysis for studying the ability of QCT and DXA to differentiate fracture was evaluated by Review Manager 5.4 (Nordic Cochrane Center, Copenhagen, Denmark) and RStudio (version 1.4.1106) with meta package, and

the results were presented in terms of weighted mean difference (WMD) along with 95% confidence intervals (CIs). Heterogeneity was assessed by Higgins inconsistency index (I^2) [22]. The randomized effect model was selected for combining effect indicators when the heterogeneity was significant (I^2 values > 50%); otherwise, the fixed effect model was used. Sensitivity analyses were performed to test the robustness of the outcomes. Deeks' funnel plot was employed to investigate the publication bias and was tested by Egger's test.

Results

Literature search

A total of 388 studies were initially identified from five databases (Fig. 1). After deleting duplicates, 300 studies were retained. After reviewing the titles and abstracts, 196 articles were excluded due to the age of subjects and article types. Among the remaining 104 studies, a comprehensive full-text review was conducted, leading to the exclusion of 98 studies. Ultimately, six articles were included in the analysis.
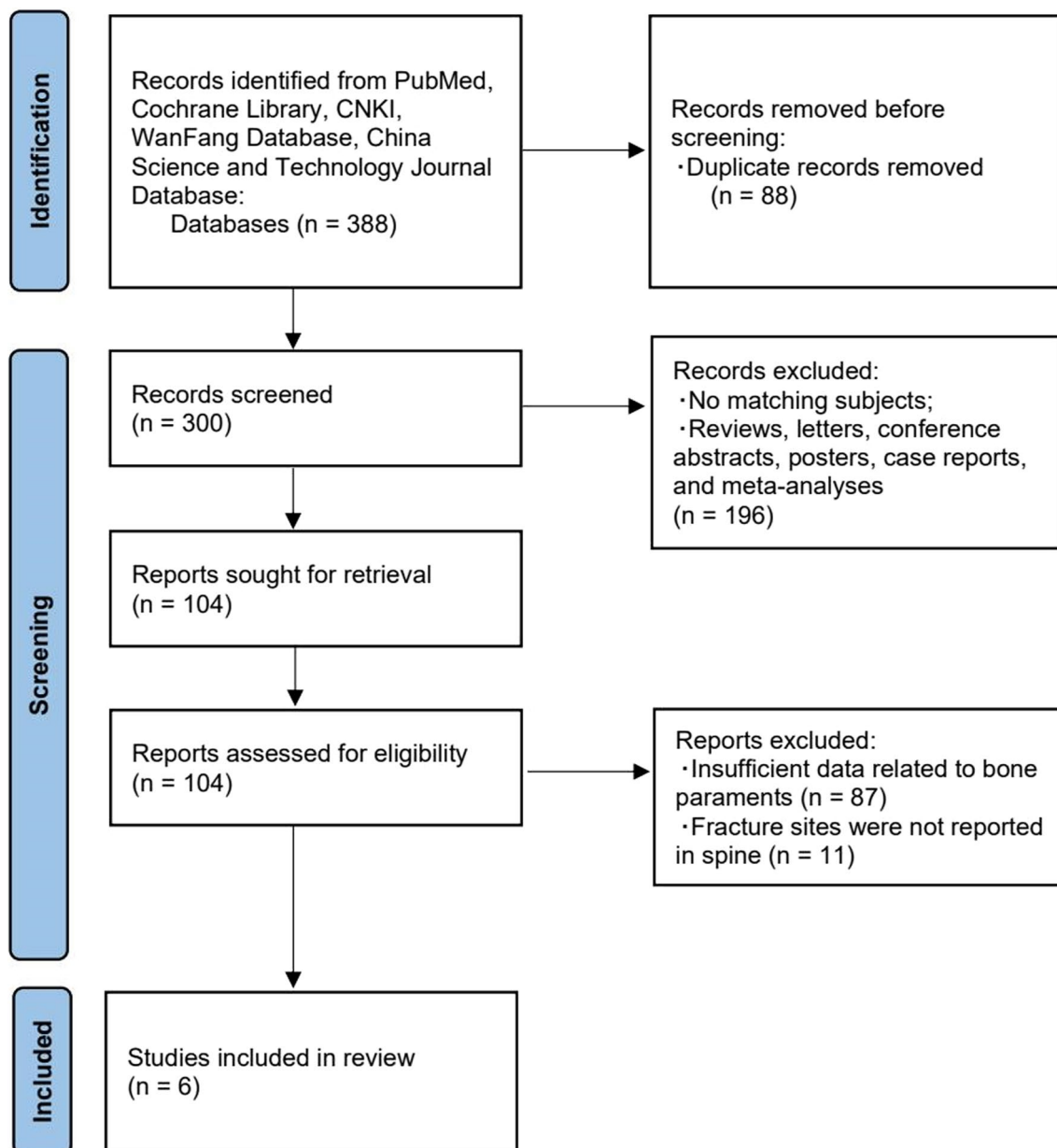

Fig. 1 PRISMA 2020 flow diagram of the study

Quality of the studies assessed by Newcastle–Ottawa scale (NOS)

The quality of the studies was assessed by Newcastle–Ottawa Quality Assessment Scale (NOS), as shown in Table 1[23–28]. All six studies included in the analysis were categorized as case–control studies. Regarding the "Selection" criteria, two out of the six studies received two stars, while the remaining four studies received three stars, indicating a moderate overall quality for this aspect. The primary quality concerns in this category were related to the inadequate representation of the case cohort and the unsatisfactory selection of the control group. In terms of "Comparability", two studies got one star each, and the other four studies were given two stars. The rationale behind scoring one star was the limited control or clarification of factors beyond age, such as height and weight. Within the "Exposure" category, all six studies were assigned three stars, signifying a high level of quality in this aspect. In summary, the NOS assessment from the six included studies indicated a moderate overall quality.

Data extraction

The outcomes of data extraction from the six studies, which employed QCT and DXA methods to assess BMD in fracture and non-fracture populations were summarized in Tables 2 and 3, respectively. A total of 610 individuals, ranging in age from 45 to 90 years, were included in this analysis. They were divided into two groups: osteoporosis with vertebral fractures in the "Fracture" and osteoporosis only in the "Non-fracture". Among the results measured by QCT expressed in mg/cm^3, the scanning sites of four studies were vertebrae and those of two studies were femur. As for DXA results reported in g/cm^2, five studies scanned the vertebrae site and one scanned the femur site.

Heterogeneity assessment of measurements related to fracture risk meta-analysis

The overall heterogeneity in the six studies on fracture risk was low. This was determined through a range of I^2 values, from 0% ($P = 0.42$) when assessed by aBMD, to 40% ($P = 0.14$) when assessed by vBMD. Moreover, after excluding studies one by one for analysis, no influential outliers

Table 1 Quality of the 6 studies assessed by Newcastle–Ottawa Scale (NOS) [23–28]

Authors and year	Selection				Comparability		Exposure			Total stars
	S1	S2	S3	S4	C1	C2	E1	E2	E3	
Cai et al. 2009 [23]	★	★		★	★		★	★	★	7
Duboeuf et al. 1995 [24]	★	★		★	★	★	★	★	★	8
Jergas et al. 1995 [25]	★			★	★	★	★	★	★	7
Rehman et al. 2002 [26]	★		★	★	★	★	★	★	★	8
Wu et al. 2005 [27]	★			★	★		★	★	★	6
Wu et al. 2009 [28]	★	★		★	★	★	★	★	★	8

S1: Definition of cases, S2: Representativeness of the cases, S3: Selection of controls, S4: Adequate control definition, C1: Comparability of cases, C2: Study controls for the basis of the analysis, E1: Ascertainment of the exposure, E2: Ascertainment of the same method used for cases and controls, E3: Non-response rate. 0–5 stars were considered low quality, 6–7 stars were considered moderate quality, 8–9 stars were considered high quality

Table 2 QCT data of measurements related to fracture risk studies [23–28]

	Study	Sample N1/N2	Sex	Fracture site	Scanned region	Fracture		Non-fracture	
						Mean	SD	Mean	SD
QCT (mg/cm^3)	Cai et al. 2009 [23]	28/33	F	Vertebrae	Vertebrae (L2-L4)	94.4	20.2	115	14.3
	Duboeuf et al. 1995 [24]	29/83	F	Vertebrae	Vertebrae (L1-L3)	79.11	23.53	97.74	32.78
	Jergas et al. 1995 [25]	55/168	F	Vertebrae	Vertebrae (L1-L3)	80.51	20.96	111.32	29.89
	Rehman et al. 2002 [26]	30/84	F	Vertebrae (T4-L5)	Vertebrae (L1-L2)	67	20	96	20
	Wu et al. 2005 [27]	26/30	F	Vertebrae	Femur	231	64	274	69
	Wu et al. 2009 [28]	11/33	F	Vertebrae	Femur	243.3	33	285.4	17.8

N1: number of fracture subjects, N2: number of non-fracture subjects, F: female, SD: standard difference

Table 3 DXA data of measurements related to fracture risk studies [23–28]

	Study	Sample N1/N2	Sex	Fracture site	Scanned region	Fracture Mean	SD	Non-fracture Mean	SD
DXA (g/cm^2)	Cai et al. 2009 [23]	28/33	F	Vertebrae	Vertebrae (L2-L4)	0.84	0.16	0.85	0.06
	Duboeuf et al. 1995 [24]	29/83	F	Vertebrae	Vertebrae (L1-L4)	0.781	0.11	0.842	0.13
	Jergas et al. 1995 [25]	55/168	F	Vertebrae	Vertebrae (L2-L4)	0.824	0.129	0.895	0.138
	Rehman et al. 2002 [26]	30/84	F	Vertebrae (T4-L5)	Vertebrae (L1-L4)	0.791	0.16	0.806	0.1
	Wu et al. 2005 [27]	26/30	F	Vertebrae	Femur	0.53	0.14	0.61	0.12
	Wu et al. 2009 [28]	11/33	F	Vertebrae	Vertebrae (L2-L4)	0.89	0.31	0.9	0.1

N1: number of fracture subjects, N2: number of non-fracture subjects, F: female, SD: standard difference

were found. In summary, the findings from the six studies were not affected by heterogeneity.

Both vBMD and aBMD discriminate fracture status

There were significant differences in vBMD detected via QCT and aBMD detected through DXA between both the vertebral fracture group and the non-fracture group ($P < 0.01$). The WMD were -27.08 (95%CI -31.24 to -22.92) for vBMD and -0.05 (95%CI -0.08 to -0.03) for aBMD, as illustrated in Figs. 2 and 3. Hence, both vBMD and aBMD effectively differentiate the fracture status, but vBMD exhibits superior discriminatory ability.

Sensitivity analysis and publication bias

After excluding studies one by one and combining the results of other studies for sensitivity analysis, no significant effect was observed (Fig. 4 and Fig. 5). Two funnel plots were constructed—one for vBMD (Fig. 6) and another for aBMD (Fig. 7)—to assess the potential presence of publication bias. Asymmetry was tested by Egger's test, yielding P-values

of 0.5418 for vBMD and 0.3846 for aBMD. These results indicated that there was no publication bias across the six studies.

Discussion

How to "quantify" osteoporosis?

The structural integrity of bones is maintained through continuous remodeling in adulthood, in which osteoclasts absorb old or damaged bones and osteoblasts format new bones [29]. With advancing age, this process becomes imbalanced, with bone absorption exceeding formation, resulting in a loss of bone mass [30]. Cortical bone loss contributes to the enlargement of the bone marrow cavity, thinning of the cortex, and reduction in BMD. Trabecular bone loss, on the other hand, leads to damage of the trabecular structure, diminished trabecular thickness, and reduced connectivity [31]. This progression develops into the current definition of osteoporosis.

Fig. 2 Forest plot of vBMD detected by QCT. Horizontal line = confidence interval; vertical line = invalid line; square mark = effect size; diamond mark = pooled effect size
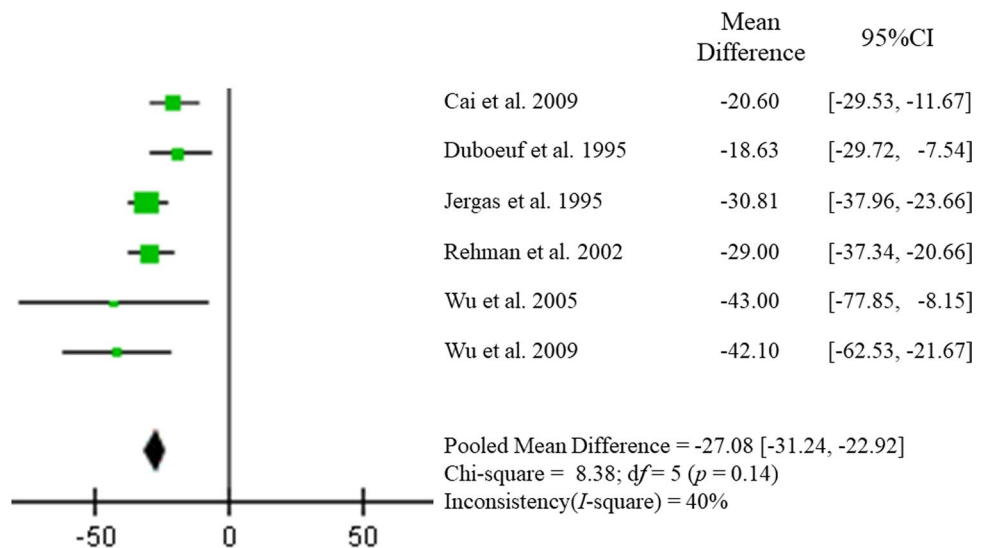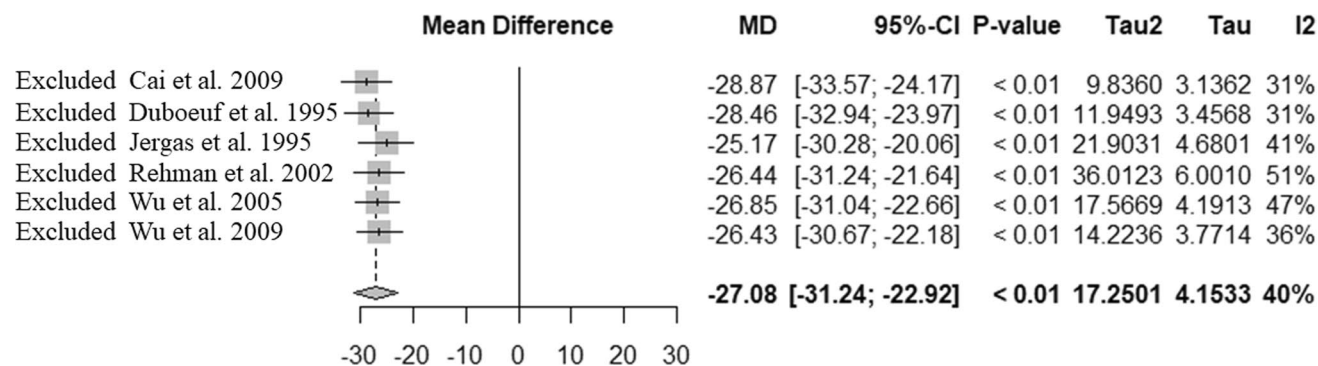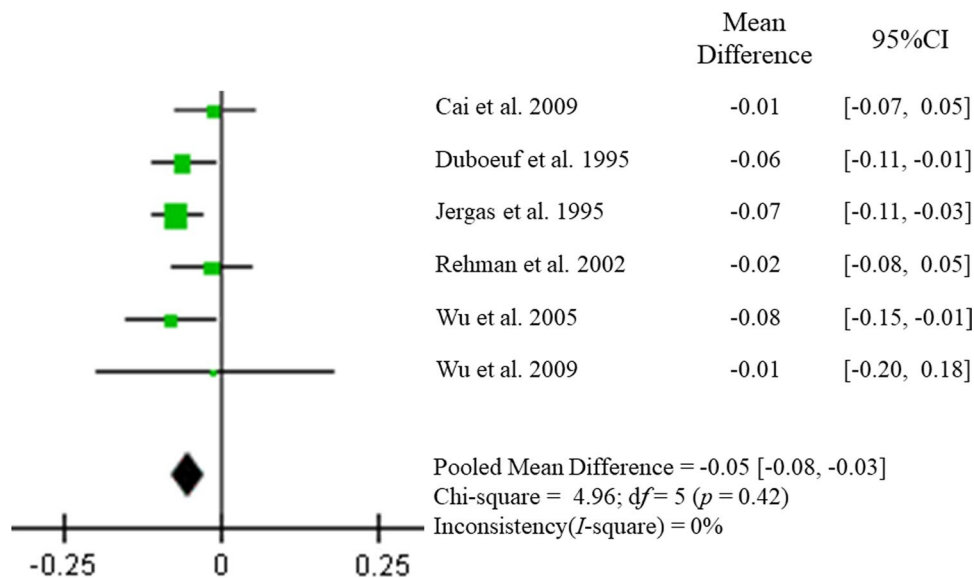
	Mean Difference	95%CI
Cai et al. 2009	-20.60	[-29.53, -11.67]
Duboeuf et al. 1995	-18.63	[-29.72, -7.54]
Jergas et al. 1995	-30.81	[-37.96, -23.66]
Rehman et al. 2002	-29.00	[-37.34, -20.66]
Wu et al. 2005	-43.00	[-77.85, -8.15]
Wu et al. 2009	-42.10	[-62.53, -21.67]

Pooled Mean Difference = -27.08 [-31.24, -22.92]
Chi-square = 8.38; df = 5 (p = 0.14)
Inconsistency(I-square) = 40%

Fig. 3 Forest plot of aBMD detected by DXA. Horizontal line = confidence interval; vertical line = invalid line; square mark = effect size; diamond mark = pooled effect size
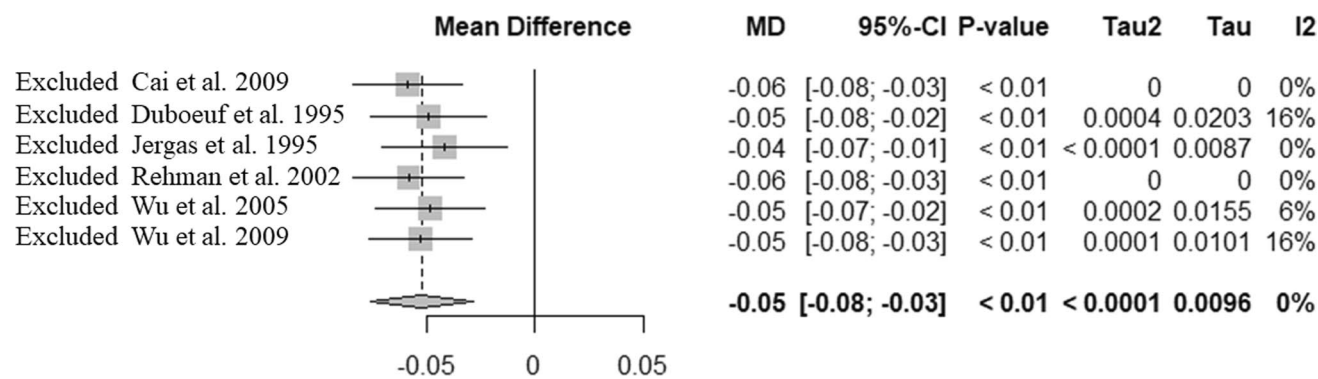

	Mean Difference	95%CI
Cai et al. 2009	-0.01	[-0.07, 0.05]
Duboeuf et al. 1995	-0.06	[-0.11, -0.01]
Jergas et al. 1995	-0.07	[-0.11, -0.03]
Rehman et al. 2002	-0.02	[-0.08, 0.05]
Wu et al. 2005	-0.08	[-0.15, -0.01]
Wu et al. 2009	-0.01	[-0.20, 0.18]

Pooled Mean Difference = -0.05 [-0.08, -0.03]
Chi-square = 4.96; df = 5 (p = 0.42)
Inconsistency(I-square) = 0%

	MD	95%-CI	P-value	Tau2	Tau	I2
Excluded Cai et al. 2009	-28.87	[-33.57; -24.17]	< 0.01	9.8360	3.1362	31%
Excluded Duboeuf et al. 1995	-28.46	[-32.94; -23.97]	< 0.01	11.9493	3.4568	31%
Excluded Jergas et al. 1995	-25.17	[-30.28; -20.06]	< 0.01	21.9031	4.6801	41%
Excluded Rehman et al. 2002	-26.44	[-31.24; -21.64]	< 0.01	36.0123	6.0010	51%
Excluded Wu et al. 2005	-26.85	[-31.04; -22.66]	< 0.01	17.5669	4.1913	47%
Excluded Wu et al. 2009	-26.43	[-30.67; -22.18]	< 0.01	14.2236	3.7714	36%
	-27.08	[-31.24; -22.92]	< 0.01	17.2501	4.1533	40%

Fig. 4 Sensitive analysis of vBMD detected by QCT. Horizontal line = confidence interval; vertical line = invalid line; square mark = effect size; diamond mark = pooled effect size

	MD	95%-CI	P-value	Tau2	Tau	I2
Excluded Cai et al. 2009	-0.06	[-0.08; -0.03]	< 0.01	0	0	0%
Excluded Duboeuf et al. 1995	-0.05	[-0.08; -0.02]	< 0.01	0.0004	0.0203	16%
Excluded Jergas et al. 1995	-0.04	[-0.07; -0.01]	< 0.01	< 0.0001	0.0087	0%
Excluded Rehman et al. 2002	-0.06	[-0.08; -0.03]	< 0.01	0	0	0%
Excluded Wu et al. 2005	-0.05	[-0.07; -0.02]	< 0.01	0.0002	0.0155	6%
Excluded Wu et al. 2009	-0.05	[-0.08; -0.03]	< 0.01	0.0001	0.0101	16%
	-0.05	[-0.08; -0.03]	< 0.01	< 0.0001	0.0096	0%

Fig. 5 Sensitive analysis of aBMD detected by DXA. Horizontal line = confidence interval; vertical line = invalid line; square mark = effect size; diamond mark = pooled effect size

There is still no perfect definition of osteoporosis. The symptom of osteoporosis is not only the loss of some vertebrae or parts of bone, but also the general defect caused by bone degeneration with age, which leads to a high risk of fracture [32]. The present consensus for diagnosing osteoporosis is based on low BMD, which correlates with decreased
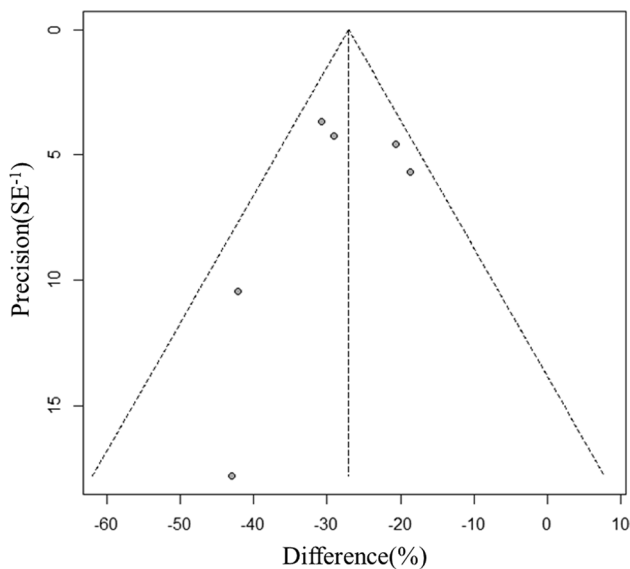
Fig. 6 Funnel plot of vBMD detected by QCT. Dots = study-level data; vertical dashed line = fixed effect (FE) estimates; oblique dashed line = theoretical 95% CI for FE estimate in absence of bias
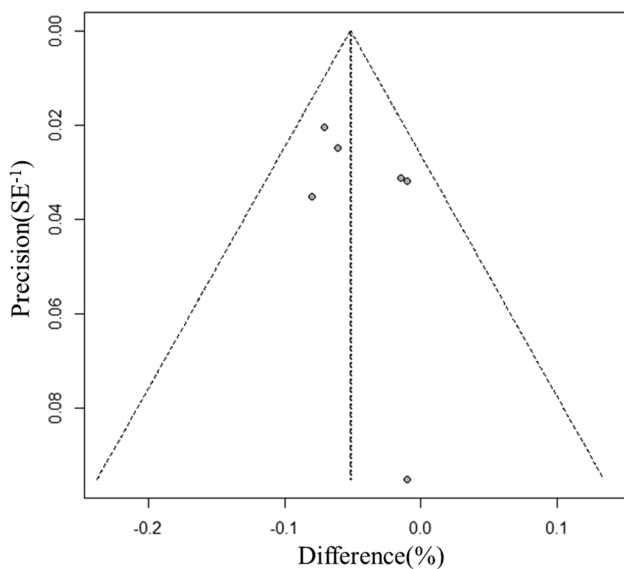

Fig. 7 Funnel plot of aBMD detected by DXA. Dots = study-level data; vertical dashed line = fixed effect (FE) estimates; oblique dashed line = theoretical 95% CI for FE estimate in absence of bias

loading strength of vertebral bodies and increased vertebral compression fracture risk. Previous studies have also proved the correlation between low BMD and an elevated risk of osteoporotic fractures [33]. Vertebral fractures, often regarded as a hallmark of osteoporosis, serve as significant indicators of compromised bone structure and diminished bone strength [34, 35].

Previous studies have documented that spinal BMD not only predicts the long-term risk of vertebral fractures, but

also has a strong correlation with other types of fractures [16, 36, 37]. The drug intervention for the treatment of osteoporosis has a significantly higher response to the prevention of vertebral fractures than other fractures, which further emphasizes the unique role of vertebral fractures in osteoporosis [38]. Therefore, the spine may be an ideal site for BMD measurement in the diagnosis of osteoporosis, which has an important reference value for vertebral fracture and overall bone loss [35].

Application of DXA and QCT in the spine

aBMD measured by DXA as a reference standard in osteoporosis diagnosis

DXA measures the aBMD by obtaining the X-ray attenuation of patients exposed to low levels of X-ray radiation. The attenuation of each pixel in the predefined region of interest is summarized and converted to aBMD in units of g/cm^2 using the previously established tissue quality attenuation coefficient [39, 40]. aBMD at the spine and hip is the reference standard for osteoporosis diagnosis. However, as our comprehension of bone microstructure advances, its significance in fracture risk prediction has encountered challenges [41, 42]. The prevalence of vertebral fractures varies across the vertebral level, with peaks in the middle of the spine (T7-T8) and the thoracolumbar junction (T12-L1). Vertebral fractures at these specific sites are more strongly associated with the risk of new fractures in the upper than in the lower spine [43]. It's important to note that DXA has certain limitations: it lacks accuracy in measuring BMD in the thoracic spine due to the influence of soft tissues and chest coverage [44]. Furthermore, DXA cannot provide detailed information about bone microstructure [45], consequently failing to adequately explain the correlation between aBMD and bone structure parameters [46]. The vertebral fracture assessment technique is an extension of DXA that attempts to evaluate vertebral fractures from a more comprehensive point of view, but certain limitations still exist, including its inability to identify vertebrae between T7-L4 and to detect common osteoporosis-related sclerosis or lytic changes [47].

vBMD measured by QCT in osteoporosis

vBMD measured by QCT requires calibrating the computed tomography values in Hounsfield units (HU) according to known density standards to calculate the equivalent density [48]. QCT can selectively measure trabecular or cortical BMD based on the region of interest, allowing further assessment of the parameters related to bone microstructure [49]. Moreover, it can accurately distinguish soft tissue compartments, minimizing the impact of extraosseous components [50]. A cross-sectional study found that QCT was

more sensitive compared to DXA in detecting osteoporosis in postmenopausal women [51]. In a cohort study, it was found that QCT performed better in the risk assessment of imminent vertebral fractures than DXA [52].

Considering radiation exposure, it is advisable to minimize the number of vertebrae measured when utilizing QCT, with L1-L2 being the most commonly recommended site for evaluation [53]. According to the American Society of Radiology, the average BMD of L1-L2 is used for radiological diagnosis of osteopenia and osteoporosis [54]. A previous study has demonstrated high concordance between thoracic and lumbar BMD measured by QCT [55]. Another study also showed a strong correlation between the average BMD of L1–L2 and the other lumbosacral vertebrae (L3–S1) [56].

Due to disparities in equipment, imaging software, and the expertise of analysts, vBMD estimated by QCT is still individualized. Nevertheless, promising strides toward standardization have been highlighted through several multi-center clinical trials [48]. We look forward to an official recommendation to provide more details such as patient variables and calibration methods to guide clinical use of QCT in measuring vBMD.

In this study, we analyzed the ability of vBMD detected by QCT and aBMD detected by DXA in distinguishing between osteoporosis patients with vertebral fractures and those without fractures. Our findings indicated that both vBMD assessed by QCT and aBMD assessed by DXA can effectively differentiate osteoporotic fractures regardless of the scanning site, and vBMD (WMD = −27.08; 95% CI −31.24 to −22.92) performed better than aBMD (WMD = −0.05; 95% CI −0.08 to −0.03). Among the six articles, the scanned site of two of QCT [27, 28] and one of DXA were at the femur, and the others scanned more than two vertebrae between L1 and L4, which was consistent with the recommendation [13, 54]. Regrettably, the precise location of vertebral fractures was not described in detail in the six articles, thereby limiting us to deeply analyzing the correlation between BMD and vertebral fractured site. Interestingly, we found that even the BMD obtained from femur scans exhibited an association with vertebral fractures, suggesting that osteoporosis was an overall degeneration of bone health.

There are limitations needed to be improved in our research. In the analysis of evaluating the ability of QCT and DXA to distinguish fractures, it would be inappropriate to conclude that QCT is superior to DXA in identifying individuals with fractures based solely on vBMD and aBMD because we didn't clear whether different units will lead to different results related to fracture risk. Also, the analysis of fracture risk based on BMD was still insufficient, and the quality of bone microstructure should be another important factor in fracture risk. However, we can deduce that osteoporosis associated with vertebral fracture risk may exhibit, on average, deficits of −27.08 in vBMD and −0.05 in aBMD, in comparison to osteoporosis without fracture. In the future, we may focus on patients with fractures and further study the application of QCT in osteoporotic fractures.

This paper demonstrated the strong correlation between BMD and osteoporotic fracture risk obtained by QCT and DXA, and identifies the superiority of QCT in predicting osteoporotic fracture risk.

Declarations

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