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Original article

Is ankle fracture related to low bone mineral density and subsequent fracture? A systematic review

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ABSTRACT

Objectives: Ankle fractures are common in the elderly. However, their association with osteoporosis remains controversial. This systematic review aims to determine the relationship between ankle fracture and bone mineral density (BMD), and to investigate the risk of subsequent fractures after ankle fracture.
Methods: MEDLINE and Scopus publications were searched from inception to March and April 2019, respectively. Articles were selected by 2 independent reviewers for cross-sectional, cohort, or case-control studies comparing BMD or subsequent fracture risk in low-energy ankle fractures patients with that of the normal population. Data extraction was performed by 2 investigators. Discrepancies were resolved with the third reviewer. Quality assessment was conducted using the modified Newcastle-Ottawa Scale.
Results: Overall, 19 articles were included. The quality assessment showed a generally low-to-moderate risk of bias among studies, mainly due to potential confounders and inadequate follow-up. Of 13 studies exploring BMD in ankle fractured-patients, lower central and peripheral BMD was found in 3 and 2 studies, respectively. The risk of subsequent fracture was examined in 11 studies with relative risks ranging from 0.7 to 4.59. An increased risk of any subsequent fractures in women, both genders, and men was found in 5, 2, and 1 articles, respectively.
Conclusions: Despite the lack of clear association with BMD, the contribution of ankle fracture to increased subsequent fracture risk and its associated microarchitectural changes cannot be overlooked. Moreover, its potential role as an early predictor of future fracture may promote secondary prevention. Further studies with longer follow-up and stricter confounder control are recommended.
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1. Introduction

Osteoporosis is a major cause of disability worldwide [1,2].Targeted screening for osteoporosis in individuals with a history of fractures enables a reasonable allocation of such limited resources since previous fractures have been found to increase the risk of future osteoporotic fragility fractures [3,4]. The fracture risk assessment tool or FRAX score has been commonly used to predict the risk of fractures in individuals. It may be used independent of BMD and the risk prediction is based on family history and prior fractures. Nevertheless, sites of previous fractures are not taken into consideration, despite each site imposing varying degrees of subsequent fractures risk [5–7]. Robinson et al concluded that prior fractures of the hip, wrist, and proximal humerus, could contribute to a significant increase in subsequent fractures at any site (OR 5.76, 3.98, and 4.87, respectively) [8]. Hence, they are generally regarded as osteoporotic fractures. Ankle fractures are a common low energy fracture in the elderly. However, they were not found to exhibit such a robust association as an osteoporosis-related fracture. This is also reflected in conflicting results from several studies [9–11]. Furthermore, findings from the studies investigating the association between ankle fractures and a decrease in BMD provided inconclusive evidence [9,10,12–14]. Although the recent evidence remains controversial whether ankle fractures are osteoporotic in nature or resulting in subsequent osteoporotic fractures, the clinical

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significance of any high-risk assessment in low energy ankle in the elderly should be emphasized. It may offer secondary preventive measures in order to alleviate the burdensome consequences of major osteoporotic fractures [3].

Therefore, the purpose of this systematic review is to investigate the relationship between ankle fracture and osteoporosis through its propensity toward higher subsequent fracture risk and lower BMD. The implication of this study is to encourage using specific fracture risks to improve early detection and risk prediction of osteoporosis. This will improve the treatment outcome and the quality of care in osteoporosis.

2. Methods

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines under approval from the Institutional Review Board Committee (MURA2019/33). We searched the electronic databases Medline (PubMed) and Scopus from inception to March 2019 and April 2019, respectively. The search terms used were as follows: ankle fractures, bone density, osteoporosis, osteopenia, postmenopausal. Additional references were then obtained by a manual search of relevant reference lists of the retrieved articles.

The titles and abstracts of all articles were initially screened independently by 2 reviewers [A.T. and N.P.] on the basis of relevance. Subsequently, the full texts of potentially eligible articles were assessed independently. Any difference in assessments was discussed with the third reviewer [T.T.] for consensus.

2.1. Eligibility criteria

We included the cross-sectional, cohort, or case-control studies that aimed to determine the association between ankle fractures and subsequent fractures or low bone mineral density in peri-/post-menopausal women or elderly men. The selected studies must be fully published in English.

Studies without comparisons with normal control (ie, non-fracture group) or background population were not included. Articles in which study populations were not exclusively elderly or had secondary osteoporosis were also excluded.

2.2. Data extraction and quality assessment

Data extraction was performed by 2 reviewers (A.T. and N.P.) using a purpose-designed form which collected details on study design, study population, number of patients with initial ankle fracture, number of patients with subsequent fractures, sites of subsequent fractures, length of follow up, BMD with site of measurement, and RR/HR/OR of subsequent fractures or ankle fracture per 1 standard deviation (SD) decrease in BMD. Any discrepancies or doubts in information extracted were resolved by agreement of the reviewers (A.T. and N.P.) and consensus with the third reviewer (T.T.).

Studies were assessed for their quality using the Newcastle Ottawa Quality Assessment Scale [15]. The scale comprises 8 items that evaluate the selection of study population, the comparability of study groups, and the ascertainment of the exposure (for case-control studies) or outcome (for cohort studies). The studies were scored from 0 to 9 stars according to the quality. Studies which scored at least 7 stars were considered of high quality, while those with 4 or lower stars were deemed to have a high risk of bias. For cross-sectional studies, we modified the scale by omitting the assessment of 'non-response rate', thus evaluating only 7 items from the original scale and awarding up to 8 stars [16].

3. Results

The initial database search identified a total of 353 articles. Ten additional records were further retrieved by manual reference searching. After duplication removal, 329 articles were screened on the basis of title and abstract reading, which excluded 285 irrelevant records. Ultimately, 19 studies fulfilled the inclusion criteria and were included in the systematic review, as described in Fig. 1. The eligible articles were published between 1993 and 2017. Ten studies were prospective cohort, 2 retrospective cohort, 1 case-control, and 6 cross-sectional. Of the 19 studies included, 11 investigated the association between ankle fracture and subsequent fractures, and 13 examined the association between ankle fracture and bone mineral density. Most of the studies included female samples (13 of 19 studies), whereas there was only 1 study which exclusively recruited male samples. Five articles studied both genders. Sample sizes ranged from 62 to 1 694 051 patients. This reflects the diversity of study settings, which ranged from studies on inpatients hospitalized with fractures to studies using electronic databases of medical beneficiaries or data from pre-existing cohorts.

After quality assessment, only 11 were considered of high quality (awarded 7 out of 9 stars or 6 out of 8 stars). Nevertheless, no studies were excluded for the reason of a high risk of bias. On average, the quality score of studies was 74.0%, indicating low-to-moderate risk of bias, mainly due to potential confounders and inadequate lengths of follow-up in cohort studies (Table 1). Of 12 cohort studies included, only 2 followed the study groups for more than 10 years, with the range of follow-up periods from 3.6 to 16 years.

3.1. Ankle fracture and subsequent fracture

Eleven studies exploring the relationship between ankle fracture and subsequent fractures reported the relative risk (95% CI) ranging from 0.7 (0.02–4.0) to 4.59 (2.45–8.61). The findings of each study are summarized in Table 2. Five studies in perimenopausal or postmenopausal women found a statistically significant association between ankle fracture and subsequent fracture at various sites [9,17–20]. Two articles suggested a greater risk of subsequent fractures in both elderly men and women [8,21]. Such a discrepancy between genders was also demonstrated in a prospective study, which showed an increase in subsequent fractures after initial ankle fractures in men (RR (95% CI) = 4.95 (2.45–8.61)), but not in women [11]. Three studies did not find any relationship between ankle fracture and subsequent fracture in the elderly [5,22,23].

3.2. Ankle fracture and BMD

Twelve out of 18 studies included in this systematic review discussed the relationship between ankle fracture and BMD. The majority of the studies (7 out of 12) did not find an association between those 2 variables. Three articles found a decrease in central BMD in ankle fracture patients when compared to the normal population, while 2 articles reported a reduction in peripheral BMD. Details of the studies are described in Table 3.

According to a cross-sectional study by Biver et al, women with prior ankle fractures in a cohort of 749 postmenopausal women in Geneva showed a decrease in BMD at the lumbar spine, femoral neck, and total hip, compared to women without fractures [9]. The number of women diagnosed with osteoporosis was also higher in the ankle fracture group, compared to the control group. Another study in 1629 postmenopausal women in Italy also demonstrated lower femoral neck BMD in the ankle fracture group [14]. These

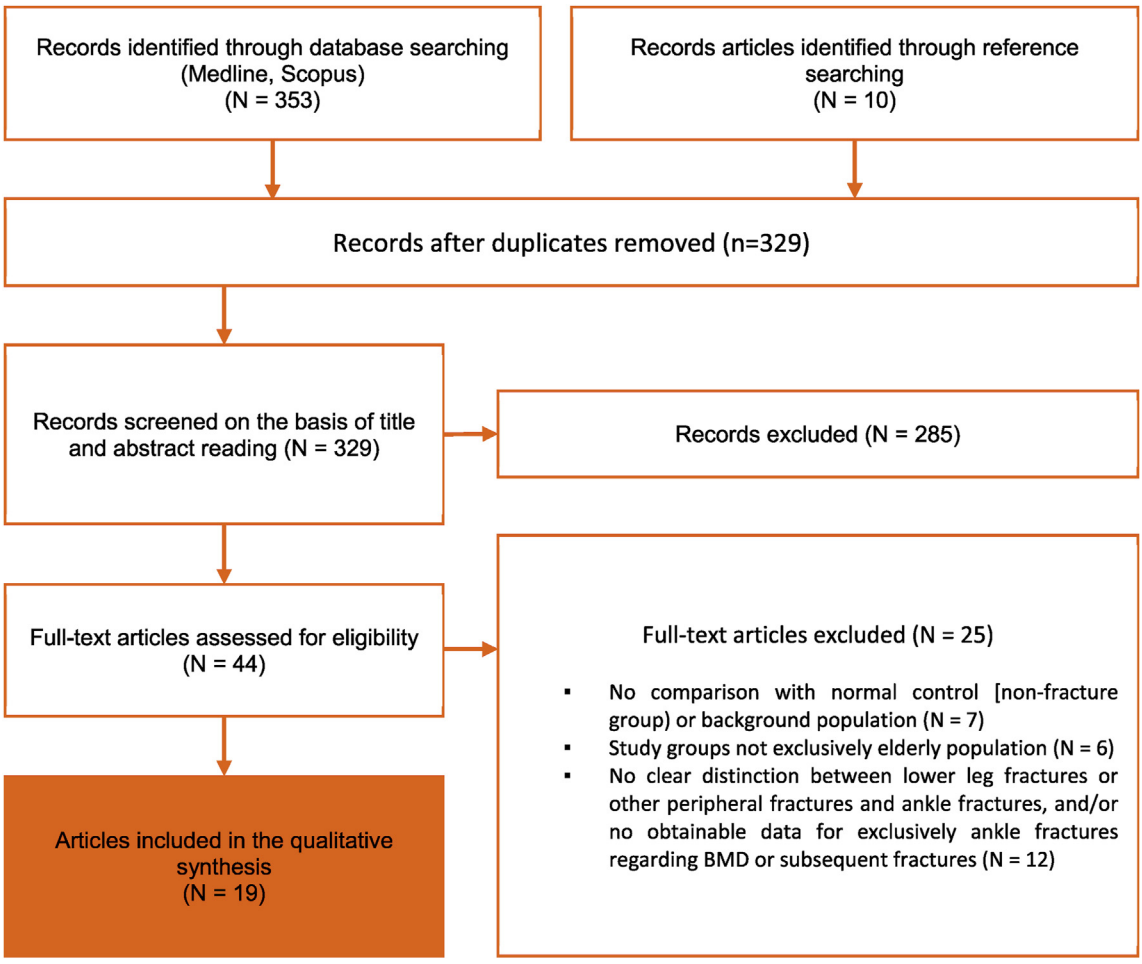

Fig. 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Table 1
Quality assessment of studies included in this systematic review.

Study [Reference]	Study design	Score awarded/Full score				Percent (%)
		Selection	Comparability	Exposure/Outcome	Total	
Biver E [9]	Cross-sectional	2/4	2/2	2/2	6/8	75.0
Center JR [11]	Prospective cohort	4/4	0/2	3/3	7/9	77.78
Ettinger B [5]	Prospective cohort	4/4	2/2	2/3	8/9	88.89
Gehlbach S [18]	Prospective cohort	3/4	1/2	2/3	6/9	66.67
Gnudi S [25]	Prospective cohort	3/4	1/2	2/3	6/9	66.67
Gnudi S [14]	Cross-sectional	3/4	0/2	2/2	5/8	62.5
Greenfield DM [20]	Cross-sectional	3/4	2/2	2/2	7/8	87.5
Ho PY [27]	Case control	3/4	1/2	1/3	5/9	55.56
Ingle BM [19]	Cross sectional	4/4	1/2	2/2	7/8	87.5
Lauritzen JB [23]	Prospective cohort	3/4	2/2	1/3	5/9	55.56
Lee DO [26]	Case-control	3/4	1/2	2/2	6/8	75.0
Morin SN [17]	Retrospective cohort	4/4	2/2	2/3	8/9	88.89
Pritchard JM [22]	Prospective cohort	4/4	2/2	1/3	7/9	77.78
Robinson CM [8]	Prospective cohort	4/4	2/2	1/3	7/9	77.78
Schuit SC [13]	Prospective cohort	3/4	1/2	2/3	6/9	66.67
Seeley DG [24]	Prospective cohort	4/4	2/2	2/3	8/9	88.89
Stein EM [12]	Cross-sectional	3/4	0/2	2/2	5/8	62.5
Stone K [10]	Prospective cohort	3/4	1/2	3/3	7/9	77.78
Taylor AJ [21]	Retrospective cohort	3/4	2/2	1/3	6/9	66.67

findings suggest that ankle fracture was considered one of the osteoporotic fractures. However, such a conclusion could not be drawn in a study by Greenfield and colleagues despite an observed decrease in femoral neck BMD Z-score after adjustment for age and weight [20]. This was because the study did not observe an increased prevalence of hip fracture in the ankle fracture group.

In addition to a decrease in central BMD, Biver et al also recognized a reduction in total radius, distal third radius, and ultra-

Table 2
List of studies investigating the relationship between ankle fracture and subsequent fracture.

Study [Reference]	Study design	Study population	Total sample	Average time of follow-up, yr)	Initial ankle fracture case	Initial non-fracture case	Associated/ Subsequent fracture type	Subsequent fracture case	Type of risk	Value (95% CI)
Biver E [9]	Cross-sectional	Geneva Retirees Cohort, Switzerland (female, mean 65 yr)	749	N/A	63	433	Any	N/A	OR	2.08 (1.24 −3.5) P = 0.006[a]
							Fragility fracture	N/A		1.89 (1.04 −3.44) P = 0.037[a]
Center JR [11]	Prospective cohort	Dubbo Osteoporosis Epidemiology Study, Australia (female and male aged ≥ 60 yr)	Total 4005 Female 2245	16	905 initial fracture, no specified data for ankle fracture	1340	Any	253 after all initial fracture, 7 after ankle fracture	RR	0.84 (0.4 −1.78)
			Male 1760	15	337 initial fracture, no specified data for ankle fracture	1423	Any	71 after all initial fracture, 10 after ankle fracture		4.59 (2.45 −8.61)[a]
Ettinger B [5]	Prospective cohort	Northern California, USA, retrieved from the Kaiser Permanente Medical care program (male ≥ 60 yr)	90825	2.4	1067	Normal population 86408	Ankle, hip, humerus, wrist	N/A	HR after adjust for all - age, cardiac related drug use, central nervous system related drug use, DM drug use, hospitalization, office visit	1 (0.5 −1.9)
						Finger fracture 841	Ankle, hip, humerus, wrist	N/A		1 (0.4 −2.6)
GehlbachS [18].	Prospective cohort	Global Longitudinal Study of Osteoporosis in Women (GLOW), 10 countries (female, mean age 68 yr)	51762	2	3201	39753	Any	N/A	HR adjusted for age, physician practice site, multiple previous fractures	1.4 (1.24 −1.58)[a]
							Hip	N/A		1.45 (0.95 −2.2)
							Spine	N/A		1.24 (0.86 −1.8)
							Other weight bearing bone	N/A		1.83 (1.52 −2.19)[a]
							Non-weight bearing bone	N/A		1.15 (0.95 −1.39)
Greenfield DM [20]	Cross-sectional	Postmenopausal women recruited at Northern General Hospital Trust, Sheffield, England (female, mean age 64.2)	478	N/A	103	375	Distal forearm	26%	OR	2.82[a]
							Hip	2%		1.84
							Spine	10%		1.43
Ingle BM [19]	Cross sectional	Postmenopausal women recruited at Northern General Hospital Trust, Sheffield, England (female, mean age 62.2)	62	N/A	31	31	Distal forearm	24%	OR	3.63[a]
							Hip	2%		2.02
Lauritzen JB [23]	Prospective cohort	Inpatient at Hvidovre Hospital, Copenhagen, Denmark (admitted fracture lumbar spine, knee, ankle) (female aged 60 −99)	451	Median 3.6 (from initial ankle fracture)	Total 200 Aged 60 −79, 182 Aged 80 −99, 18		Hip	8	RR	1.3 (0.6 −2.7)
							Hip	7		1.5 (0.6 −3.1)
							Hip	1		0.7 (0.02 −4.0)
Morin SN [17]	Retrospective cohort	Women undergoing baseline clinical BMD from 1990 to 2007 from the database of Manitoba, Canada (female, mean age 64.3)	39991	5.3	1694	29878	Major osteoporotic fracture	N/A	HR adjusted for decades of age, femoral neck BMD	1.3 (1.08 −1.57)
Pritchard JM [22]	Prospective cohort	Females with or without DM from Population Health Information System (POPULIS) data repository at the Manitoba Centre for Health Policy (MCHP), Canada from 1987 to 2007 (female, mean age 67.9)	12205	4.8	559	11646	Major osteoporotic fracture	66	HR adjusted for age, BMI, femoral neck BMD, previous major osteoporotic fracture, number of ADGs 1.17	(0.79 −1.73), P = 0.316
Robinson CM [8]	Prospective cohort	Inpatients and outpatients with fracture at Edinburgh Orthopaedic Trauma Unit,	22060	3.6	3508	Baseline population	Hip	N/A	RR	1.3 (0.95 −1.82)
							Wrist	N/A		

Table 2 (*continued*)

Study [Reference]	Study design	Study population	Total sample	Average time of follow-up, yr)	Initial ankle fracture case	Initial non-fracture case	Associated/ Subsequent fracture type	Subsequent fracture case	Type of risk	Value (95% CI)
		Scotland, United Kingdom (female and male aged ≥ 45)								2.03 (1.62 −2.51)[a]
							Proximal humerus	N/A		1.96 (1.32 −2.81)[a]
							Ankle	N/A		4.53 (3.57 −5.66)[a]
							Any	N/A		2.24 (1.89 −2.59)[a]
Taylor AJ [21]	Retrospective cohort	5% random sample of Medicare beneficiaries from 2000 to 2005, obtained from Center of Medicare and Medicaid Services (CMS) Chronic Condition Warehouse (male and female aged ≥ 65)	1694051	4.2 person-year	13454	1525735	Hip	N/A	IRR adjusted for gender, race, age, year, urbanicity, geographic region, income	0.99 (0.91 −1.08)
							Spine	N/A		1.14 (1.04 −1.25)[a]
							DER + Ulna	N/A		1.27 (1.12 −1.43)[a]
							Humerus	N/A		0.96 (0.82 −1.11)
							Ankle	N/A		N/A
							Tibia + Fibula	N/A		2.6 (2.19 −3.09)

OR, odds ratio; RR, relative risk; HR, hazard ratio; CI, confidence interval; BMD, bone mineral density; BMI, body mass index; ADG, ambulatory diagnostic group; IRR, incidence rate ratio; DM, diabetes mellitus; N/A, not applicable.

[a] Statistically significant; all ages are in years.

distal radius BMD in 63 women with ankle fractures [9]. In a prospective cohort of 9704 non-black women in the United States with 10.4 years of follow up, ankle fracture was also found to be related to reduced peripheral BMD with the hazard ratios (95% CI) of 1.28 (1.13–1.44), 1.18 (1.05–1.33), and 1.15 (1.02, 1.30) per 1 SD decrease in BMD for distal radius, proximal radius, and calcaneus, respectively [10].

Contrary to the above findings, several authors pointed out the dissociation between ankle fracture and lower BMD. A study in 9704 women aged 65 or older in the United States did not find a statistically significant association between ankle fracture and the BMD of the distal radius, proximal radius, calcaneus, femoral neck, or spine [24]. Three other large cohort studies also revealed no association between femoral neck BMD and ankle fractures. In 2000, Gnudi et al conducted a prospective cohort study in 254 postmenopausal women to compare the efficacy of BMD in detecting fractures with that of ultrasound transmission velocity (UTV) at the distal radius and patella [25]. In 13 ankle fractures examined, distal radius BMD was not correlated with the risk of ankle fracture. Another study investigating bone microarchitecture in postmenopausal women demonstrated no statistical difference in BMD at the lumbar spine, total hip, femoral neck, and radius between the ankle fracture group and the control group. A study in Korean patients also found no association between ankle fracture and BMD of the hip or spine [26]. In a cross-sectional study comparing BMD of postmenopausal women with and without ankle fractures, there was no association between ankle fracture and the BMD of the lumbar spine, total ankle, or any regions of the ankle after adjusting for weight [19]. Intriguingly, a prospective case-control study in 18 ankle fracture patients in Hong Kong revealed that the ankle fracture group even had significantly higher hip and spine BMD compared to the age-matched hip fracture group and general background population [27].

4. Discussion

The overall quality of the studies in this systematic review was moderate to high, with the potential confounders including lack of adjustment for possible confounding variables in some studies and possible referral bias. Control subjects (those without fractures) who were sent for bone density measurement were more likely to have lower bone density and fracture risk compared to the healthy background population. A longer follow-up period is recommended to obtain more reliable data. We proposed the cut-off point for an adequate follow-up period to be 10 years. This is based on our hypothesis that ankle fracture is a relatively early manifestation of osteoporosis and the cut-off point should be consistent with the predictability of fracture by FRAX score.

The majority of studies in this systematic review showed an increase in subsequent fracture incidences after initial ankle fractures. However, one study by Ettinger did not find a rise in subsequent hip, humerus or wrist fracture following an ankle fracture [5]. This is probably due to a relatively short mean follow-up period of 22 months, given that ankle fracture may be an early manifestation of osteoporosis. Pritchard et al also found no relationship between a prior ankle fracture and subsequent major osteoporotic fracture [22]. Nonetheless, the authors stated that one of the significant risk factors of ankle fracture found in the study was the history of major osteoporotic fracture. This confirmed the association of major bone fracture and its risk of subsequent peripheral fractures, including the ankle. A few studies reported a higher incidence of wrist fractures but not hip fractures, leading to a suggestion that ankle fractures may be an indicator of subsequent appendicular fractures [19,20]. These studies, however, were limited by small sample sizes and cross-sectional design which is incapable of detecting long-term consequences. Moreover, heavier habitus, predominant in ankle fracture groups of both studies were considered as a confounding factor by providing a protective effect against hip fracture due to more soft tissue padding around the hip during falls [14,28].

Only 4 articles included in this systematic review revealed a decrease in central or peripheral BMD in ankle fractures. Gnudi et al found no relationship between distal radius BMD and ankle fracture but a decreased ultrasound transmission velocity of the patella (UTV-P) in the ankle fracture group [25]. Regression analysis showed that UTV-P can be used to predict future ankle fractures. Interestingly, UTV-P was found to be able to differentiate subjects

Table 3
List of studies investigating the relationship between ankle fracture and bone mineral density.

Study [Reference]	Study design	Study population	Total sample	Average time of follow-up, yr	Initial ankle fracture case	Initial non-fracture case	Subsequent fracture case	BMD mode of measurement	BMD location	BMD fracture (SD)	BMD non-fracture (SD)	Type of risk	Risk of fracture per 1 SD decrease in aBMD (95% CI)
Biver E [9]	Cross-sectional	Geneva Retirees Cohort, Switzerland (female, mean age 65)	749	N/A	63	433	N/A	Hologic QDR Discovery Instrument	aBMD LS	0.87 (0.15)	0.935 (0.152)	OR adjusted for age, height, weight, years after menopause, calcium and protein intake, physical activity adjusted for adjusted for age, height, weight, years after menopause, calcium and protein intake, physical activity age, height, weight, years after menopause, calcium and protein intake, physical activity	1.92 (1.42 −2.60)[a]
									aBMD FN	0.678 (0.114)	0.717 (0.106)		1.97 (1.42 −2.74)[a]
									aBMD TH	0.811 (0.107)	0.855 (0.112)		2.16 (1.54 −3.03)*
									aBMD DER	0.614 (0.067)	0.639 (0.065)		1.60 (1.20 −2.13)[a]
									aBMD UDR	0.382 (0.063)	0.404 (0.06)		1.62 (1.21 −2.17)[a]
									aBMD TR	0.509 (0.062)	0.534 (0.059)		1.69 (1.26 −2.27)[a]
Gnudi S [25]	Prospective cohort	Postmenopausal woman (female, mean age 58)	254	5.47 ± 1.05	0	254	13	Norland 2780	BMD-DER -1SD			RR adjusted for age	0.24 (0.02 −2.64)
Gnudi S [14]	Prospective cohort	Postmenopausal women who had BMD FN measurement at Modulo Dipartimentale di Medicina Interna, Istituti Ortopedici Rizzoli in Bologna, Italy (female, mean age 64.9)	2235	N/A	108	1629	N/A	Norland XR 36 pencil beam	aBMD FN	674.1 (103.8)	700 (107.7)		
Greenfield DM [20]	Cross-sectional	Postmenopausal women recruited at Northern General Hospital Trust, Sheffield, England (female, mean age 64.2)	478	N/A	103	375	N/A	Lunar DPX Densitometer	aBMD LS	1.082 (0.17)	1.069 (0.189)		
									aBMD FN	0.858 (0.141)	0.845 (0.134)		
									aBMD Troch	0.783 (0.141)	0.742 (0.134)		
									BMD WT	0.75 (0.172	0.728 (0.167)		
Ho PY [27]	Case-control	Women aged > 60 years admitted with ankle fracture at University Teaching Hospital, Hong Kong between 2002 and 2003 (female, mean age 74)	N/A	N/A	18	N/A	N/A	Norland XR 36	aBMD FN	−1.7	−2.28		
									aBMD LS	−1.67	N/A		
Ingle BM [19]	Cross sectional	Postmenopausal women recruited at Northern General Hospital Trust, Sheffield, England (female, mean age 62.2)	62	N/A	31	31	N/A	Hologic QDR 1000/W	aBMD LS	0.92 (0.06)	0.92 (0.06)		
									aBMD 1/4 ankle	0.73 (0.06)	0.76 (0.04)		
									aBMD mid ankle	0.61 (0.03)	0.59 (0.03)		
									aBMD ultradistal ankle	0.61 (0.03)	0.6 (0.04)		
									aBMD total ankle	0.64 (0.03)	0.63 (0.03)		
Lee DO [26]	Cross-sectional	Patients visiting Myongji Hospital in Korean 2006−2015 (female and male, mean age 68.1)	229	N/A	116	113	N/A	Discovery W (Hologic)	aBMD LS	0.837 (0.157)	0.847 (0.157)		
									aBMD FN	0.631 (0.122)	0.654 (0.116)		
									aBMD Troch				

										0.564 (0.112)	0.583 (0.111)		
Morin SN [17]	Retrospective cohort	Women undergoing baseline clinical BMD from 1990 to 2007 from the database of Manitoba, Canada (female, mean age 64.3)	39991	5.3	1694	29878	N/A	Lunar DPX Densitometer, Lunar Prodigy				HR adjusted for decades of age, FN BMD	1.3 (1.08 −1.57)[a]
Pritchard JM [22]	Prospective cohort	Females with or without DM from Population Health Information System (POPULIS) data repository at the Manitoba Centre for Health Policy (MCHP), Canada from 1987 to 2007 (female aged ≥ 50)	12205	4.8	559	11646	17	Lunar DPX, Lunar Prodigy	aBMD FN			RR after multivariate for medical conditions and medication use	0.91 (0.82, 1.01)
Schuit SC [13]	Prospective cohort	Female and male aged at least 55 years old who participated in the Rotterdam study (female and male aged ≥ 55)	Total 5794	6.8				Lunar DPX-L densitometer				HR age adjusted for predictive value of FN BMD per gender specific SD decrease	1.2 (0.8 −1.7)
			Male 2437	6.8									1 (0.5 −2.2)
			Female 3357	6.8									1.1 (0.7 −1.6)
Seeley DG [24]	Prospective Cohort	Non-black women aged > 65 years from population-based listing from Baltimore, Minneapolis, The Monongahela Valley, Portland, USA (female, mean age 71.7)	9704	5.9 ± 1.2	0	9704	191	OsteoAnalyzer and Hologic QDR 1000	aBMD DER	0.35 (0.08)	0.36 (0.09)	RR after multivariate analysis	1.15 (0.98 −1.35)
									aBMD proximal radius	0.63 (0.1)	0.63 (0.1)	RR before multivariate analysis	1.08 (0.93 −1.26)
									aBMD calcaneus	0.4 (0.1)	0.4 (0.1)		0.98 (0.85 −1.14)
									aBMD FN	0.65 (0.11)	0.64 (0.11)		0.96 (0.82 −1.13)
									aBMD LS	0.87 (0.6)	0.85 (0.17)		0.93 (0.8 −1.08)
Stein EM [12]	Cross-sectional	Postmenopausal women aged > 60 years old or more than 10 years past menopause were recruited at Columbia University Medical Center, or Helen Hayes Hospital (female, mean age 68.5)	129	N/A	17	112	N/A	Hologic QDR-4500, Lunar Prodigy	aBMD LS	0.911 (0.021)	0.927 (0.014)		
									aBMD TH	0.809 (0.028)	0.809 (0.012)		
									aBMD FN	0.674 (0.022)	0.684 (0.009)		
									aBMD 1/3R	0.607 (0.024)	0.613 (0.007)		
									aBMD UDR	0.354 (0.016)	0.379 (0.006)		
Stone KL [10]	Prospective cohort	Non-black U.S. women aged 65 and older from the study of osteoporotic fracture from Baltimore, Minneapolis, The Monongahela Valley, Portland, USA (female, mean age 71.7)	9704	10.4 years (peripheral BMD), 8.5 years (central BMD)			303	OsteoAnalyzer and Hologic QDR 1000	aBMD DER			HR age adjusted for predictive value	1.28 (1.13 −1.44)[a]
									aBMD Proximal radius				1.18 (1.05 −1.33)[a]
									aBMD calcaneus				1.15 (1.02 −1.3)[a]
									aBMD LS				1.1 (0.95 −1.27)
									aBMD total hip				1.07 (0.92 −1.25)
									aBMD FN				1.06 (0.92 −1.23)

aBMD, areal bone mineral density; LS, lumbar spine; FN, femoral neck; TH, total hip; DER, distal end radius; UDR, ultra-distal radius; TR, total radius; Troch, trochanter; WT, Ward's triangle, 1/3R = 1/3 Radius; DM, diabetes mellitus; HR, hazard ratio; RR, relative risk; SD, standard deviation; N/A, not applicable.

[a] Statistically significant; all ages are in years.

with fragility fractures of the spine from the normal population [29,30]. Ingle et al also reported a decrease in ultrasound velocity measured at the calcaneus in the ankle fracture group [19]. Change in ultrasound velocity could reflect changes in bone quality including trabecular separation, orientation, connectivity, and porosity, as well as bone stiffness and elasticity [29,31,32]. Lee et al did not find an association between central BMD and ankle fracture in their cross-sectional study [26]. However, using the elderly who visited the hospital for BMD check-up carried a risk of referral bias.

Biver et al in the study in the GERICO cohort found lower central and peripheral BMD as well as a higher percentage of osteoporotic women in the ankle fracture group [9]. The authors, in the same study, also noted an alteration in bone microstructure: ankle fracture group exhibited lower total vBMD, trabecular bone density, trabecular number, trabecular thickness, and higher trabecular spacing and distribution at the distal radius. Microstructural changes were also detected at the distal tibia. Similar changes were observed, but to a greater degree, in elderly women with prior forearm fractures which are generally considered as osteoporotic fractures. Although another study by Stein et al did not find a decrease in BMD in 17 ankle fracture patients [12], microarchitectural changes were detected from high-resolution peripheral quantitative computed tomography (HR-pQCT), demonstrating lower trabecular number, lower whole bone stiffness, and higher trabecular spacing at the radius and tibia. With these findings, the authors concluded that ankle fractures were related to generalized bone loss and fragility as shown by these microstructural changes, and thus should be treated as osteoporotic fractures, regardless of BMD. Such changes were limited to the trabecular component, which may explain the preservation of BMD in those with ankle fractures since cortical bones were the main component detected in BMD. Microarchitectural changes in both radius and tibia indicated a generalized bone loss in the ankle fracture group. These changes were also consistent with the changes found in fragility fractures, independent of aBMD, in women from the OFELY cohort [33–35]. Vico L and Wang J also observed lower volumetric bone density and trabecular number in fragility fracture of other sites [36,37]. Lee et al reported lower bone attenuation and more complex fracture configuration in the elderly with ankle fractures when compared to their younger counterparts, supporting their osteoporotic feature [38].

Our findings support the theory that ankle fracture is one of frailty, osteoporotic fractures. This can be explained by an increase in subsequent fractures found in the majority of the studies included in this systematic review. Despite its lack of strong connection to decreased central or peripheral BMD, ankle fracture is found to be subject to microarchitectural changes, particularly in the trabecular component, consistent with other osteoporotic fractures, but to a lesser extent. This suggests that ankle fracture can be a very early expression of osteoporosis. Therefore, prevention of subsequent fracture including major osteoporotic fractures may be beneficial after an ankle fracture following a low-to-moderate trauma.

The relative risk of re-fractures was observed to decrease with advancing age in 2 studies [8,18]. The study in GLOW cohort found a relative risk of any fractures following an ankle fracture of 2.4 in women younger than 65 [18]. The relative risk gradually decreased to 1.0 in women over 85 years of age, indicating no excess risk compared to women without fractures. The same trend was evident in preceding/index fractures of other sites. Kanis et al reported a decrease in subsequent hip fracture following any fractures with progressing age, likely owing to the higher mortality rate of fractures in older individuals [39]. Consistent with Kanis, Robinson et al also found a decline of the relative risk of re-fractures in their large prospective cohort [8], which can be explained by the increase in incident fractures with advancing age which obviates the incidence of re-fracture in the population. The author also noted a higher relative risk of re-fracture in men than in women, partly due to greater alcohol intake, which could lead to more frequent falls and reduced bone mass. These findings imply that interventions to prevent subsequent fractures, such as fall prevention, are more likely to be effective from an economic viewpoint in younger individuals.

To our best knowledge, this study represents the first systematic review exclusively exploring ankle fracture in the elderly and its association to osteoporosis by means of BMD and subsequent fracture risk. The strengths of this review are in its adherence to the PRISMA guideline and quality assessment of each study recruited in the review.

The limitation includes the fact that we limited our search to 2 electronic databases and publications in English. However, the databases used are among the most optimal search tools for biomedical research with wider journal ranges [40]. Studies included have diverse designs and cover diverse population groups, which represent a low risk of selection bias. Meta-analysis could not be performed in this study due to the heterogeneous nature (ie, the method of BMD assessment, population group, and the follow-up period) of the included studies. Prospective cohorts with longer follow-up time and larger sample size are required to further delineate the risk of each type of subsequent fractures with higher power of the test. Further studies with a larger sample size on microarchitectural changes and mechanical bone property in subjects with ankle fracture would be beneficial to elucidate its relationship to bone fragility.

5. Conclusions

Despite the lack of clear association between ankle fracture and BMD, the contribution of ankle fractures to an increased subsequent fracture risk cannot be overlooked. Bone microarchitectural changes, in consistence with other frailty fractures, have also been detected, indicating the likelihood of ankle fracture being osteoporotic in nature. Its potential role as an early predictor of future fracture may aid in secondary prevention. Further studies on the association between ankle fracture and the risk of osteoporosis in the elderly should be conducted with a longer follow-up period and a stricter confounder control.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

CRediT author statement

Atiporn Therdyothin: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing - original draft. **Nacharin Phiphopthatsanee:** Data curation, Resources, Writing - review & editing. **Wiwat Wajanavisit:** Writing - review & editing. **Patarawan Woratanarat:** Supervision, Validation. **Sukij Laohajaroensombat:** Conceptualization. **Tulyapruek Tawonsawatruk:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Supervision, Writing - review & editing.

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