MK4 Osteoporosis Research

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Kodama and Okamoto	Brain & Development. 2017 (in press)	Osteoporosis in adults with cerebral palsy		n = 16; median age 56 years 13 volunteers also had epilepsy and were taking anticonvulsant medications	MK4 45 mg/day	12 months	**Bone laboratory markers:** MK4 improved laboratory markers associated with bone health. **Bone density:** Bone density improved 5% after six months and 9% after twelve months.	Not reported

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Shikano and Kineko	*Internal Medicine*. 2016; 55(15):1997-2003	Prednisone-induced osteoporosis	Prospective, observational study	n = 60 (21 men, 39 women); mean age 55 years.	MK4 45 mg/day orally or no MK4 All volunteers continued to receive prednisone (30-60 mg/day) and all volunteers also took bisphosphonate medications.	18 months	**Bone laboratory markers:** MK4 improved laboratory markers associated with bone health. **Bone density:** Bone density was maintained in the MK4 group. **Fractures:** There were zero fractures in people taking MK4, while 5% of those taking no MK4 fractured.	Not reported

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Jiang and Zhang	*Clinical Intervention in Aging*. 2014; 9:121-7	Postmenopausal osteoporosis	Multicenter, randomized, double-blinded, double- dummy, noninferiority, positive drug-controlled clinical trial	n = 213 (all women); mean age 64 years.	MK4 group: 45 mg/day plus calcium 500 mg/day Vitamin D2 (alfacalcidiol) group: 0.5 micrograms (mcg)/day plus calcium 500 mg/day	12 months	**Bone laboratory markers:** MK4 improved laboratory markers associated with bone health. **Bone density:** MK4 improved bone density 1.2% in the lumbar spine and 2.7% in the hip. **Fractures:** Fractures were decreased in the MK4+calcium group compared to those taking just vitamin D2+calcium.	Minor and not statistically different than taking the vitamin D. The researchers concluded that MK4 "was well tolerated and safe in the study population," and that MK4 "is an effective and safe choice" for people with osteoporosis

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Je and Joo	*Journal of Korean Medical Science*. 2011; 26(8):1093-8.	Postmenopausal osteoporosis	Randomized, controlled clinical trial	n = 78 (all women); mean age approx. 68 years	MK4 Group: MK4 45 mg/day, plus calcium 630 mg/day and vitamin D 400 IU/day Control Group: Calcium 630 mg/day and vitamin D 400 IU/day	6 months	**Bone laboratory markers:** Improved lab markers associated with bone health in the MK4 group, but not in the Control Group. **Bone density:** Bone density improved in the MK4 group, but did not improve in the control group.	Three people complained of a nausea sensation two times after taking MK4, but no other complaints were reported.

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Je and Joo	*Journal of Korean Medical Science*. 2011; 26(8):1093-8.	Postmenopausal osteoporosis	Randomized, controlled clinical trial	n = 78 (all women); mean age approx. 68 years	MK4 Group: MK4 45 mg/day, plus calcium 630 mg/day and vitamin D 400 IU/day Control Group: Calcium 630 mg/day and vitamin D 400 IU/day	6 months	**Bone laboratory markers:** Improved lab markers associated with bone health in the MK4 group, but not in the Control Group. **Bone density:** Bone density improved in the MK4 group, but did not improve in the control group.	Three people complained of a nausea sensation two times after taking MK4, but no other complaints were reported.
Shiraki and Itabashi	*Journal of Bone and Mineral Metabolism*. 2009; 27(3):333-40	Postmenopausal osteoporosis	Randomized, prospective study	n = 109 (all women); mean age approx. 68 years	MK4 Group: 45 mg/day Control Group: Calcium aspartate 1,200 mg/day (providing 133.8 mg elemental calcium)	6 months	**Bone laboratory markers:** Improved lab markers associated with bone health in the MK4 group, but not in the Control Group.	Minor, and no different than control group

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Binkley and Harke	*Journal of Bone and Mineral Research*. 2009; 24(6):983-91	Postmenopausal osteoporosis	Double-blind, placebo-controlled study	n = 381 (all women); mean age 62.5 years	MK4 45 mg/day orally or phylloquinone 1 mg/day orally or placebo	12 months	**Bone laboratory markers:** Improved lab markers associated with bone health.	None
Inoue and Fujita	*Journal of Bone and Mineral Metabolism*. 2009; 27(1):66-75	Postmenopausal osteoporosis	Open-labeled	n = 4,378 (all women); mean age 68 years	MK4 45 mg/day orally alone or with calcium (1.2 to 3 grams) orally per day	48 months	**Fractures:** Fractures were decreased in those taking MK4+calcium.	Minor and statistically lower incidence in MK4 monotherapy group
Knapen and Schurgers	*Osteoporosis International*. 2007; 18(7): 963–972.	Postmenopausal osteoporosis	Randomized, placebo-controlled	n = 325 (all women); mean age 66 years	45 mg/day orally or placebo	36 months	**Bone density:** Bone mineral content and bone strength improved in those those taking MK4.	Minor, and no different than placebo group

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Purwosunu and Muharram	*Journal of Obstetrics and Gynaecology Research*. 2006; 32(2):230-4.	Postmenopausal osteoporosis	Double-blind, randomized, placebo-controlled	n = 63 (all women); mean age 60 years	MK4 group: MK4 45 mg/day orally plus calcium carbonate 1500 mg/day orally Control group: placebo plus calcium carbonate 1500 mg/day orally	48 weeks	**Bone density:** MK4 increased bone density 1.74%, while those not taking MK4 lost bone density.	Two minor gastrointestinal symptoms, which subsided after temporary cessation of therapy.
Sasaki and Kusano	*Journal of Bone and Mineral Metabolism*. 2005; 23(1):41-7	Osteoporosis in people with chronic glomerulonephritis taking prednisone	Randomized, controlled	n = 20 (12 men, 8 women), mean age 40 years	MK4 15 mg/day orally plus glucocorticoids (prednisone) or glucocorticoids without MK4	12 months	**Bone density:** MK4 preserved bone mineral density (BMD) while those not taking MK4 lost BMD.	None
Ochiai and Nakashima	*Bone*. 2004; 34(3):579-83.	Hypoparathyroidism in people with chronic renal failure in patients on dialysis	Randomized, controlled	n = 33 (18 men, 15 women) mean age 65 years	MK4 45 mg/day orally or no MK4	12 months	**Bone laboratory markers:** MK4 improved lab markers associated with bone health.	Not reported

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Sato and Kanoko	*Bone*. 2005; 36(1):61-8.	Osteoporosis in people with Alzheimer's disease	Randomized, controlled	n = 200 (all women); mean age 78 years	MK4 45 mg/day orally, plus vitamin D 1000 IU/day orally and calcium 600 mg/day orally, or no MK4	24 months	**Bone density:** MK4 increased bone density. Those not taking MK4 lost bone density. **Fractures:** In the group taking MK4 there were two hip fractures compared with fifteen hip fractures in those not taking MK4, an 87% reduction.	Three patients in the intervention group experienced gastrointestinal symptoms such as epigastric discomfort and nausea, but they subsided within a week without discontinuing MK4 or ergocalciferol. No patient in the intervention group experienced liver or renal dysfunction.

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Yonemura and Fukasawa	*American Journal of Kidney Diseases*. 2004; 43(1):53-60	Osteoporosis in people with chronic glomerulone-phritis taking prednisone	Randomized, controlled	n = 60 (28 men, 32 women), mean age 32 years	Group A: control (glucocorticoids only) Group B:MK4 (45 mg/day) orally plus glucocorticoids Group C: vitamin D alone, plus glucocorticoids Group D: MK4 (45 mg/day) plus vitamin D and glucocorticoids.	24 months	**Bone density:** Those taking just glucocorticoids lost BMD. Those taking just vitamin D or vitamin D plus MK4 had their bone density maintained. However, those taking just vitamin D also had an increase in serum calcium, while serum calcium did not increase in those taking vitamin D plus MK4.	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Nakashima and Yorioka	*Bone*. 2004; 34(3):579-83.	Hypoparathy-roidism in people with chronic kidney failure on dialysis with underlying chronic glomerulone-phritis, nephrosclerosis and diabetes mellitus	Randomized, noncontrolled	n = 32 hemodialysis patients (19 men and 13 women) with low parathryoid hormone (PTH); mean age 58 years	MK4 45 mg/day orally	12 months	**Bone laboratory markers:** MK4 improved bone laboratory markers (eg, undercarboxylated osteocalcin)	None
Iketani and Kiriike	*Psychiatry Research*. 2003; 117(3):259-69.	Osteoporosis in young women with anorexia nervosa	Controlled	n = 39 (all women); mean age 22 years	MK4 45 mg/day orally or no MK4	10.8 months	**Bone density:** MK4 preserved bone density compared with those not receiving MK4	None
Shiomi and Nishiguchi	*American Journal of Gastroenterol-ogy,* 2002: 97 (4): 978-81.	Osteoporosis in women with cirrhosis of the liver and viral hepatitis	Randomized, controlled	n = 50 (all women); mean age 60 years	MK4 45 mg/day orally or no MK4	24 months	**Bone density:** MK4 preserved bone density compared with those not taking MK4	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Sato and Honda	*Bone*. 2002; 31(1):114-8.	Osteoporosis in people with Parkinson's disease	Randomized, controlled	n = 120 (all women); mean age 71.9 years	MK4 45 mg/day orally or no MK4	12 months	**Bone density:** MK4 inreased bone density 0.9% while those who did not take MK4 had a loss of 4.3% **Fractures:** There was one fracture in the MK4 group and ten fractures in people not taking MK4. The MK4 group experience 90% fewer hip fractures.	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Ushiroyama and Ikeda	*Maturitas*. 2002; 41(3):211-21.	Postmenopausal osteoporosis	Randomized, controlled	n = 172 (all women); mean age 53 years	Group A: MK4 45 mg/day orally Group B: vitamin D3 1 µg/day orally Group C: MK4 plus vitamin D3 Group D: Control group	24 months	**Bone density:** MK4+Vitamin D increased bone density nearly 5% while those taking MK4 alone had a 0.14% increase in bone density.	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Bunyaratavej and Penkitti	*Journal of the Medical Association of Thailand*. 2001; 84 Suppl 2:S553-9.	Osteoporosis	Randomized, controlled	n = 83 (all women)	MK4 group: MK4 45 mg/day orally plus calcium 800 mg/day orally Control group: calcium 800 mg/day orally	12 months	**Bone laboratory markers:** MK4 Improved lab markers associated with bone health compared to those taking calcium alone. **Bone density:** MK4 improved bone density compared to those taking calcium alone.	Two cases of mild skin rash that subsided upon discontinuation of MK4

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Inoue and Sugiyama	*Endocrine Journal*. 2001; 48(1):11-8.	Osteoporosis in children taking prednisone who have Juvenile rheumatoid arthritis, systemic lupus erythrematosus, dermatomyosi-tis, muscular gravis, autoimmune hepatitis, lymphoid interstitial pneumonia, IgA nephropathy, nephrotic syndrome, mebranoprolife-rative glomerulone-phritis dystrophy, or myasthenia gravis	Randomized, controlled	n = 18 (5 boys, 13 girls), ages 4 to 14 years	Group A: MK4 (2 mg/kg/day) plus glucocorticoid Group B: MK4 (2 mg/kg/day) pluse Vitamin D (0.03 µg/kg/day) plus glucocorticoid	12 weeks	**Bone density:** MK4 maintained bone density while those not taking MK4 lost bone density.	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Nishiguchi and Shimoi	*Journal of Hepatology*. 2001; 35(4):543-5.	Osteoporosis in people with primary biliary cirrhosis (PBC) stages I-IV	Randomized, controlled	n = 30 (all women); mean age 55 years	MK4 45 mg/day orally or no MK4	24 months	**Bone density:** MK4 increased bone density by 0.3%, while those not taking MK4 lost 3.5%.	None
Iwamoto and Takeda	*Journal of Orthopaedic Science*. 2000; 5(6):546-51.	Postmenopau-sal osteoporosis	Randomized	n = 92 (all women); mean age 64 years	Group A: vitamin D3 0.75 µg/day orally Group B: MK4 45 mg/day orally Group C: MK4 plus vitamin D3 Group D: calcium lactate 2000 mg /day orally	24 months	**Bone density:** MK4 plus Vitamin D increased bone density compared to all other groups.	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Shiraki and Shiraki	*Journal of Bone and Mineral Research*. 2000; 15(3):515-21.	Postmenopausal osteoporosis	Randomized, open-label, controlled trial	n = 241 (all women); mean age 67 years	Group A: MK4 45 mg/day orally plus calcium 150 mg/day orally Group B: calcium 150 mg/day orally	24 months	**Bone density:** MK4 maintained bone density compared to those not taking MK4. **Fractures:** MK4 group experienced 60% fewer fractures compared with the calcium-only group, including, including a 54% decrease in vertebral fractures.	Not reported

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Iwamoto and Kosha	*Maturitas*. 1999; 31(2):161-4.	Postmenopausal osteoporosis	Randomized, controlled	n = 72 (all women)	Group A: no intervention control Group B: conjugated equine estrogen 0.625 mg/day orally and medroxyprogesterone 2.5 mg/day orally Group C: vitamin D3 1000 mg/day Group D: MK4 45 mg/day	12 months	**Bone density:** MK4 increased bone density while bone density decreased in the control group.	Not reported

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Sato and Honda	*Bone*. 1998; 23(3):291-6.	Osteoporosis in people with hemiplegia following stroke	Randomized, controlled	n = 108 (65 men, 78 women); mean age 66 years	MK4 45 mg/day orally or no MK4	12 months	**Bone density:** MK4 increased bone density by 4.7% compared to a loss of 4.7% in the group not taking MK4 **Fractures**: There were no fractures in the MK4 group and one fracture in the group not taking MK4.	None
Yonemura and Kimura	*Calcified Tissue International*. 2000; 66(2):123-8	Osteoporosis in adults with chronic glomerulone-phritis who are taking prednisone	Randomized, controlled	n = 20 (14 men, 16 women), mean age 28 years	Group A: Prednisolone orally Group B: MK4 (45 mg/day) orally plus prednisolone orally	10 weeks	**Bone density:** MK4 maintained bone density while those not taking MK4 lost bone density.	None

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Somekawa and Chigughi	*The Journal of Clinical Endocrinology and Metabolism*. 1999; 84(8):2700-4.	Osteoporosis in women with estrogen-dependent diseases (eg, endometriosis and leiomyomas) being treated with leuprolide	Randomized, controlled	n = 110 (all women); mean age 46.2 years	Group A: leuprolide (Lupron, Eligard) Group B: leuprolide plus MK4 45 mg/day orally Group C: leuprolide plus vitamin D3 0.5 µg/day orally Group D: leuprolide plus MK4 and vitamin D3	6 months	**Bone density:** MK4 slowed the bone loss from estrogen deprivation.	Not reported

Study	Citation	Diagnoses	Design	Volunteers	MK4 Dose	Duration	Outcomes	Adverse Events
Sugiyama and Tanaka	*Journal of Bone and Mineral Research*. 1999; 14(8):1466-7.	Osteoporosis in a girl with Arnold-Chiari deformity	Case report	n = 1 (girl); age 8 years	MK4 2 mg/kg/day and vitamin D3 0.05 µg/kg/day	15 months	**Bone density:** MK4 plus vitamin D increased bone density.	None
Nagasawa and Fujii	*Lancet*. 1998; 351(9104):724.	High cholesterol in people with chronic renal failure on peritoneal dialysis		n = 17 (8 men, 9 women); ages 36-70 years	MK4 45 mg/day orally	1 year	**Total Cholesterol:** MK4 significantly reduced total cholesterol.	Not reported