

Supplementary Tables

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Table S1 Characteristics of the outcomes in eligible studies

Study	Bone markers	BTMs assessments	BTMs time point (month)	Fasting	BMD site	BMD measurements	BMD time point (month)
Greenspan 1998[1]	U-NTX/Cre; DPD/Cr OC; Bone ALP	ELISA NR	Baseline, 6	Yes	TH; FN; TR; InterTR; Spine (PA spine; lateral spine); TB	DXA	Baseline, 30
Garnero 1999[2]	Bone ALP	NR	Baseline, 3, 6, 24	Yes	LS	DXA	Baseline, 24
Watts2001[3]	Bone ALP	EIA	Baseline, 3, 6, 12	Yes	LS(L1-L4); FN; TR; TB	DXA	Baseline, 3,6,12,18, 24, 36
Drake 2003[4]	Bone ALP, U-NTX	NR	baseline; 3, 6, 12, 18	Yes	LS(L1-L4); FN; TB;	DXA	Baseline,6,12,18,24
Eastell2003[5]	CTX/Cre; NTX/Cre	Automated analyser	Baseline, 3, 6	Yes	LS(L1-L4); FN;	DXA	baseline
Ravn 2003[6]	U-CTX/Cre;U-NTX Total OC	ELISA RIA; ELISA	Baseline, 6, 12, 48	Yes	Spine; Hip; total body; wrist	DXA	Baseline,48
Greenspan 2005[7]	Bone ALP; Intact OC U-NTX	NR NR ELISA	Baseline, 6	Yes	Hip (TH; FN; TR; interTR); Spine (PA spine; lateral spine)	DXA	Baseline,36
Neonen 2005[8]	S-CTX; bone ALP; PINP Total OC; TRACP-5b DPD	Commercial IA In-house IA HPLC	Baseline, 3, 6, 12	Yes	LS	DXA	Baseline,12

(Continued) **Table S1** Characteristics of the outcomes in eligible studies

Study	Bone markers	BTMs assessments	BTMs time point (month)	Fasting	BMD site	BMD measurements	BMD time point (month)
Iwamoto 2005[9]	U-NTX/Cre	NR	Baseline, 3, 6, 12	Yes	LS	DXA	Baseline,12
Takada2012 [10]	S-NTX	NR	0, 6	Yes	FN; InterTR	DXA	0, 12
Iikuni2012 [11]	U-NTX	NR	Baseline,3	Yes	LS	DXA	Baseline, 12
Majima2008 [12]	Bone ALP	EIA	Baseline,3,6,12	Yes	LS(L2-L4); FN; TR	DXA	0, 6, 12
	S-NTX	ELISA					
Lu2017 [13]	OCN	IA	Baseline,2,3,4,7	Yes	LS	DXA	Baseline, 2,3, 4,7
Eastell2011 [14]	S-CTX	ELISA	Baseline,6,12,24,36	Yes	LS; TH	DXA	Baseline, 6, 12, 24, 36
	PINP	RIA					
	TRACP-5b	ELISA					
	Bone ALP	IA					
Chen2005 [15]	Bone ALP	Two-site IRMA	Baseline,3,6,12	NR	LS; FN	DXA	Baseline,12,18
	PICP; PINP	RIA					
	NTX/Cre	ELISA					
	DPD/Cre	Enzyme IA					
Tsujimoto2011 [16]	PINP	RIA	Baseline,3,6,12	Yes	LS; FN; TH	DXA	Baseline,3,6,12
	S-CTX	ELISA					
	Bone ALP	Ostase assay					
Delmas2000[17]	OC; bone ALP	IRMA	Baseline,3,6	Yes	LS	DXA	Baseline,6,12,24,
	S/U-CTX	ELISA					
Riis1995 [18]	pBGP	RIA	Baseline,3,6,12,24	Yes	Spine	DXA	Baseline,24
	S-ALP	IA					
	U-HPR/Cre	Spectrophotometric method					

(Continued) **Table S1** Characteristics of the outcomes in eligible studies

Study	Bone markers	BTMs assessments	BTMs time point (month)	Fasting	BMD site	BMD measurements	BMD time point (month)
Okabe2004 [19]	S- β -CTX	ECL	Baseline,1,3,6	Yes	LS(L2-L4)	DXA	Baseline,6
	S-ICTP	RIA					
	DPD/Cre	HPLC					
Zhan1999 [20]	PYD/Cre; DPD/Cre	HPLC	Baseline,6,12,24,36	NR	TB; LS(L2-L4); FN	DXA	Baseline,6,12,24,36
Chen1996 [21]	S-ALP	IA	Baseline,3,6,12	Yes	LS	DXA	Baseline,12
	PYD/Cre; DPD/Cre	HPLC					
	OC	RIA					
Kim2005 [22]	U-NTX	ELISA	Baseline,3,6,12	Yes	LS(L1-L4); FN	DXA	Baseline,12
	OC	RIA					

ALP alkaline phosphatase, BGP bone γ -hydroxy glutamic acid protein, BMD bone mineral density (g/cm²), BSP bone sialoprotein, CLIA chemiluminescence analysis, Cre corrected for creatinine, CTX C-terminal crosslinking telopeptide of type I collagen, DPA dual photon absorptiometry, DPD deoxypyridinoline, DXA dual energy X-ray absorptiometry, ECL electrochemiluminescence, ELISA enzyme-linked immunosorbent assay, FN femoral neck, HPLC high-performance liquid chromatography, HYP hydroxyproline, IA immunoassay, ICTP C-terminal crosslinking telopeptide of type I collagen generated by MMPs, InterTR intertrochanter, IRMA immunoradiometric assay, LS lumbar spine, NR not report, NTX N-terminal crosslinking telopeptide of type I collagen, OC osteocalcin, PICP procollagen type I C propeptide, PINP procollagen type I N propeptide, p~ plasma, PYD pyridinoline, RIA radioimmunoassay, t~ total, TB total body, TH total hip, TR trochanter, TRACP-5b tartrate-resistant acid phosphatase 5b, S serum, U urine, wk week

Table S2 Summary correlation coefficients of subgroup analyses by group of bone site

COR	Heterogeneity	Included studies	Effects model	BTMs	Bone site
-0.26 [-0.37; -0.14]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.63$	Greenspan2005a; Watts2001a	Fixed	Bone ALP	FN
-0.26 [-0.34; -0.18]	$I^2 = 4\%$, $\tau^2 = 0.0003$, $p = 0.37$	Eastell2011; Tsujimoto2011a; Watts2001(b,c)	Fixed	Bone ALP	LS
-0.23 [-0.36; -0.09]	not applicable	Watts2001a	Fixed	Bone ALP	TB
-0.29 [-0.39; -0.19]	$I^2 = 14\%$, $\tau^2 = 0.0017$, $p = 0.31$	Greenspan2005(b,d); Tsujimoto2011b	Fixed	Bone ALP	TH
-0.26 [-0.33; -0.18]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.83$	Greenspan2005(e,h); Majima2008; Watts2001(b,c)	Fixed	Bone ALP	TR
-0.30 [-0.48; -0.10]	not applicable	Kim2005	Fixed	OC	FN
-0.27 [-0.41; -0.12]	$I^2 = 28\%$, $\tau^2 = 0.0055$, $p = 0.24$	Ravn2003a; Lu2017	Fixed	OC	LS
-0.39 [-0.53; -0.22]	$I^2 = 47\%$, $\tau^2 = 0.0157$, $p = 0.17$	Ravn2003(c,d)	Fixed	OC	TB
-0.36 [-0.49; -0.23]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.80$	Green1998a; Ravn2003(e,f)	Fixed	OC	TH
-0.32 [-0.53; -0.07]	not applicable	Greenspan1998b	Fixed	OC	TR
-0.20 [-0.37; -0.02]	not applicable	Tsujimoto2011a	Fixed	S-CTX	FN
-0.24 [-0.39; -0.08]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$	Nenonen2005; Eastell2011a	Fixed	S-CTX	LS
-0.33 [-0.46; -0.20]	$I^2 = 46\%$, $\tau^2 = 0.0097$, $p = 0.17$	Eastell2011b; Tsujimoto2011b	Fixed	S-CTX	TH
-0.32 [-0.48; -0.14]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.58$	Kim2005a; Greenspan1998c	Fixed	U-NTX	FN
-0.34 [-0.37; -0.31]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.59$	Iwamoto2005(a,b,c); Kim2005b; Iikuni2012	Fixed	U-NTX	LS
-0.44 [-0.58; -0.29]	$I^2 = 43\%$, $\tau^2 = 0.0136$, $p = 0.18$	Greenspan1998d; Ravn2003c	Fixed	U-NTX	TB
-0.39 [-0.50; -0.26]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.53$	Greenspan2005a; Greenspan1998e; Ravn2003d	Fixed	U-NTX	TH
-0.35 [-0.48; -0.20]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$	Greenspan2005b; Greenspan1998f	Fixed	U-NTX	TR

ALP alkaline phosphatase, CI confidence interval, DPD deoxypyridinoline, FN femoral neck, LS lumbar spine, OC osteocalcin, S-CTX serum C-terminal crosslinking telopeptide of type I collagen, TB Total body, TH Total hip, TR Trochanter, U-NTX urine N-terminal crosslinking telopeptide of type I collagen

Table S3 Summary correlations of subgroup analyses by group of intervention

COR (95%CI)	Heterogeneity	Included studies	Effects model	BTMs	Intervention
-0.27 [-0.32; -0.21]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.48$	Greenspan2005(b,e); Watts2001(a,b,c,d,e,f)	Fixed	Bone ALP	ALN10
-0.30 [-0.47; -0.10]	not applicable	Greenspan2005a	Fixed	Bone ALP	ALN10+HRT
-0.26 [-0.46; -0.03]	not applicable	Eastell2011	Fixed	Bone ALP	DMAB
-0.29 [-0.42; -0.15]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.62$	Greenspan2005(d,h)	Fixed	Bone ALP	HRT
-0.28 [-0.48; -0.05]	not applicable	Majima2008	Fixed	Bone ALP	RLX
-0.21 [-0.33; -0.09]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.81$	Tsujimoto2011(a,b)	Fixed	Bone ALP	TPTD
-0.37 [-0.45; -0.28]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$	Ravn2003(a,c,d,e,f); Green1998(a,b)	Fixed	OC	ALN5
-0.20 [-0.38; -0.01]	not applicable	Lu2017	Fixed	OC	CCT
-0.30 [-0.48; -0.10]	not applicable	Kim2005	Fixed	OC	HRT
-0.44 [-0.57; -0.31]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.71$	Eastell2011(a,b)	Random	PINP	DMAB
0.31 [0.19; 0.42]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.38$	Tsujimoto2011; Chen2005	Random	PINP	TPTD
-0.24 [-0.44; -0.01]	Not applicable	Nenonen2005	Fixed	S-CTX	ALN5
-0.34 [-0.48; -0.19]	$I^2 = 46\%$, $\tau^2 = 0.0120$, $P=0.17$	Eastell2011(a,b)	Fixed	S-CTX	DMAB
-0.23 [-0.35; -0.10]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$	Tsujimoto2011(a,b)	Fixed	S-CTX	TPTD
-0.35 [-0.46; -0.23]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.97$	Kim2005a; Greenspan2005(a,b)	Fixed	U-NTX	ALN10
-0.35 [-0.42; -0.28]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.44$	Greenspan1998(c,d,e,f); Iwamoto2005(a,b,c); Ravn2003(c,d)	Fixed	U-NTX	ALN5
-0.29 [-0.47; -0.08]	Not applicable	Kim2005b	Fixed	U-NTX	HRT
-0.35 [-0.38; -0.31]	Not applicable	Iikuni2012	Fixed	U-NTX	RLX

ALN Alendronate, ALN10 10 mg/d ALN, ALN5 5mg/d ALN, ALP alkaline phosphatase, CCT calcitonin, CI confidence interval, DMAB Denosumab, DPD deoxypyridinoline, FN femoral neck, LS lumbar spine, OC osteocalcin, RLX Raloxifene, S-CTX serum C-terminal crosslinking telopeptide of type I collagen, TB Total body, TH Total hip, TPTD Teriparatide, TR Trochanter, U-NTX urine N-terminal crosslinking telopeptide of type I collagen

Table S4 Summary correlations of subgroup analyses by group of the time duration of BTMs measurements

COR (95%CI)	Heterogeneity	Included studies	Effects model	Bone markers	Time point of BTMs measurements (month)
0.32 [0.22; 0.40]	$I^2 = 39\%$, $\tau^2 = 0.0053$, $p = 0.19$	Chen2005a, Tsujimoto2011(a,b)	Fixed	Bone ALP	0
-0.28 [-0.48; -0.05]	not applicable	Majima2008	Fixed	Bone ALP	3
-0.26 [-0.31; -0.22]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$	Eastell2011; Greenspan2005(a,b,d,e,h); Tsujimoto2011(a,b); Watts2001(a,b,c,d,e,f)	Fixed	Bone ALP	6
0.33 [0.13; 0.50]	Not applicable	Kim2005a	Fixed	OC	0
-0.20 [-0.38; -0.01]	not applicable	Lu2017	Fixed	OC	4.7
-0.32 [-0.41; -0.23]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$	Ravn2003(a,c,e); Ravn2003(c,e); Kim2005	Fixed	OC	6
-0.46 [-0.59; -0.30]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$	Ravn2003(d,f)	Fixed	OC	12
0.42 [0.34; 0.50]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.40$	Chen2005c; Tsujimoto2011(c,d)	Fixed	PINP	0
0.36 [0.20; 0.50]	Not applicable	Chen2005b	Fixed	PICP	0
0.39 [0.27; 0.49]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.66$	Tsujimoto2011(e,f)	Fixed	SCTX	0
-0.23 [-0.34; -0.12]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.89$	Nenonen2005; Tsujimoto2011(a,b)	Fixed	SCTX	3
-0.34 [-0.48; -0.19]	$I^2 = 46\%$, $\tau^2 = 0.0120$, $p = 0.17$	Eastell2011(a,b)	Fixed	SCTX	6
0.37 [0.30; 0.44]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.97$	Chen2005e; Greenspan1998(a,b,c,d); Kim2005(b,c,d)	Fixed	UNTX	0
-0.32 [-0.39; -0.24]	$I^2 = 28\%$, $\tau^2 = 0.0022$, $p = 0.25$	Iwamoto2005a; Kim2005b; Iikuni2012	Random	UNTX	3
-0.36 [-0.42; -0.28]	$I^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$	Kim2005a; Greenspan2005(a,b,c); Iwamoto2005b; Greenspan1998(d,e,f); Ravn2003d	Random	UNTX	6
-0.43 [-0.61; -0.21]	$I^2 = 57\%$, $\tau^2 = 0.0180$, $p = 0.13$	Iwamoto2005c; Ravn2003c	Random	UNTX	12

ALP alkaline phosphatase, CI confidence interval, OC osteocalcin, PICP procollagen type I C propeptide, PINP procollagen type I N propeptide, S-CTX serum C-terminal crosslinking telopeptide of type I collagen, U-NTX urine N-terminal crosslinking telopeptide of type I collagen

Table S5 Summary correlations of subgroup analyses by group of the time duration of BMD measurements

COR (95%CI)	Heterogeneity	Included studies	Effects model	BTM	Time point of the BMD measurements (month)
-0.27 [-0.34; -0.20]	$I^2 = 0\%, \tau^2 = 0, p = 0.59$	Majima2008; Tsujimoto2011(a,b); Watts2001(a,b)	Fixed	Bone ALP	12
-0.20 [-0.34; -0.06]	Not applicable	Watts2001b	Fixed	Bone ALP	24
-0.27 [-0.33; -0.21]	$I^2 = 0\%, \tau^2 = 0, p = 0.85$	Eastell2011; Greenspan2005(a,b,d,e,h); Watts(a,b,c)	Fixed	Bone ALP	36
-0.30 [-0.48; -0.10]	Not applicable	Kim2005	Fixed	OC	12
-0.32 [-0.47; -0.14]	$I^2 = 0\%, \tau^2 = 0, p = 0.95$	Green1998(a,b)	Fixed	OC	30
-0.39 [-0.48; -0.28]	$I^2 = 0\%, \tau^2 = 0, p = 0.73$	Ravn2003(a,c,d,e,f)	Fixed	OC	48
-0.23 [-0.34; -0.12]	$I^2 = 0\%, \tau^2 = 0, p = 0.89$	Nenonen2005; Tsujimoto2011(a,b)	Fixed	S-CTX	12
-0.34 [-0.48; -0.19]	$I^2 = 46\%, \tau^2 = 0.0120, p = 0.17$	Eastell2011(a,b)	Fixed	S-CTX	36
-0.34 [-0.37; -0.31]	$I^2 = 0\%, \tau^2 = 0, p = 0.72$	Kim2005(a,b); Iwamoto2005(a,b,c); Iikuni2012	Fixed	U-NTX	12
-0.33 [-0.44; -0.21]	$I^2 = 0\%, \tau^2 = 0, p = 0.96$	Greenspan1998(c,d,e,f)	Fixed	U-NTX	30
-0.34 [-0.46; -0.21]	$I^2 = 0\%, \tau^2 = 0, p = 0.99$	Greenspan2005(a,b)	Fixed	U-NTX	36
-0.52 [-0.64; -0.37]	$I^2 = 0\%, \tau^2 = 0, p = 0.82$	Ravn2003(c,d)	Fixed	U-NTX	48

ALP alkaline phosphatase, CI confidence interval, OC osteocalcin, S-CTX serum C-terminal crosslinking telopeptide of type I collagen, U-NTX urine N-terminal crosslinking telopeptide of type I collagen

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