# MK4 Clinical Trials

| Study | Design | Volunteers | MK4 Dose | Duration | Outcomes | Side Effects |
|---|---|---|---|---|---|---|
| Ma and Ma, 2022;10:979649 | Systematic review and meta-analysis | n = 5,413 postmenopausal women ages 45-81 years old from 10 randomized, controlled clinical trials | 45 mg/day | 12-48 months | **Bone density:** MK4 improved bone density.<br><br>**Bone strength:** MK4 maintained bone strength as indicated by a significant, 62% fewer fractures in volunteers taking MK4 compared to those not taking it. | No difference in adverse reactions in those taking MK4 compared to controls. The authors concluded MK4 is "safe." |
| Kodama and Okamoto, 2017;39(10):846 - 850 | Case series | n = 16; median age 56 years<br><br>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.<br><br>**Bone density:** Bone density improved 5% after six months and 9% after twelve months. | Not reported |

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| Shikano and Kineko 2016; 55(15):1997-2003 | Prospective, observational study | n = 60 (21 men, 39 women); mean age 55 years. | MK4 45 mg/day or no MK4<br><br>All volunteers continued prednisone (30-60 mg/day) and all volunteers took bisphosphonate medications. | 18 months | **Bone laboratory markers:** MK4 improved laboratory markers associated with bone health.<br><br>**Bone density:** Bone density was maintained in the MK4 group.<br><br>**Bone strength:** MK4 maintained bone strength as indicated by zero fractures in people taking MK4 versus fractures in 5% of those not taking MK4. | Not reported |

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| Huan and Wan 2015; 26(3):1175-1186 | Meta-analysis of 19 randomized, controlled clinical trials | n = 6759 postmenopausal women | 45 mg/day or no MK4 | Various | **Bone strength:** MK4 maintained bone strength as indicated by a significant, 53% fewer fractures in women taking the MK4 compared to those not taking it. | Not reported |
| Jiang and Zhang 2014; 9:121-7 | Multicenter, randomized, double-blinded, double- dummy, noninferiority, positive controlled clinical trial | n = 213 (all women); mean age 64 years. | MK4 group: 45 mg/day plus calcium 500 mg/day<br>Vitamin D2 (alfacalcidol) group: 0.5 micrograms (mcg)/day plus calcium 500 mg/day | 12 months | **Bone laboratory markers:** MK4 improved laboratory markers associated with bone health.<br>**Bone density:** MK4 improved bone density 1.2% in the lumbar spine and 2.7% in the hip.<br>**Bone strength:** Fractures were decreased in the MK4+calcium group compared to those taking just vitamin D2+calcium. | The researchers concluded that MK4 "was well tolerated and safe," and that MK4 "is an effective and safe choice." |

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| Je and Joo 2011; 26(8):1093-8 | 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<br><br>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.<br><br>**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 2009; 27(3):333-40 | Randomized, prospective study | n = 109 (all women); mean age approx. 68 years | MK4 Group: 45 mg/day<br><br>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 |
| Binkley and Harke 2009; 24(6):983-91 | Double-blind, placebo-controlled study | n = 381 (all women); mean age 62.5 years | MK4 45 mg/day or phylloquinone 1 mg/day orally or placebo | 12 months | **Bone laboratory markers:** Improved lab markers associated with bone health. | None |

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| Inoue and Fujita 2009; 27(1):66-75 | Open-labeled | n = 4,378 (all women); mean age 68 years | MK4 45 mg/day alone or with calcium (1.2 to 3 grams) orally per day | 48 months | **Bone strength:** MK4 maintained strong bones as indicated by a decrease in fractures in people taking MK4+calcium. | Minor and statistically lower incidence in MK4 monotherapy group |
| Knapen and Schurgers 2007; 18(7): 963–972 | Randomized, placebo-controlled | n = 325 (all women); mean age 66 years | 45 mg/day 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 |
| Cockayne and Adamson 2006;166(12):1256-1261 | Meta-analysis of 13 randomized, controlled clinical trials | | 45 mg/day no MK4 | Various | **Bone strength:** Bone strength was maintained as indicated by a significant, 60% fewer vertebral fractures and 76% fewer nonvertebral fractures in people taking MK4 compared to those not taking MK4. | Not reported. |

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| Knapen and Schurgers 2007; 18(7): 963–972 | Randomized, placebo-cont rolled | n = 325 (all women); mean age 66 years | 45 mg/day 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 |
| Purwosunu and Muharram 2006; 32(2):230-4 | Double-blind, randomized, placebo-cont rolled | n = 63 (all women); mean age 60 years | MK4 group: MK4 45 mg/day plus calcium carbonate 1500 mg/day orally<br>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 temporarily stopping the MK4 |
| Sasaki and Kusano 2005; 23(1):41-7 | Randomized, controlled | n = 20 (12 men, 8 women), mean age 40 years | MK4 15 mg/day plus glucocorticoids (prednisone) or glucocorticoids without MK4 | 12 months | **Bone density:** MK4 supported healthy bone mineral density (BMD) while those not taking MK4 lost BMD. | None |

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| Ochiai and Nakashima 2004; 34(3):579-83 | Randomized, controlled | n = 33 (18 men, 15 women) mean age 65 years | MK4 45 mg/day or no MK4 | 12 months | **Bone laboratory markers:** MK4 improved lab markers associated with bone health. | Not reported |
| Yonemura and Fukasawa 2004; 43(1):53-60 | Randomized, controlled | n = 60 (28 men, 32 women), mean age 32 years | Group A: control (glucocorticoids only)<br><br>Group B:MK4 (45 mg/day) plus glucocorticoids<br><br>Group C: vitamin D alone, plus glucocorticoids<br><br>Group D: MK4 (45 mg/day) plus vitamin D and glucocorticoids | 24 months | **Bone density:** Those taking just glucocorticoids lost BMD.<br><br>Those taking just vitamin D or vitamin D plus MK4 maintained bone density. Those taking only vitamin D, however, also had an increase in serum calcium, while serum calcium did not increase in those taking vitamin D plus MK4. | None |

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| Nakashima and Yorioka 2004; 34(3):579-83 | Randomized, noncontrolled | n = 32 hemodialysis patients (19 men and 13 women) with low parathyroid hormone (PTH); mean age 58 years | MK4 45 mg/day | 12 months | **Bone laboratory markers:** MK4 improved bone laboratory markers (eg, undercarboxylated osteocalcin) associated with bone health. | None |
| Iketani and Kiriike 2003; 117(3):259-69 | Controlled | n = 39 (all women); mean age 22 years | MK4 45 mg/day or no MK4 | 11 months | **Bone density:** MK4 supported healthy bone density compared with those not receiving MK4. | None |
| Shiomi and Nishiguchi 2002: 97 (4): 978-81 | Randomized, controlled | n = 50 (all women); mean age 60 years | MK4 45 mg/day or no MK4 | 24 months | **Bone density:** MK4 preserved bone density compared with those not taking MK4. | None |

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| Ushiroyama and Ikeda 2002; 41(3):211-21 | Randomized, controlled | n = 172 (all women); mean age 53 years | Group A: MK4 45 mg/day<br>Group B: vitamin D3 1 µg/day<br>Group C: MK4 plus vitamin D3<br>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 |
| Bunyaratavej and Penkitti 2001; 84 Suppl 2:S553-9 | Randomized, controlled | n = 83 (all women) | MK4 group: MK4 45 mg/day plus calcium 800 mg/day<br>Control group: calcium 800 mg/day | 12 months | **Bone laboratory markers:** MK4 Improved lab markers associated with bone health compared to those taking calcium alone.<br>**Bone density:** MK4 improved bone density compared to those taking calcium alone. | Two cases of mild skin rash that subsided upon discontinuation of MK4 |
| Inoue and Sugiyama 2001; 48(1):11-8 | Randomized, controlled | n = 18 (5 boys, 13 girls), ages 4 to 14 years | Group A: MK4 (2 mg/kg/day) plus glucocorticoid<br>Group B: MK4 (2 mg/kg/day) plus Vitamin D (0.03 µg/kg/day) and glucocorticoid | 12 weeks | **Bone density:** MK4 maintained bone density while those not taking MK4 lost bone density. | None |

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|---|---|---|---|---|---|---|
| Nishiguchi and Shimoi 2001; 35(4):543-5 | 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 2000; 5(6):546-51 | Randomized | n = 92 (all women); mean age 64 years | Group A: vitamin D3 0.75 µg/day<br>Group B: MK4 45 mg/day<br>Group C: MK4 plus vitamin D3<br>Group D: calcium lactate 2000 mg /day | 24 months | **Bone density:** MK4 plus Vitamin D increased bone density compared to all other groups. | None |
| Yonemura and Kimura 2000; 66(2):123-8 | Randomized, controlled | n = 20 (14 men, 16 women), mean age 28 years | Group A: Prednisolone<br>Group B: MK4 (45 mg/day) orally plus prednisolone | 10 weeks | **Bone density:** MK4 maintained bone density while those not taking MK4 lost bone density. | None |

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|---|---|---|---|---|---|---|
| Shiraki and Shiraki 2000; 15(3):515-21 | Randomized, open-label, controlled trial | n = 241l women; mean age 67 years | Group A: MK4 45 mg/day plus calcium 150 mg/day<br>Group B: calcium 150 mg/day | 24 months | **Bone density:** MK4 maintained bone density compared to those not taking MK4.<br>**Bone strength:** MK4 maintained strong bones as indicated by 60% fewer fractures in the group taking MK4 compared with the calcium-only group. | Not reported |
| Somekawa and Chigughi 1999; 84(8):2700-4 | Randomized, controlled | n = 110 (all women); mean age 46.2 years | Group A: leuprolide (Lupron, Eligard)<br>Group B: leuprolide plus MK4 45 mg/day<br>Group C: leuprolide plus vitamin D3 0.5 µg/day<br>Group D: leuprolide plus MK4 and vitamin D3 | 6 months | **Bone density:** MK4 supported healthy bone density. | Not reported |

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|---|---|---|---|---|---|---|
| Iwamoto and Kosha 1999; 31(2):161-4 | Randomized, controlled | n = 72 women | Group A: no intervention control<br>Group B: conjugated equine estrogen 0.625 mg/day and medroxyprogesterone 2.5 mg/day<br>Group C: vitamin D3 1000 mg/day<br>Group D: MK4 45 mg/day | 12 months | **Bone density:** MK4 increased bone density while bone density decreased in the control group. | Not reported |
| Sugiyama and Tanaka 1999; 14(8):1466-7 | 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 1998; 351(9104):724 | Case series | n = 17 (8 men, 9 women); ages 36-70 years with chronic kidney failure on dialysis | MK4 45 mg/day | 1 year | **Total Cholesterol:** MK4 promoted healthy cholesterol levels. | Not reported |

# MK4 Laboratory Studies

| Molecular Effect | Benefit | Studies |
|---|---|---|
| Binds to the steroid and xenobiotic receptor (SXR)/pregnane X receptor (PXR) | By binding to these receptors, MK4 activates genes that promote the creation of osteoblasts, which build new bone. | Ichikawa T, Horie-Inoue K, Ikeda K, et al. 2006;281(25):16927-16934.<br>Igarashi M, Yogiashi Y, Mihara M, et al.. 2007;27(22):7947-7954.<br>Tabb MM, Sun A, Zhou C, et al. 2003;278(45):43919-43927. |
| Inhibits NF-kB | NF-kB helps regulate inflammation. Elevated levels of NF-kB are associated with increased inflammation, which in turn stimulates the production of osteoclasts. It also helps osteoclasts stay alive longer, giving them more time to destroy bone. Healthy inflammation balance is important for maintaining strong bones. | Ichikawa T, Horie-Inoue K, Ikeda K 2006; 281 (25):16927-16934.<br>Ide Y, Zhang H, Hamajima H, et al. 2009; 22(3): 599-604.<br>Ozaki I, Zhang H, Mizuta T, et al. 2007 Apr 1;13(7):2236-45.<br>Yamaguchi M, Weitzmann MN. 2011;27(1): 3-1. |
| Reduces RANKL activity | RANKL is a cellular receptor that's involved in bone health. Increased RANKL activity damages bone. MK4 reduces RANKL activity, which is associated with improved bone health. | Wu WJ, Kim MS, Ahn BY. 2015;6(10): 3351-3358. |

| Molecular Effect | Benefit | Studies |
|---|---|---|
| Activates the following genes: growth differentiation factor 15 (GDF15), Stanniocalcin, Tenascin-c and bone morphogenic protein-2 (BMP-2). | These genes are involved in promoting healthy bone collagen. Healthy collagen is crucial for bone health and strength. | Akbari S, Rasouli-Ghahroudi AA. 2018; 2018:4629383.<br>Ichikawa T, Horie-Inoue K, Ikeda K, et al. 2006;281(25):16927-16934.<br>Ichikawa T, Horie-Inoue K, Ikeda K, et al. 2007;39(4):239-247. |
| Increases calcium binding to bone. | MK4 enhances the ability of vitamin D to add calcium to bone. | Miyake N, Hoshi K, Sano Y, et al. 2001;12(8):680-687. |
| Supports healthy bone marrow stem cell production. | MK4 supports bone stem cell health, which is important for the creation of healthy red blood cells, white blood cells and platelets. | Fujishiro A, Iwasa M, Fujii S, et al. 2020;112(3): 316-33 0. |

| Molecular Effect | Benefit | Studies |
|---|---|---|
| Inhibits matrix metalloproteinase (MMP). | MMP plays a key role in regulating the immune system, and lowering MMP activity is associated with improved immune health and healthy cell structure. | Ide Y, Zhang H, Hamajima H, et al. 2009; 22(3): 599-604.<br>Naim A, Pan Q, Baig MS. 2017;7(4):367-372. |
| Decreases serum alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP). | Decreasing these blood proteins is associated with cellular health and healthy cell division. | Nouso, K, Uematsu S, Shiraga K, et al. 2005:11(42): 6722-6724. |

| Molecular Effect | Benefit | Studies |
|---|---|---|
| Increases caspase-3. | Caspase-3 helps regulate the lifecycle of cells. Caspase-3 is associated with healthier cells. | Miyazawa K, Yaguchi M, Gotoh A, et al. 2001 Jul;15(7):1111-7.<br>Nishimaki J, Miyazawa K, Yaguchi M, et al. 1999 Sep;13(9):1399-405. |
| Increases protein kinase A (PKA). | PKA is involved in regulating glycogen, sugar and lipid metabolism. | Otsuka M, Kato N, Shao R-X, et al. 2004; 40(1):243-51. |
| Decreases cyclin D1. | Cyclin D1 is involved in regulating the lifecycle of cells. Decreasing cyclin D1 is associated with healthier cells. | Ozaki I, Zhang H, Mizuta T, et al. 2007 Apr 1;13(7):2236-45. |