ORIGINAL ARTICLE

Low bone mineral density and fractures in stages 3–5 CKD: an updated systematic review and meta-analysis

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Abstract

Summary The utility of bone mineral density (BMD) testing in chronic kidney disease (CKD) is not known. We performed a meta-analysis of studies reporting on BMD and fracture in CKD. All but one study was cross-sectional. BMD was lower in those with CKD and fractures compared to those without fractures.

Introduction CKD is associated with an increased risk of fracture. The utility of dual energy X-ray absorptiometry (DXA) to assess fracture risk in CKD is unknown.

Methods We performed an updated meta-analysis and systematic review of published studies that reported on the association between DXA and fracture (morphometric spine or clinical nonspine) in predialysis and dialysis CKD. We identified 2,894 potential publications, retrieved 292 for detailed review, and included 13. All but one study was cross-sectional and three reported on the ability of DXA to discriminate fracture status in predialysis CKD. Results were pooled using a random effects model and statistical heterogeneity was assessed using the I^2 statistic.

Results BMD was statistically significantly lower at the femoral neck, lumbar spine, the 1/3 and ultradistal radius in subjects with fractures compared to those without regardless of dialysis status. For example, femoral neck BMD was 0.06 g/cm^2 lower in dialysis subjects and 0.102 g/cm^2 lower in predialysis subjects with fractures compared to those without. Lumbar spine BMD was 0.05 g/cm^2 lower in dialysis subjects and 0.108 g/cm^2 lower in predialysis subjects with fractures compared to those without. Our meta-analysis was limited to studies with small numbers of subjects and even smaller numbers of fractures. All of the studies were observational and only one was prospective. There was statistical heterogeneity at the lumbar spine, 1/3 and ultradistal radius.

Conclusions Our findings suggest that BMD can discriminate fracture status in predialysis and dialysis CKD. Larger, prospective studies are needed.

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Introduction

Chronic kidney disease (CKD) is a risk factor for fracture. Compared to otherwise healthy men and women, those with CKD stages 3 to 5 have at least a twofold increase in the risk of fracture including hip fracture [1]. Among those on dialysis, the risk increases by fourfold, independent of age and sex [2]. Further, compared to those without CKD, patients with CKD who have a fracture have higher morbidity and mortality.

Bone mineral density (BMD) measurement by dual energy X-ray absorptiometry (DXA) is the gold standard to assess fracture risk in healthy men and women [3, 4]. The utility of DXA to predict fracture risk in CKD is unclear for two reasons. First, there are only a few, mainly cross-sectional studies, with small numbers of study subjects that have reported on DXA to discriminate fracture status. Second, men and women with CKD may have underlying metabolic bone disease, such as hyperparathyroidism and/or adynamic bone disease, which increase fracture risk independent of BMD by DXA [5]. Indeed, the uncertainty concerning the utility of DXA in CKD is reflected in the 2009 Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines, which outline that "In patients with CKD stages 3-5D with evidence of Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) we suggest that BMD testing not be performed routinely because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B)" [6].

In 2007, we performed a meta-analysis to determine whether BMD by DXA was associated with fractures in CKD. Our meta-analysis included cross-sectional studies in subjects with stage 5D CKD. We found that BMD at all sites, except the femoral neck, was significantly lower in subjects with stage 5D CKD with fractures [7]. However, our conclusions were limited due to the small numbers of subjects and the heterogeneity of the studies. Since our original publication, additional studies have reported on the association between fractures and DXA, both in those with stage 5D CKD and predialysis. As a result, we performed an updated meta-analysis; the purpose of which was to reevaluate the association between DXA and fracture in stage 5D CKD and to determine if DXA is associated with fractures in predialysis CKD.

Methods

Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [8]. On May 26, 2013, an experienced medical librarian (TR) developed and conducted a computerized search of the electronic databases (Ovid) MEDLINE since 1946, (Ovid) EMBASE since 1947, and all databases in The Cochrane Library, Issue 4 of 12, April 2013. Using our original meta-analysis as a seed article, we performed a "related citations" in PubMed to identify items most similar to it. In addition, two investigators (SAJ and RCB) hand-searched cited references of published reviews of renal osteodystrophy. We did not limit searches or inclusion criteria by year. We did not search for abstracts and we did not include unpublished studies or studies not published in English. We attempted contact with authors to clarify published data if

needed. The complete search strategy is available in Appendix 1.

We included all cross-sectional and longitudinal studies that included men and women (regardless of menopausal status), 18 years and older, with diagnosed CKD (irrespective of stage or type of dialysis). We included studies that measured BMD by means of DXA with any of the Lunar (Lunar Corp, Madison, WI, USA), Hologic (Hologic Inc, Bedford, MA, USA), or Norland (Norland Medical Systems Inc, Lake Forest, CA, USA) machines at any of the total hip, femoral neck, lumbar spine, one third radius, midradius, or ultradistal radius. If BMD was reported as anything other than absolute values (grams per square centimeter), we contacted the investigator to obtain the raw data.

Our outcome of interest was osteoporotic (or fragility) fracture, defined according to the World Health Organization as a fracture that occurs after minimal trauma, such as a fall from a standing height or less [9]. We included clinical fractures (including clinical spine) and spine fractures identified by means of vertebral morphometry.

Data extraction

We selected studies and extracted data according to a standard Cochrane protocol [8, 10]. All the investigators independently reviewed the abstracts and identified potential manuscripts for retrieval. We established study eligibility by consensus, using previously defined inclusion criteria. Two investigators (DDP and RCB) independently reviewed eligible studies for study characteristics and clinical relevance, and if appropriate extracted study data. We used consensus and a third reviewer (SAJ), if necessary, to resolve disagreements.

We abstracted the following information onto pretested standardized data collection forms: number of subjects, population characteristics (age, weight, body mass index (BMI), sex, and, for women, menopausal status, and age at menopause), stage, duration and etiology of CKD, and for those on dialysis, characteristics of dialysis (hemodialysis, peritoneal dialysis, and dialysis vintage), use of calcium, vitamin D, phosphate binders, bisphosphonates, the presence of diabetes, and DXA measurement characteristics (type of machine and sites measured). We also abstracted data on the mechanism by which the fracture occurred, the methods used to document fractures (self-report, radiology report, or review of radiographs), fracture site, total number of fractures in the study, and in stage 5D, the relationship of fracture occurrence to dialysis therapy (before or since starting dialysis). Our data abstraction form is available upon request.

Those of us who did the systematic review were not masked to authors, institution, or journal of publication. The use of nonmasked reviewers is accepted in meta-analyses and has not been shown to bias results [11].

Risk of bias assessment

We used the Newcastle-Ottawa Scale (NOS) to assess the risk of bias for our studies. The tool, developed specifically for nonrandomized studies (cohort and case control), evaluates the selection of the study group, the comparability of the groups, and the exposure (for case–control studies) or the outcome of interest (for cohort studies). Details of the NOS tool have been described elsewhere [12, 13] but briefly, studies can receive a maximum of ten stars: five for the study group selection, two for comparability between groups, and three for the outcome.

Data synthesis

When appropriate, we pooled estimates of effect across studies. We categorized data by site of BMD measurement and formed sub groups for dialysis and predialysis subjects. We compared the mean difference in BMD (g/cm^2), between fracture and nonfracture subjects using a DerSimonian and Laird random effects model [14] and reported results with associated 95 % confidence intervals.

We conservatively quantitatively assessed statistical heterogeneity using the I^2 statistic judging values of <25 % to be minimal, <50 % to be moderate, and 50 % or greater to be substantial [15]. To investigate clinical heterogeneity, we made a post hoc decision to compare differences in BMD by fractures status in predialysis and dialysis CKD. To investigate methodological heterogeneity, we made a post hoc decision to subgroup the data by studies which did and did not adjust for both subject age and weight; both age and weight are robust and independent risk factors for low BMD and fractures [16]. We visually conducted a sensitivity analysis based on study design, and when data allowed and when appropriate, we visually inspected for funnel plot asymmetry to assess for publication bias. We conducted all analyses using the Cochrane Collaboration's data management software, RevMan 5.2.

Results

Our search identified 2,894 potential publications. Of these, we retrieved 292 for more detailed assessment, from which we excluded: 160 as they did not provide information on fracture, 45 because data was available only in abstract form, 23 because the manuscript was not in English, 23 because they did not present original data (review articles or commentaries), 19 because they did not report BMD by fracture status, and 9 because they did not report BMD by DXA (Fig. 1). As such, we added seven studies [17–23] to the six previous studies [24–29] in our updated meta-analysis.

Of the 13 studies included in our meta-analysis, 3 included subjects with predialysis stages 3 to 5 CKD [18, 19, 23], and 1 was prospective [22]. There were a total of 1,785 subjects; 989 men. Note that all subjects had known intrinsic CKD. Mean subject age, by study, ranged from 58 (SD±13) [25] to 78 (IQR=66 to 84) years [18]. Only six studies reported body weight [17, 19, 23, 26, 28, 29], and six [17–19, 21, 23, 26] reported on the presence of risk factors that are associated with BMD and fractures such as smoking, physical activity, calcium, and vitamin D intake. Duration of dialysis therapy ranged across studies from 36.8 (SD±3.1) [26] to 86.4 (SD±9.6) months [24]. Of the 13 studies, 9 [17, 19, 20, 23–28] reported on the cause of CKD; of the subjects in these studies (n= 1,054), 341 (32 %) reported diabetes as the cause of CKD while 251 (24 %) reported that glomerulonephritis was the cause of CKD (Table 1).

All but one study [27] reported on spine fractures. All spine fractures (n=230; 221 morphometric spine fractures and 9 clinical spine fractures) were confirmed by review of radiographs or radiology reports, and only one study specified the occurrence of the spine fracture in relation to dialysis [20]. All but one study [29], reported on nonspine fractures; eight of these studies [17–21, 23, 25, 26] stated that they included only low-trauma fractures. All studies except two [21, 22] stated that fractures were confirmed by radiology, and only four studies [17, 20, 26, 28] explicitly commented on the occurrence of fractures in relation to initiation of dialysis therapy (Table 2).

BMD was significantly lower at the femoral neck, lumbar spine, the 1/3 and ultradistal radius in subjects with fractures compared to subjects without fractures regardless of dialysis status (Fig. 2). For example, femoral neck BMD was 0.06 g/cm^2 lower in dialysis subjects and 0.102 g/cm^2 lower in predialysis subjects with fractures compared to those without fractures. Lumbar spine BMD was 0.05 g/cm^2 lower in dialysis subjects and 0.108 g/cm^2 lower in predialysis subjects with fractures compared to those without fractures.

In predialysis subjects, BMD at the total hip was lower in those with fractures but there was no difference in BMD at the total hip by fracture status in those on dialysis. BMD at the midradius was lower in dialysis subjects with fractures compared to those without fractures and was not reported in predialysis. Of note, there were no statistical differences in BMD at any sites by dialysis status (p=0.31).

Further subgroup analyses comparing pooled effects across studies that adjusted for age and weight were performed. Data allowed for BMD at the femoral neck, total hip, and lumbar spine to be compared. We found no difference in the overall effect for any these sites, regardless of dialysis status (Appendix 2).

Fig. 1 Studies reviewed, included, and excluded in the meta-analysis
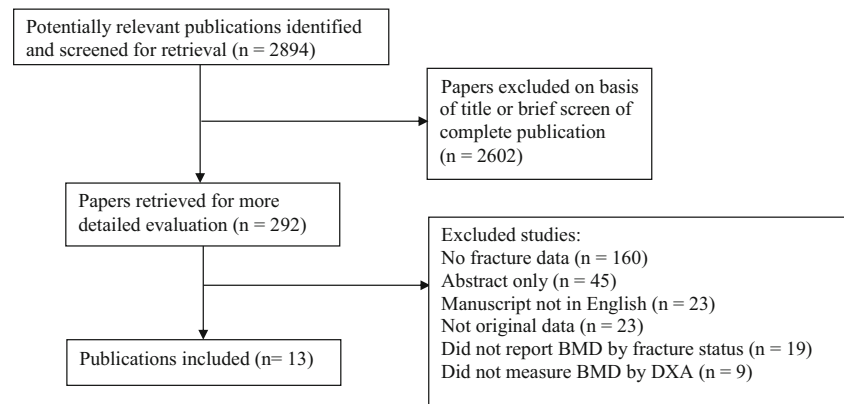
Overall, the risk of bias in the studies was low: three studies received 6.5 stars [20–22], one study received 6.75 stars [18], three studies received 7 stars [25, 27, 29], one study received 7.75 stars [19], and five studies received 8 stars [17, 23, 24, 26, 28] out of a total 10. Details of this rating can be found in Appendix 3.

Statistical heterogeneity was considerable between studies reporting BMD at the lumbar spine (88 %), 1/3 radius (over 70 %), and the ultradistal radius (94 %). BMD in fracture and nonfracture groups measured at the lumbar spine was the only outcome reported in a sufficient number of studies to assess for potential publication bias by funnel plot. There was some asymmetry to the plot, which would suggest some publication bias within studies reporting this outcome, however, the number of studies and respective sample sizes were small making this assessment inconclusive.

Discussion

Our meta-analysis demonstrates that BMD is lower in predialysis and dialysis patients with fractures compared to those without fracture. The exception to this finding was BMD at the midradius which was not reported in predialysis subjects and BMD at the total hip, which did not differ by fracture status in dialysis subjects. Note that only two studies [17, 22] reported on BMD at the total hip among those on dialysis and there were only 73 fractures—thus lack of power might explain our failure to demonstrate an association. Our findings are consistent with our previous meta-analysis, studies in men and women with other chronic diseases, as well as studies in otherwise healthy men and women, all of which demonstrate an association between low BMD and fracture [9, 30–32].

Of note, we found that BMD was low at both cortical (such as the 1/3 radius) and trabecular sites (such as the lumbar spine) among those with fractures compared

to those without. This finding is consistent with what has been reported with higher resolution imaging such as high-resolution peripheral quantitated computed tomography (HRpQCT). Studies using HRpQCT demonstrate a decrease in both trabecular and cortical components in predialysis [18, 19, 23] and dialysis patients with fractures [21]. The decrease in both trabecular and cortical bone components raises the possibility that hyperparathyroidism is not the only factor contributing to decreases in bone mass in these patients; hyperparathyroidism typically causes catabolic effects on cortical bone and anabolic effects on trabecular bone [33]. Our ability to definitively comment of the role of PTH on bone in this meta-analysis is limited by the fact that we did not evaluate serum PTH levels. As well, there was substantially statistical heterogeneity at both the trabecular and cortical bone sites, which limits our conclusions about the ability of BMD to discriminate fracture status by site.

The findings from our updated meta-analysis add to the post hoc prospective analyses of the pivotal osteoporosis fracture trials; these trials included subjects with age-related decreases in renal function (as low as stage 4) and all reported that low BMD was associated with fracture, that BMD increased with treatment, and that the increase in BMD was associated with a decrease in fracture [34–38]. Our findings are also consistent with what has been reported in the only published prospective study in CKD. The study by Iimori and colleagues enrolled 462 subjects with stage 5D CKD and followed them for a median of 40 months [22]. The investigators reported 46 incident fractures and low BMD at the total hip, femoral neck, and/or 1/3 radius was able to predict fracture occurrence.

Our meta-analysis has some limitations. Overall, the number of subjects in the studies was small and there were few fractures. There was substantial heterogeneity at the lumbar spine, 1/3 and ultradistal radius, which limits our ability to definitively conclude that BMD at

Table 1 Characteristics of included studies

Study	Subjects (total no. of subjects)	Subjects (no. of men)	Study sample	Mean age±SD (years)	Mean weight±SD (kg)	Stage of CKD	Cause of renal failure	BMD sites
Yamaguchi et al., 1996	124	59	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	62.5±15.8	NR	Stage 5D	GN=56, DM=30, PCKD=13, other=25	Lumbar spine (L1–L4), 1/3 radius, ultradistal radius
Fontaine et al., 2000	88	51	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	58±13	NR	Stage 5D	GN=17, DM=12, PCKD=15, HTN=14, Other=30	Femoral neck, lumbar spine (L2–L4), 1/3 radius, midradius, ultradistal radius
Jamal et al., 2002	104	71	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	69.4±9.1	72.1±15	Stage 5D	DM=41, GN=33, HTN=16, other=14	Femoral neck, lumbar spine (L2–L4)
Kaji et al., 2002	183	101	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	65±11.5	NR	Stage 5D	GN=83, DM=56, other=44	Lumbar spine (L2–L4), 1/3 radius, ultradistal radius
Urena et al., 2003	70	44	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	60.7±14.11	62.91±13.61	Stage 5D	GN=16, DM=10, PCKD=9, HTN=6, other=29	Femoral neck, lumbar spine (L2–L4), midradius
Inaba et al., 2005	114	0 (all women)	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	73.11±5.87	49.19±9.15	Stage 5D	NA	Lumbar spine, 1/3 radius
Jamal et al., 2006	52	37	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	65.8±9.0	72.3±15.6	Stage 5D	DM=16, GN=12, HTN=5, Other=19	Total hip, femoral neck, lumbar spine (L1–L4)
Nickolas et al., 2010	91	48	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	70.70±9.0	79.24±15.11	Median stage fracture=33 (ml/min); median stage nonfracture=30 (ml/min)	DM/HTN=65, Nephritis/Nephrosis=6, Other=20	Total hip, femoral neck, lumbar spine (L1–L4), 1/3 radius, ultradistal radius
Ambrus et al., 2011	130	71	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	59±14	NR	Stage 5D	GN=39, DM=29, HTN=20, PCKD=14, other=29	Femoral neck, lumbar spine, 1/3 radius
Cejka et al., 2011	74	40	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	59±15	NR	Stage 5D	NR	Femoral neck, lumbar spine (L1–L4), ultradistal radius
Iimori et al., 2011	462	296	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	60.10±12.88	NR	Stage 5D	NR	Total hip, femoral neck, lumbar spine (L2–L4), 1/3 radius
Nickolas et al., 2011	82	46	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	Fracture median, 78 (IQR=66 to 84); nonfracture median, 69 (IQR=62 to 76)	NR	Median stage fracture=25 (ml/min); median stage nonfracture=28 (ml/min)	NR	Total hip, femoral neck, lumbar spine (L1–L4), 1/3 radius, ultradistal radius
Jamal et al., 2012	211	125	Convenience sample from a hospital-affiliated outpatient hemodialysis unit	63.3±15.5	78.8±18.5	Mean in stage 3 (fracture)=12; mean in stage 4 (fracture)=29; mean in stage 5 (fracture)=33; mean in stage 3 (nonfracture)=54; mean in Stage 4 (nonfracture)=46; mean in stage 5 (nonfracture)=37	GN=40, DM=82, HTN=9, other=80	Total hip, lumbar spine (L1–L4), 1/3 radius, ultradistal radius

NR not reported, *DM* diabetes mellitus, *GN* glomerulonephritis, *PCKD* polycystic kidney disease, *HTN* hypertension

Table 2 Characteristics of fractures

Reference	No. of fractures		Method of fracture identification		Relation of fracture occurrence to dialysis		Type of trauma	
	Spine	Nonspine	Spine	Nonspine	Spine	Nonspine	Spine	Nonspine
Yamaguchi et al., 1996	14	13	Radiographs to assess prevalent vertebral fractures	Self-report confirmed by review of medical records	Not specified	Not specified	Not specified	Not specified
Fontaine et al., 2000	2	14	Radiographs to assess prevalent vertebral fractures	Patient interviews confirmed by review of medical records	Not specified	Not specified	Low trauma	Low trauma
Jamal et al., 2002	34	28	Radiographs to assess prevalent vertebral fractures	Patient interviews confirmed by review of radiograph or radiology report	Not specified	16 before and 12 after onset of dialysis	Not specified	Low trauma
Kaji et al., 2002	–	14 (hip)	NA	Review of radiograph or radiology report	Not specified	Not specified	Not specified	Not specified
Urena et al., 2003	6	21	Radiographs to assess prevalent vertebral fractures	Patient interviews confirmed by review of radiograph or radiology report	Not specified	After initiation of dialysis	Mostly low trauma	Mostly low trauma
Inaba et al., 2005	21	–	Radiographs to assess prevalent vertebral fractures	NA	Not specified	Not specified	Not specified	Not specified
Jamal et al., 2006	12	20	Radiographs to assess prevalent vertebral fractures	Self-report confirmed by review of radiograph or radiology report	Not specified	After initiation of dialysis	Not specified	Low trauma
Nickolas et al., 2010	22	27	Radiographs to assess prevalent vertebral fractures	Self-report confirmed by review of radiograph or radiology report	Not specified	Not specified	Low trauma	Low trauma
Ambrus et al., 2011	3	18	Radiographs to assess prevalent vertebral fractures	Patient interviews confirmed by review of radiograph or radiology report	After initiation of dialysis	After initiation of dialysis	Low trauma	Low trauma
Cejka et al., 2011	21	9	Radiographs to assess prevalent vertebral fractures	Patient interviews	Not specified	Not specified	Low trauma	Low trauma
Iimori et al., 2011	31	44	Radiographs to assess prevalent vertebral fractures	Self-report	Not specified	Not specified	Not specified	High or low trauma
Nickolas et al., 2011	21	14	Radiographs to assess prevalent vertebral fractures	Self-report confirmed by review of radiograph or radiology report	Not specified	Not specified	Low trauma	Low trauma
Jamal et al., 2012	43	34	Radiographs to assess prevalent vertebral fractures	Self-report confirmed by review of radiograph or radiology report	Not specified	Not specified	Not specified	Low trauma

NA not applicable

a

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Dialysis Patients								
Iimori 2012	0.646	0.176	46	0.743	0.163	416	62.7%	-0.10 [-0.15, -0.04]
Jamal 2006	0.84	0.21	27	0.85	0.16	25	37.3%	-0.01 [-0.11, 0.09]
Subtotal (95% CI)			73			441	100.0%	-0.06 [-0.15, 0.02]

Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 1 (P = 0.14); I² = 55%
Test for overall effect: Z = 1.53 (P = 0.13)

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.2 Non-dialysis patients								
Jamal 2012	0.85	0.15	74	0.95	0.15	137	49.2%	-0.10 [-0.14, -0.06]
Nickolas 2010	0.84	0.171	32	0.923	0.17	59	23.7%	-0.08 [-0.16, -0.01]
Nickolas 2011	0.783	0.11	23	0.943	0.196	59	27.1%	-0.16 [-0.23, -0.09]
Subtotal (95% CI)			129			255	100.0%	-0.11 [-0.15, -0.07]

Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 5.43 (P < 0.00001)

-0.2 -0.1 0 0.1 0.2
BMD lower in fracture   BMD higher in fracture

Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31); I² = 3.4%

b

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Dialysis Patients								
Ambrus 2011	0.66	0.18	21	0.72	0.14	109	9.5%	-0.06 [-0.14, 0.02]
Cejka 2011	0.573	0.048	24	0.6764	0.037	50	34.4%	-0.10 [-0.13, -0.08]
Fontaine 2000	0.62	0.13	11	0.73	0.12	77	9.5%	-0.11 [-0.19, -0.03]
Iimori 2012	0.567	0.133	46	0.636	0.141	416	22.8%	-0.07 [-0.11, -0.03]
Jamal 2002	1.3	0.23	54	1.3	0.25	50	7.7%	0.00 [-0.09, 0.09]
Jamal 2006	0.76	0.182	27	0.79	0.14	25	8.4%	-0.03 [-0.12, 0.06]
Urena 2003	0.766	0.182	18	0.807	0.149	51	7.6%	-0.04 [-0.13, 0.05]
Subtotal (95% CI)			201			778	100.0%	-0.07 [-0.10, -0.04]

Heterogeneity: Tau² = 0.00; Chi² = 9.60, df = 6 (P = 0.14); I² = 37%
Test for overall effect: Z = 5.04 (P < 0.00001)

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.2 Non-dialysis patients								
Nickolas 2010	0.677	0.127	32	0.755	0.154	59	41.8%	-0.08 [-0.14, -0.02]
Nickolas 2011	0.621	0.0718	23	0.747	0.134	59	58.2%	-0.13 [-0.17, -0.08]
Subtotal (95% CI)			55			118	100.0%	-0.11 [-0.15, -0.06]

Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 1 (P = 0.21); I² = 38%
Test for overall effect: Z = 4.47 (P < 0.00001)

-0.2 -0.1 0 0.1 0.2
BMD lower in fracture   BMD higher in fracture

Test for subgroup differences: Chi² = 1.40, df = 1 (P = 0.24); I² = 28.4%

c

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Dialysis Patients								
Ambrus 2011	0.92	0.22	21	0.97	0.2	109	7.6%	-0.05 [-0.15, 0.05]
Cejka 2011	0.8167	0.066	24	0.9	0.0559	50	12.7%	-0.08 [-0.11, -0.05]
Fontaine 2000	0.85	0.16	11	0.95	0.14	77	7.7%	-0.10 [-0.20, -0.00]
Iimori 2012	0.571	0.164	46	0.614	0.174	416	11.4%	-0.04 [-0.09, 0.01]
Inaba 2005	0.533	0.0855	21	0.583	0.1179	93	11.9%	-0.05 [-0.09, -0.01]
Jamal 2002	0.86	0.17	54	0.87	0.17	50	10.2%	-0.01 [-0.08, 0.06]
Jamal 2006	1.19	0.24	27	1.08	0.21	25	6.3%	0.11 [-0.01, 0.23]
Kaji 2002	0.892	0.048	14	0.92	0.013	169	13.0%	-0.03 [-0.05, -0.00]
Urena 2003	1.071	0.2402	19	1.118	0.2499	51	6.0%	-0.05 [-0.17, 0.08]
Yamaguchi 1996	0.76	0.053	27	0.9058	0.02224	97	13.2%	-0.15 [-0.17, -0.13]
Subtotal (95% CI)			264			1137	100.0%	-0.05 [-0.09, -0.01]

Heterogeneity: Tau² = 0.00; Chi² = 74.19, df = 9 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.45 (P = 0.01)

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.2 Non-dialysis patients								
Jamal 2012	1.01	0.2	74	1.1	0.22	137	47.6%	-0.09 [-0.15, -0.03]
Nickolas 2010	0.957	0.173	32	1.069	0.203	59	26.1%	-0.11 [-0.19, -0.03]
Nickolas 2011	0.938	0.151	23	1.06	0.192	59	26.3%	-0.12 [-0.20, -0.04]
Subtotal (95% CI)			129			255	100.0%	-0.10 [-0.14, -0.06]

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 5.05 (P < 0.00001)

-0.2 -0.1 0 0.1 0.2
BMD lower in fracture   BMD higher in fracture

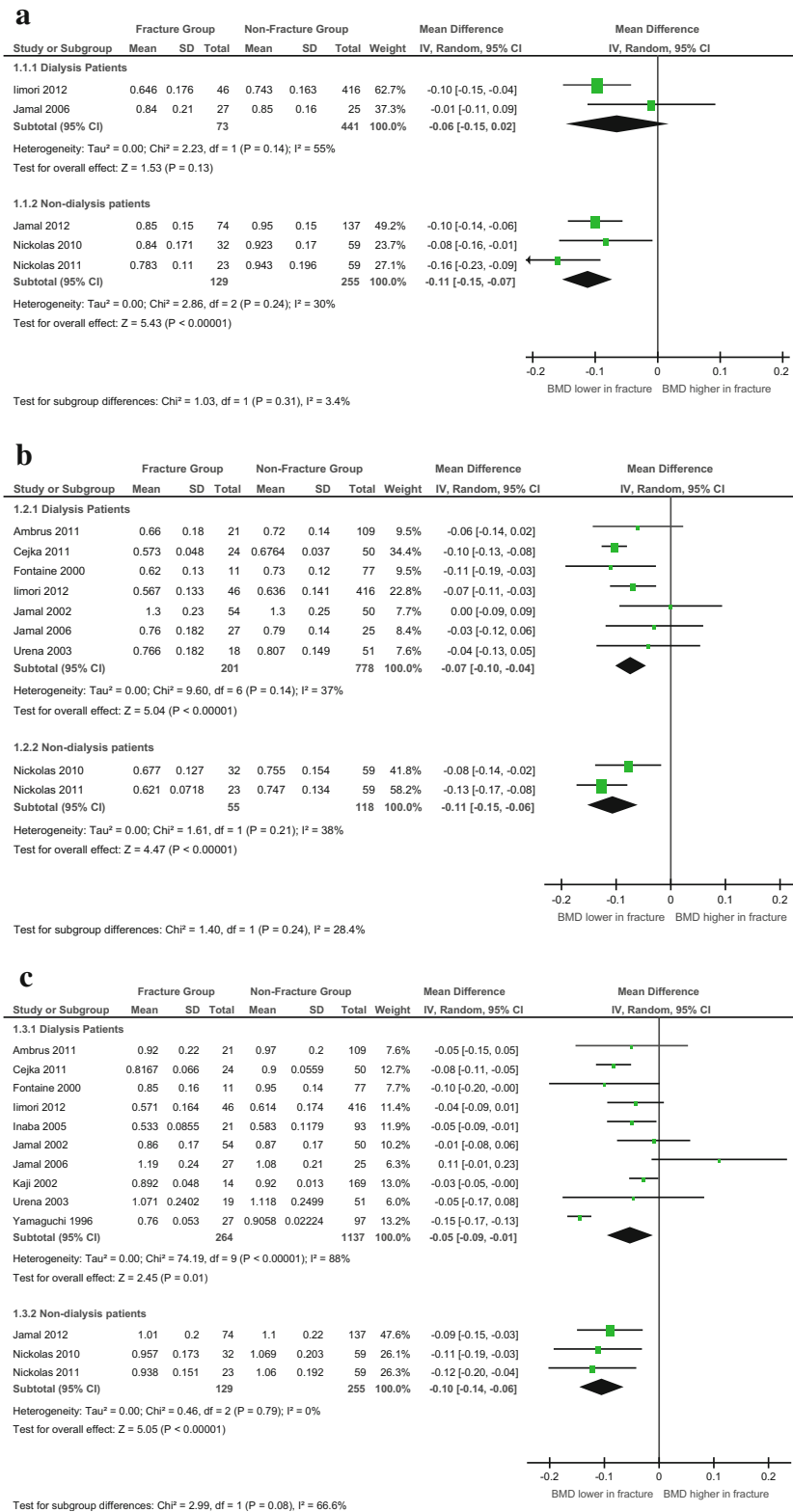Test for subgroup differences: Chi² = 2.99, df = 1 (P = 0.08); I² = 66.6%

Fig. 2 The association between total hip BMD and fracture (**a**), femoral neck BMD and fracture (**b**), lumbar spine BMD and fracture (**c**), 1/3 radius BMD and fractures (**d**), midradius BMD and fractures (**e**), and ultradistal BMD and fractures (**f**) by dialysis status

these sites can discriminate fracture status. None of the studies were randomized trials, most did not report or adjust for potential factors associated with both fracture and BMD and only one study was prospective.
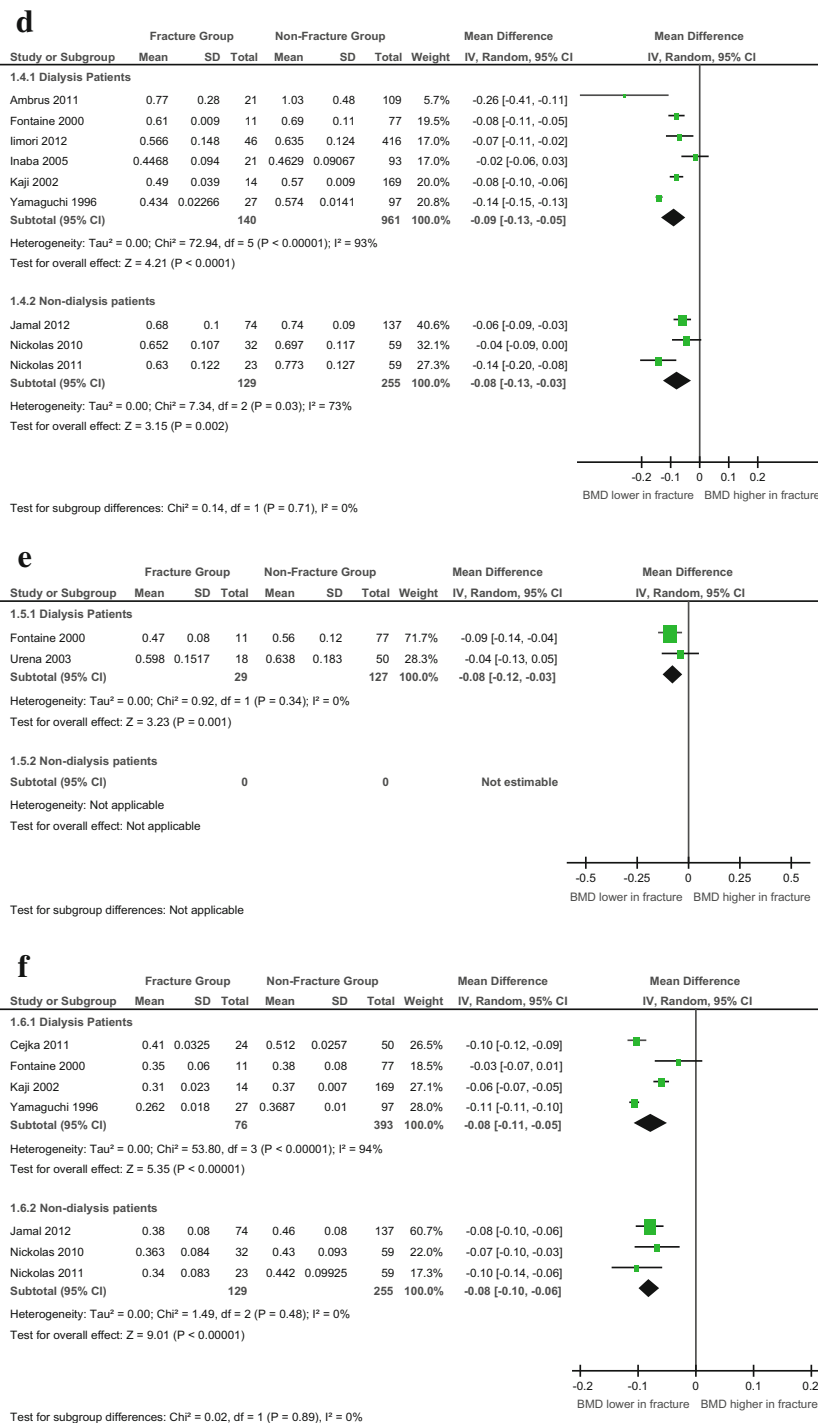
Fig. 2 (continued)

In conclusion, our meta-analysis indicates that BMD is low in predialysis and dialysis patients with fractures. These findings, considered together with the recent prospective study in CKD, and post hoc analyses of the pivotal fracture trials suggests that BMD may be clinically useful in assessing fracture risk in CKD, different than what has been suggested in the KDIGO guidelines [6]. Clearly, prospective studies to confirm that low BMD is independently associated with fractures and that low BMD predicts fractures in predialysis and dialysis CKD are needed.

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